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Drug utilisation research in neonates:

A step towards rational prescribing

Asma Al-Turkait

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‘In dedication to my parents for their patience and prayers that accompanied me during this journey. All my family members and friends for their endless support. My home country Kuwait for giving me this opportunity. And most importantly, every person who is passionate about improving child health.’

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ABSTRACT

Background Since the initiation of drug utilisation research in the 1960s, the research in this area has continued to grow over the years, and in 2015 this search term reached over 20,000 hits in Medline. Whilst this area of research is known to be used in assessing the rational use of drugs, including prescribing, less is known about it in the neonatal population. In the UK, a drug utilisation study across neonatal units was conducted in 2009, but several limitations were observed that hinders a true representation of drug use patterns on a national level. Also, this study highlighted future research needs in one of the most challenging areas in neonatal medicine, which is managing patent ductus arteriosus (PDA). Ibuprofen is one of the drugs used to manage PDA; however, the rising reports of its adverse effects from observational studies requires further evaluation on when to use this agent, especially with the emergence of paracetamol as a suggestive alternative. In light of these existing gaps in knowledge, this thesis has been formulated to address a general question of 'Where are we at when it comes to rational prescribing of drugs in one of the most vulnerable populations towards adverse effects from drugs?'. The aim was designed to assess the rational use of drugs in neonates at the very first step of the drug use process, which is prescribing. As a result, several questions were answered, and others set for future research.

Methods An updated literature review was undertaken to provide an overall picture of neonatal drug utilisation studies across different regions. Then, this was narrowed to the UK setting by a retrospective pharmaco-epidemiological study investigating drug use patterns in England and Wales from 2010 to 2017 using the National Neonatal Research Database (NNRD), a large database from participating neonatal units across the UK. Having identified the drug use patterns and changes on drug use over time from 2010 to 2017, a follow up analysis to investigate the changes in drugs used in PDA was undertaken to explore the current practice in this condition. This was followed by a systematic review and meta-analyses of adverse effects of ibuprofen when used in preterm neonates with PDA to illuminate the safety profile of this popular agent. As a final explorative step, investigating the drugs' prescribing contents were looked at across neonatal drug formularies and/or clinical practice guidelines across UK neonatal units.

Results The findings of the drug utilisation literature review have shown that drug use patterns are similar globally, especially in Europe, with antibiotics remaining the most frequently prescribed drugs. In the retrospective pharmaco-epidemiological study, 638,843 neonates across 187 neonatal units in England and Wales (from 2010 to 2017) were included in the final analysis. The number of drugs prescribed per neonate (median (range, IQR)) was 2 (0-69, 0-3), with extremely preterm neonates received the highest number of drugs, 17 (0-69, 12-25). Across the entire cohort, the most frequently prescribed drug was benzylpenicillin, prescribed to 355,679 (56%) of neonates at least once during their hospital stay, closely followed by gentamicin which was prescribed to 347,713 (54%) of neonates. Drug

changes over time have also been explored; those with an overall increase in their use over the eight-year period across the entire cohort were sodium, benzylpenicillin, gentamicin, and pulmonary surfactants, whereas those with overall decrease were cefotaxime, domperidone, ranitidine, and ocular chloramphenicol. Across England and Wales, 18,181 (30%) of very and extremely preterm neonates had a record of PDA from 2010 to 2017. The analysis of different PDA treatment modalities has shown that ibuprofen was prescribed at least once to 27% of neonates with PDA, indomethacin to eight percent, and surgery to six percent, whereas 65% of neonates with PDA have not been recorded with any treatment (indomethacin and/or ibuprofen and/or surgery). A total of 90 studies were included in the systematic review of adverse effects of ibuprofen, with the largest number of neonates (3,831) receiving ibuprofen were recruited within 26 retrospective studies and accounted for half of the extracted adverse effects (2,264/4,700). Ibuprofen was discontinued in 56 neonates because of GI bleeding and renal toxicity. Inconsistencies in the dosage regimen of drugs with harm potential (e.g., gentamicin, caffeine) were found in the collected drug formularies.

Conclusion Understanding how drugs are prescribed and the pattern of their use over time in any neonatal care setting is important as a primary step towards rational prescribing. This thesis provides a benchmark for referral when prioritising research agendas in neonates, especially in the UK. However, the resources (such as NNRD) used to assess drug utilisation need to be improved to provide more in-depth understanding of drug use in neonates and to detect any inappropriate/irrational prescribing in this population.

PEER-REVIEWED PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

PUBLISHED PAPERS

- Al-Turkait, A.; Szatkowski, L.; Choonara, I.; Ojha, S. Review of Drug Utilization Studies in Neonatal Units: A Global Perspective. Int. J. Environ. Res. Public Health 2020, 17, 5669.

PUBLISHED ABSTRACTS

- Al-Turkait A, Abramson J, Choonara I, et al. P018 RENAL adverse events and gastro-intestinal bleeding with ibuprofen use in preterm neonates with patent ductus arteriosus (PDA). Archives of Disease in Childhood 2019;104: e2.

ORAL PRESENTATIONS

- Systematic review and meta-analysis of adverse events of Ibuprofen in preterm neonates with Patent Ductus Arteriosus (PDA), Nottingham Paediatric Research Showcase Conference 2018, 21st June 2018, Nottingham, UK.
- Developing a tool to detect inappropriate prescribing in neonates (TIP-N): An insight from a retrospective pharmaco-epidemiological study in neonatal units in the UK, Neonatal Clinical Pharmacology and Drug Development workshop, 20th June 2019, Derby, UK.

POSTER PRESENTATIONS

- Renal adverse events and gastro-intestinal bleeding with ibuprofen use in preterm neonates with patent ductus arteriosus (PDA), 24th Annual Neonatal and Paediatric Pharmacists Group (NPPG) Conference, 9-11 November 2018, Bristol, UK.
- Developing a tool to detect inappropriate prescribing in neonates: A pharmaco-epidemiological study of neonatal units in the UK, 3rd Congress of joint European Neonatal Societies (jENS), 17-21 September 2019, Maastricht, Netherlands.

AWARDS

- Awarded for 'The Students Choice' Prize in the Sue Watson Postgraduate Oral Presentation, 24th May 2019, Nottingham, UK.

LIST OF ABBREVIATIONS

ADRs	Adverse Drug Reactions
ARF	Acute Renal Failure
BAPM	British Association of Perinatal Medicine
BNF-C	British National Formulary for Children
BPD	Bronchopulmonary Dysplasia
BUN	Blood Urea Nitrogen
BW	Birth weight
CAP	Caffeine for Apnoea
CI	Confidence Interval
COI	Conflicts of interest
CLD	Chronic Lung Disease
CODAC	Cause of Death & Associated Conditions
CONSORT	Consolidated Standards of Reporting Trials
CPRD	Clinical Practice Research Database
DUR	Drug utilisation research
EOS	Early Onset Sepsis
FDA	Food and Drug Administration
GA	Gestational age
GI	Gastro-intestinal
GORD	Gastro-Oesophageal Reflux Disease
HES	Hospital Episode Statistics
IQR	Interquartile Range
IV	Intravenous
IVH	Intraventricular Haemorrhage
JBI	Joanna Briggs Institute
LBW	Low Birth Weight
LNU	Local Neonatal Unit
LOS	Late Onset Sepsis
MHRA	Medicines and Healthcare products Regulatory Agency
NAS	Neonatal Abstinence Syndrome

NDAU	Neonatal Data Analysis Unit
NEC	Necrotising Enterocolitis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NNAP	National Neonatal Audit Programme
NNRD	National Neonatal Research Database
NPPG	Neonatal and Paediatric Pharmacists Group
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PDA	Patent Ductus Arteriosus
PGE2	Prostaglandin E2
PKPD	Pharmacokinetics/Pharmacodynamics
PN	Parenteral Nutrition
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PVL	Periventricular leukomalacia
RDS	Respiratory Distress Syndrome
ROB	Risk of Bias
ROP	Retinopathy of Prematurity
RR	Risk Ratio
SCU	Special Care Unit
SD	Standard Deviation
SR	Systematic review
TPN	Total Parenteral Nutrition
UK	United Kingdom
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organisation
WHO-ATC	World Health Organisation-Anatomical Therapeutic Chemical

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CHAPTER 1 INTRODUCTION

In critical care settings such as neonatal care, any inappropriate use of drugs is a great risk, especially to vulnerable neonates at the start of their lives (1). The World Health Organisation (WHO) estimates that more than 50% of drugs are prescribed, dispensed or sold inappropriately (2). This has driven researchers towards exploring the best ways to rationalise the use of drugs. In response, this thesis aims to address some of the gaps concerning the rational use of drugs in the neonatal population.

1.1 Rational use of medicines in neonates

The WHO defines the rational use of medicines as "the use of medicines so that individual patients receive medicines that are appropriate to their clinical needs, in doses in accordance with their own individual requirements, for the appropriate period of time, and at the lowest or reasonable cost to both the individual and the community" (3). This definition has been cited over the years and used extensively in research to evaluate the process of drug use within any healthcare system or organisation.

Prescribing is the first step in any medication use process. The complexity of prescribing to the neonatal population stems from several factors that include the lack of licensed formulations and limited evidence-based information on dosing and indication of drugs suitable for this population (1). Lack of universally standardised and accepted guidelines on drug prescribing and individualising drug therapy in neonatal care adds a further challenge when prescribing to neonates (4,5). The concept of 'one size fits all' cannot be

applied when deciding on dosage considerations in this population. This is due to the rapid changes in neonates' body surface area and weight that necessitates continual dosing alterations (4,5).

Another obstacle when prescribing in neonates, particularly in preterm neonates, is the immaturity of their organs, which alters the pharmacokinetics and pharmacodynamics (PKPD) of the drugs and may consequently predispose them to various adverse drug reactions (5). The potential significant harm from inappropriate prescribing in neonates adds a further twist to the problem. This is emphasised by an observational study that reported a three-fold increase in the potential adverse events that occurred as a result of medication errors in neonatal care settings compared to adult settings (6). This study included paediatric inpatients, of which 16% were neonates. Overall, they reported that 79% of the potential adverse events were at the prescribing stage. However, the nature of the potential adverse events, including those that occurred in neonates, were not stated in the study.

Hence, prescribing constitutes a crucial step in the drug use process. It needs to be rationalised, especially in the neonatal population who are at greater risk of harmful effects of the drugs.

1.2 Drug utilisation research in neonatal medicine

Drug utilisation research (DUR) is a tool that can be used as a benchmark to explore the prescribing patterns in a healthcare system and to assist researchers in prioritising the research agenda for improving practice (7). It is defined as the research into “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” (8). Since its introduction, several terms were developed to further define the methods and domains used in this area of research, such as pharmaco-epidemiology, pharmaco-surveillance and pharmaco-vigilance. Pharmaco-epidemiology is the application of epidemiology to investigate the clinical use of drugs in a particular population. DUR is an essential part of pharmaco-epidemiological studies to provide an insight into the pattern of drug use and drug prescribing. DUR uses either a descriptive approach to portray a drug use pattern in a population or an analytical approach to further illuminate drug use by linking these data to morbidity, quality of healthcare, and treatment outcomes (8).

1.2.1 Previous reviews of drug utilisation in neonates

So far, three systematic reviews have been conducted with an overall aim of providing an insight into drug prescribing patterns in neonates (9–11). However, two of those reviews have yielded a small number of studies that investigated drug use in neonatal care units (≤ 20 studies) (9,10). The most recent review of the literature in this field was published by Allegaert et al. (11). It provides an updated overview of the characteristics, objectives, methods, and patterns of drug use in hospitalised neonates (11). In this paper, Allegaert et al. updated a previous systematic review search by Rosli et al. and found an increasing number of studies investigating drug utilisation in neonates. This review further extended their findings to descriptively include patterns of certain drug classes that are used in neonates, such as opioids, gastro-intestinal (GI) drugs, respiratory stimulants, and anti-epileptics.

Despite the availability of these reviews that summarise the drug utilisation studies across different neonatal care settings, there remain limited comparisons of different prescribing practices between different regions of the world (Table 1). This is pivotal as studies describing drug use in neonates are accumulating, and emerging evidence suggests wide variation in practices across the globe (11).

Table 1. Comparison between previously published reviews on drug utilisation

Criteria	Krzyzaniak 2016 (9)	Rosli 2017 (10)	Allegaert 2019 (11)
Description	SR to provide an overview of medicine use worldwide which includes identifying most frequently prescribed drugs	SR to determine drug prescribing patterns for hospitalised neonates which includes identifying most frequently prescribed drugs	Review to update a previous SR (Rosli et al. 2017) with a focus on research objectives, methods and patterns
Number of studies	19	20	30 in addition to Rosli et al., (Total: 50)
Search strategy	• Databases: Google Scholar, MEDLINE/PubMed, Scopus and EMBASE • Dates: 2000 to 2016 • Search terms: MeSH terms: neonate, NICU, drug utilisation, prescription pattern	• Databases: Medline, CINAHL, EMBASE, and PubMed • Dates: From inception to August 2016 • Search terms: Combination of neonates(s), newborn, infants WITH drug utilization, defined daily doses, and anatomical therapeutic chemical classification	• Databases: Medline Ovid, Web of Science, EMBASE • Dates: Updated the search of Rosli et al. (2016) from August 2016 to August 2018 • Search terms: Refer to Rosli et al. (2016)
Limitation(s)	• Only English language studies • Excluded single class of drugs (such as antibiotics)	• Only English language studies • Excluded conference abstracts	• Overview of the literature on drug use research methods and objectives without highlighting the most frequently prescribed drugs across regions

MeSH, medical subject heading; SR, systematic review

1.3 Drug utilisation studies in the UK

1.3.1 Overview of neonatal population and care in the UK

1.3.1.1 Birth statistics from England and Wales

There were 657,076 live births in England and Wales in 2018, a decrease of 3.2% since 2017 and 10% decrease since the most recent peak of live births in 2012 (12) (Figure 1).

Prematurity is the leading cause of death in children under five years (13). The WHO estimates that 15 million neonates are born prematurely, every year with one million deaths because of complications of preterm birth (13). In the UK, approximately 60,000 neonates are born prematurely per year (one in every 13 neonates born in the UK) (14).

The calculated rate of preterm births in England and Wales was found to be almost constant, ranging from 75 per 1,000 live births in 2014 to 79 per 1,000 live births in 2018 (Figure 2).

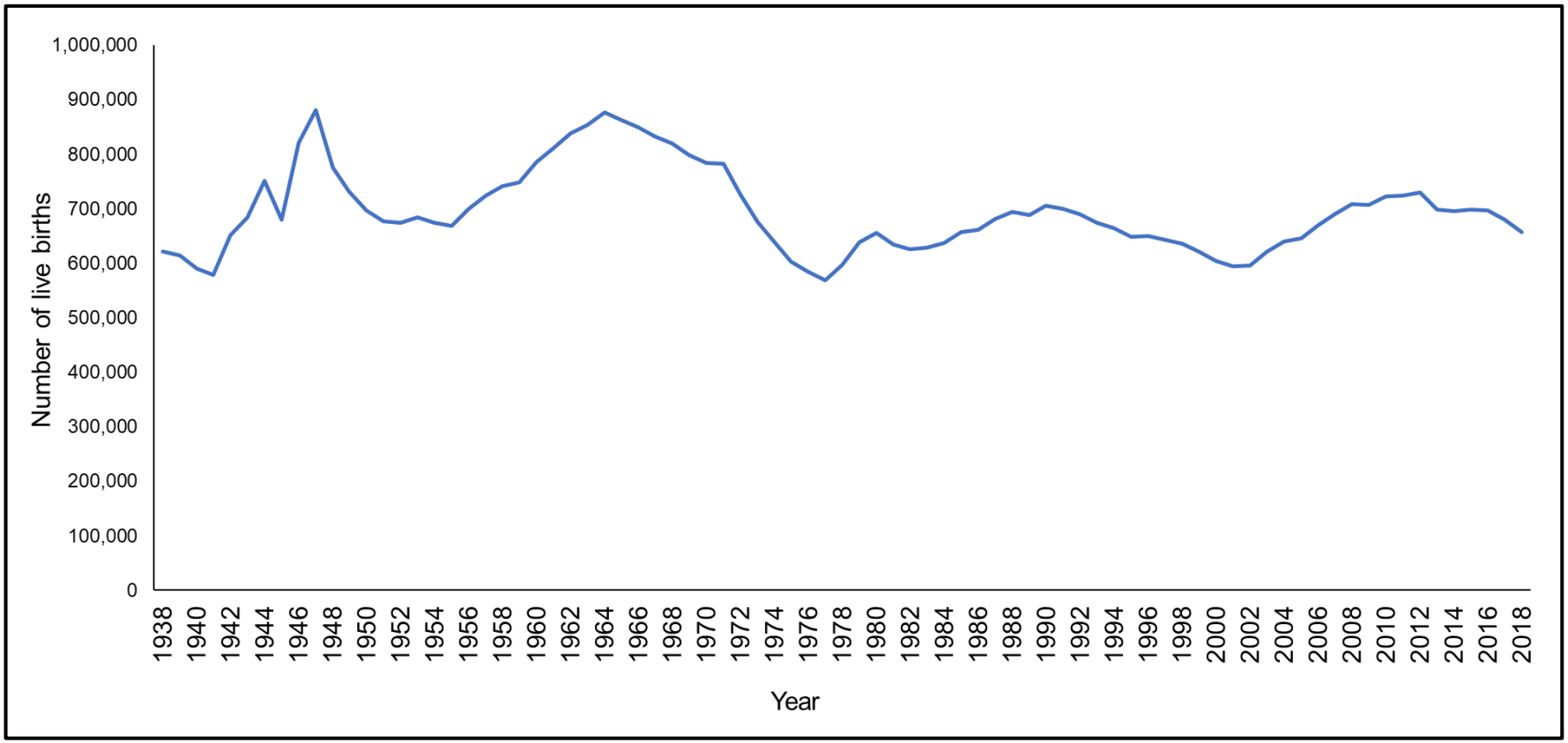


Figure 1. Number of live births in England and Wales

Source: The Office for National Statistics (ONS) [15]

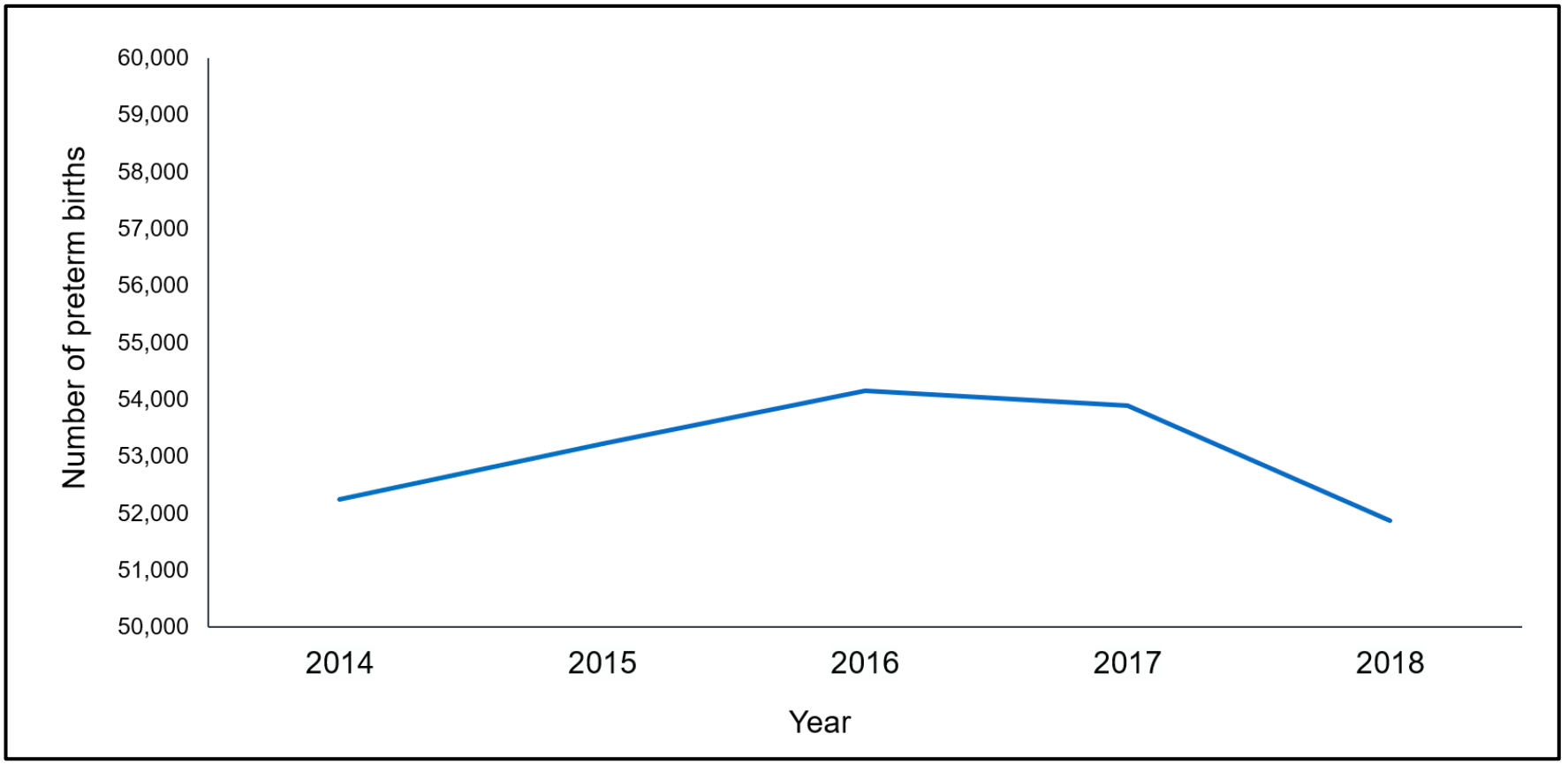


Figure 2. Number of preterm births (< 37 weeks gestation) in England and Wales

Source: The Office for National Statistics (ONS) [16]

1.3.1.2 Neonatal mortality from the UK

Neonatal mortality rate indicates the number of deaths during the first 28 completed days of life per 1000 live births in a given year or other period (17). The neonatal mortality rate was lowest in England and Wales in 2014, with a rate of 2.5 per 1,000 live births (12). The rate following that year has increased reaching 2.8 per 1,000 live births in 2018 (Figure 3).

A recent perinatal mortality surveillance report was released by the UK maternal, newborn and infant clinical outcome review programme in October 2019 (18). In 2017, 12.2% of neonatal deaths were due to extreme prematurity classified as a primary cause of death. Other reasons are shown in Figure 4.

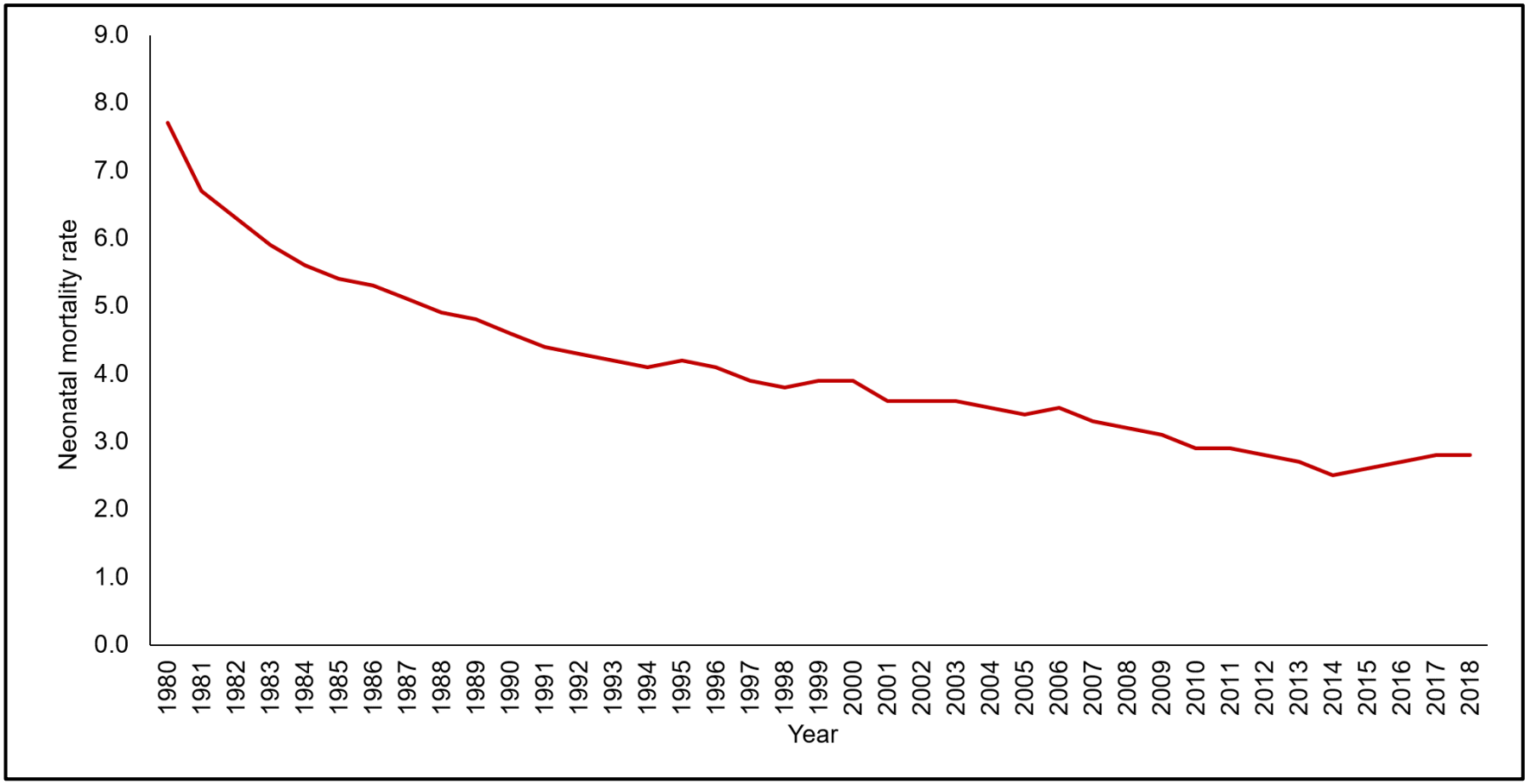


Figure 3. Neonatal mortality rate in England and Wales

Source: The Office for National Statistics (ONS) [15]

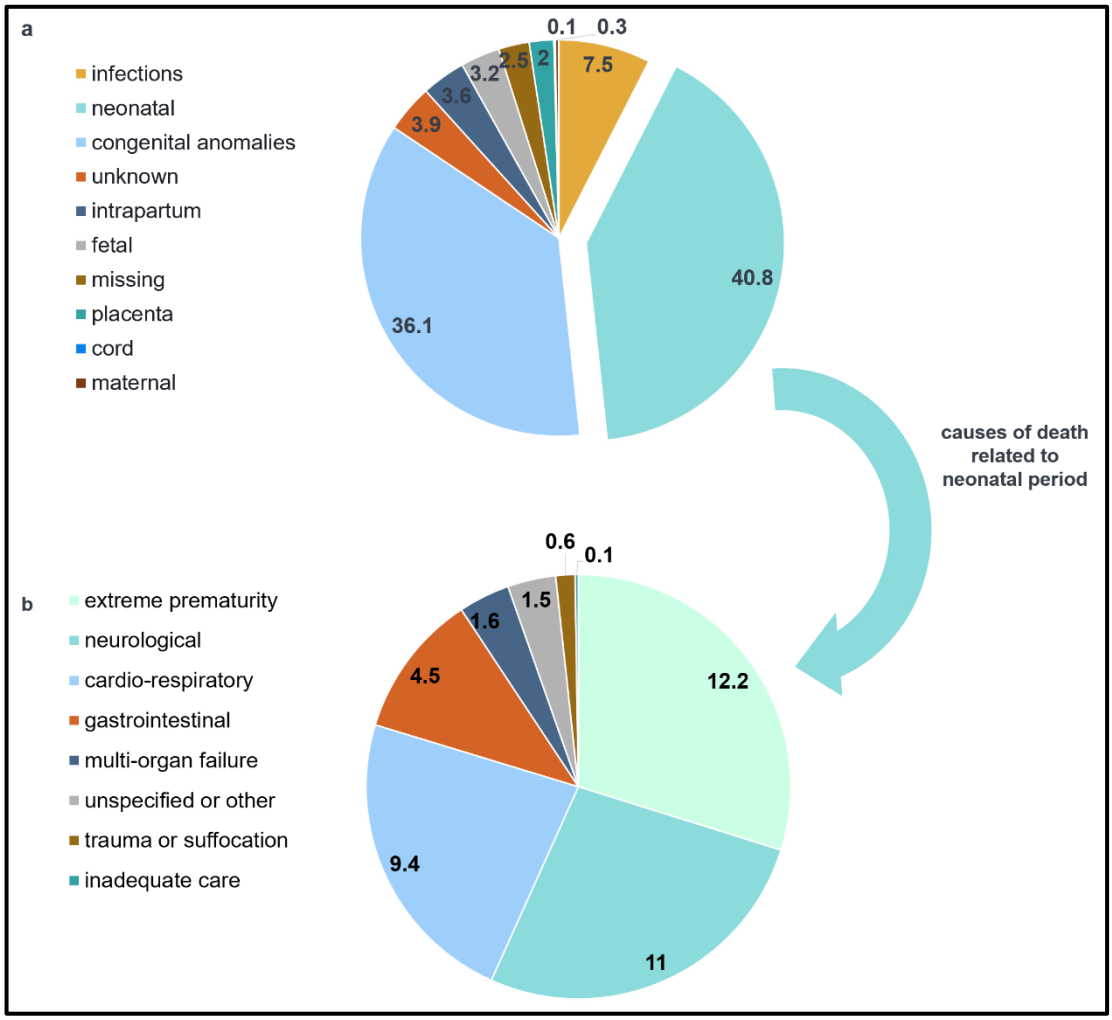


Figure 4. Causes of neonatal death across UK and crown dependencies in 2017 using the Cause of Death & Associated Conditions (CODAC) classification a. Neonatal deaths according to CODAC 'level 1' classification b. Neonatal deaths according to CODAC 'level 2' classification

1.3.1.3 Neonatal care in the UK

The National Neonatal Audit Programme (NNAP) in 2019 estimated that one in seven neonates in the UK received neonatal care due to prematurity, low birth weight (LBW), or need for other specialist treatment (19). Most of these admissions, around 60%, are for those born at full term gestation (20,21).

Across the UK, there are approximately 195 neonatal units with three different levels of service within the National Health Service (NHS) (22,23). Each of these levels functions to provide the specialist care that is tailored towards the needs of neonates (24). These levels are categorised according to the complexity of care provided by the British Association of Perinatal Medicine (BAPM) according to 2011 definition into special care unit (SCU-level one), local neonatal unit (LNU-level two), and neonatal intensive care unit (NICU-level three) (24).

Level one (SCU) of neonatal care provides care for singleton births born at gestational age (GA) > 32 weeks and birth weight (BW) > 1000 g. However, neonates born between 30-32 weeks can be admitted to this level provided that their BW is > 1000 g and not requiring intensive care. This level is known for its initial and short-term care and involve stabilisation of neonates prior to their transfer to other unit levels (LNUs or NICUs), or caring for neonates in need of special or post-surgical care following their return from those units. Services provided can include neonates requiring phototherapy, having an intravenous (IV) cannula, needing observation or continuous monitoring and those on feeding by nasogastric or jejunal or gastrostomy.

Level two (LNU) is a high dependency unit providing additional services to those provided by SCUs and is dedicated to providing care for singleton births with GA > 27 weeks, multiple births with GA > 28 weeks provided that their BW > 800 g. LNU provides limited intensive care and is responsible for ongoing post-surgical care and care for transferred neonates from other network neonatal units. Also, this level is responsible for stabilising neonates before their NICU transfer. This level includes neonates requiring non-invasive respiratory support, parenteral nutrition (PN) and continuous drug infusions (except prostaglandin and/or insulin).

Level three (NICU) represents the highest level in terms of neonatal care for neonates who are mostly unwell and unstable. Similarly, this level provides all the services provided by SCUs and LNUs in addition to other complex services. This unit level provides neonatal services for neonates with GA ≥ 23 weeks, and any neonate requiring complex or prolonged intensive care.

Neonatal units in the UK are organised as collaborative regional operational delivery networks to provide high quality specialist neonatal care and improve the survival of neonates admitted to neonatal units (25,26). These networks involve collaboration between tertiary and non-tertiary neonatal units to transfer neonates in need for a high level of care to a tertiary unit vs. step-down transfer for those requiring less level of care to a non-tertiary unit within the same network (27). This was emphasized following the recommendation by the department of health to reorganise neonatal services into clinical networks in 2003 (25).

1.3.2 Paucity of drug utilisation studies in the UK

There are a limited number of drug utilisation studies in the UK, and only two were found across the literature (28,29). The most recent one was conducted in 2009. A scoping survey was used as a data collection tool to collect the results over two week period from 116 neonatal units. This study reported that the most frequently prescribed drugs were gentamicin, followed by benzylpenicillin and vitamin K. This study was limited mainly by the low response rate. Only 42% of units responded (n=49) to the survey, limiting the ability to generalise the findings of this study.

The second study was also a prospective study, by Conroy et al., aimed to determine the extent of use of unlicensed or off label drugs in a single neonatal unit (29).

1.3.3 Neonatal drug formularies and clinical practice guidelines

Quality, which is considered a determinant of irrational practice, is assessed through the comparison of current practices against the local drug formularies and guidelines (7). Drug use across neonatal care units (including dosing, formulations, and direction) differs widely. This is related to the setting, availability, and accessibility of the drug depending on the country, licensing and off-labelling status, and national and international guidelines (9,10). This will consequently affect the available prescribing information within any neonatal drug formulary or any clinical practice guidelines.

The previous study by Conroy et al. exploring the nature of off label and unlicensed drugs have reported that benzylpenicillin accounted for the highest number off-label prescription in terms of its dosage (29). Benzylpenicillin prescribed 120 mg/kg/day, followed by 240 mg/kg/day is higher than the licensed dose (50-75 mg/kg/day). This suggests differences in terms of the recommendations of the product licence and the current prescribing practice. Interestingly, this study has pointed out the fact that different doses of benzylpenicillin contained within different commonly used neonatal prescribing formularies. However, this study was a single centre study so these findings may not be generalisable.

In the UK, the British National Formulary for Children (BNF-C), published by the British Medical Association and the Royal Pharmaceutical Society, is considered the standard of drug prescribing and dosing guide. It meets the WHO standards for national formularies (28) and widely used in the UK. Neonatal units often have their own local or regional resources in which they use it in conjunction with the BNF-C.

No study has explored whether prescribing information in those formularies and other clinical practice guidelines is similar or different to national guidelines.

1.3.4 A dilemma in neonatal pharmacotherapy: Medical management of patent ductus arteriosus (PDA) in preterm neonates

PDA is a cardiovascular complication of prematurity in which the ductus arteriosus fails to close after birth. The ductus arteriosus is a vital blood vessel that connects the aorta and the pulmonary artery to allow blood flow

between these arteries during fetal life. Normally, the ductus arteriosus closes within a few days after birth as the lungs expand and blood is redirected from the right side of the heart, through the lung, back to the left side of the heart and out to the body (30). In PDA, the ductus arteriosus remains open leading to increased risk of complications such as heart failure and reduced blood flow to vital organs (e.g. kidney and GI tract). It has been estimated that PDA affects approximately 25% of preterm neonates born at GA < 33 weeks (31). In most term neonates (GA ≥ 37 weeks) PDA closes by 72 hours, whereas it takes longer in preterm neonates (32).

Small to moderate PDA tends to close spontaneously, therefore treatment is not required, especially in those born at GA > 28 weeks (33). However, larger PDA may require medical or surgical intervention as they are also associated with adverse outcomes (33). Several treatment strategies have been investigated in terms of their efficacy and safety in the management of PDA.

Treatment strategies can be divided into three main categories: conservative, pharmacological and surgical. *Conservative treatment* includes fluid restriction, ventilator support, and increased positive end expiratory pressure. Several recent studies have shown that non-intervention strategies (i.e. conservative strategy) were not associated with an increase risk in morbidity and/or mortality (34–37). Conservative strategy has proven its successfulness in neonates with a BW > 1000 g with few risk factors of having PDA (33,38). *Pharmacological treatment* is often reserved to preterm neonates with LBW and diagnosed with PDA as persistent PDA in this population is associated with a higher risk of mortality (33). Two non-steroidal

anti-inflammatory drugs (NSAIDs), indomethacin and ibuprofen, have been approved for PDA closure. This is due to their inhibitory effect on the release of prostaglandins, which play a role in maintaining ductal patency. Both have been associated with similar closure rates but differ in terms of their adverse effect profile (detail in section 1.3.4.1). Paracetamol is the most recent drug used in PDA, as it has a similar effect of NSAIDs in decreasing circulating prostaglandins but with different mechanism by acting at the peroxidase site of prostaglandin H2 synthetase (33). Paracetamol was found to be most effective when started in preterm neonates during their first week of life (39). Despite its better tolerability when compared to ibuprofen, paracetamol is associated with increased level of hepatic enzymes (38). *Surgical ligation* strategy can be considered when pharmacological measures failed to close PDA, often beyond the fourth week of life (40). This strategy is also considered in neonates where PDA results in cardiac, renal or respiratory failure (38).

1.3.4.1 Why is the management of PDA a dilemma?

There is a long-standing debate concerning the optimum management of PDA in preterm neonates. The most important questions of ‘when’ and ‘whether’ to treat PDA, especially in extremely preterm neonates (GA < 28 weeks). This question remains unanswered despite more than four decades of investigating the outcomes of different treatment strategies (41–44). The use of pharmacological interventions (indomethacin, ibuprofen, and most recently paracetamol) is one of the most extensively researched areas in

PDA. However, much uncertainty still exists about the long-term benefits of attempting to close the PDA with these agents.

The most recent Cochrane systematic review on the safe and effective use of ibuprofen in PDA was published in February 2020 (45). The systematic review updated previous reviews and supported their conclusion by indicating that ibuprofen is as effective as indomethacin in PDA closure. The review has also concluded that ibuprofen remains the drug of choice as it was found to be associated with a lower risk of NEC and transient renal insufficiency when compared to indomethacin. Another recent Cochrane review published in January 2020 investigated the efficacy and safety of paracetamol when used in PDA (46). This review concluded that paracetamol is as effective as ibuprofen in PDA closure and was associated with lower risk of GI bleeding when compared to ibuprofen. One of the reasons for the lack of clear evidence is the fact that clinical trials have not yet fully addressed the issue of clinically relevant, long term benefits in their research question (47,48). A recent review by Bentiz and Bhombal interestingly aimed to focus on long term benefits of NSAIDs in PDA closure. This review conducted a meta-analysis of 51 RCTs (1980-2016) that used NSAIDs (indomethacin, ibuprofen) and paracetamol in PDA. It concluded that there was no significant difference in long term outcomes, including neurodevelopmental outcomes, when managing PDA with or without the use of these drugs (48).

PDA was flagged as one of the areas in need for further research by clinicians who participated in the Turner et al. survey in 2009 (28). Over a decade has passed and PDA management continues to be debated. Several

systematic reviews have investigated the efficacy of pharmacological agents in PDA closure. However, not many have focussed on the problems related to use of these agents in preterm neonates.

1.3.4.2 Adverse effects of ibuprofen in neonates with PDA

To date, there is not enough evidence to suggest that one pharmacological management strategy is superior to another in the management of PDA (49). Therefore, quantifying the risks of adverse effects associated with pharmacological agents may assist neonatologists in their clinical judgement for selecting the appropriate management strategy when treating PDA, or indeed in deciding whether to use or not to use pharmacological management.

Despite the fact that ibuprofen is the preferred pharmacological agent when compared to indomethacin, there have been several observational studies that have reported adverse effects following its use. Ibuprofen was found to be associated with several reports of pulmonary hypertension (50–52), GI bleeding (53), and acute renal failure (54). Currently, there is no systematic review that provides comprehensive information of all the reported adverse effects associated with ibuprofen use in preterm neonates. Several Cochrane systematic reviews were conducted to derive a useful conclusion on the efficacy and safety of ibuprofen for use as a guidance for neonatologists when managing PDA in preterm neonates. These reviews only included RCTs or quasi-randomised trials. Some were conducted to collate studies where ibuprofen was used for PDA prophylaxis (55–58) and others where ibuprofen was used for PDA treatment (47,59–61).

1.4 Thesis aim and objectives

This thesis intends to shed light on some of the topics surrounding drug utilisation in neonates in the UK. The main aim sets out to assess the rational use of drugs in neonatal care units within areas in the UK. Several objectives emerged to achieve this aim based on the previous introductory sections which are summarised in Figure 5.

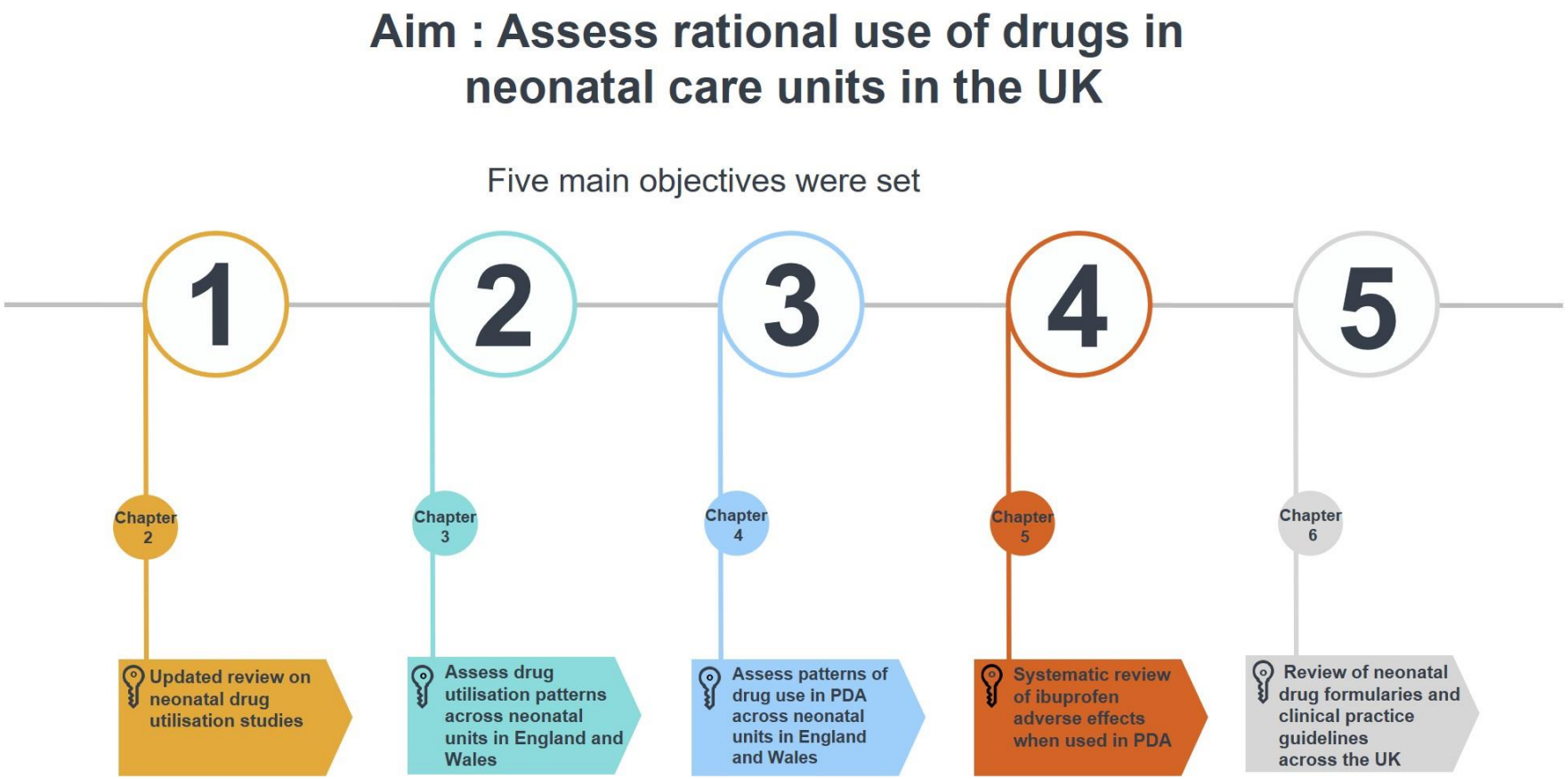


Figure 5. Aim and objectives of the presented thesis

1.5 Outline of subsequent chapters

The next chapter is an updated review of neonatal drug utilisation studies and a comparison of the patterns of drug use across different regions. In light of findings from this review, drug utilisation patterns across neonatal units in England and Wales using a national database was then investigated in general and the results of this study are reported in Chapter 3. Chapter 4 reports the results of drug utilisation patterns that are used for PDA using the same national database. Chapter 5 reveals the findings of a systematic review and meta-analyses of adverse effects of ibuprofen when used in PDA management. This is followed by another study presented in Chapter 6, which describes the available prescribing information in the collected neonatal drug formularies and/or clinical practice guidelines from neonatal units in the UK. The findings of each study are discussed within the context of each chapter, but the overall implications for practice and future research are discussed in-depth in Chapter 7.

CHAPTER 2 REVIEW OF DRUG UTILISATION STUDIES IN NEONATAL UNITS

This work has been published in the International Journal of Environmental Research and Public Health in August 2020, vol.17, issue 16. A copy is attached in 9.1.

2.1 Introduction

Drug utilisation research (DUR) is needed particularly in neonatal medicine due to several factors that constitute a challenge to prescribers when deciding on the safest medicines for neonates. These challenges include the lack of universally standardised and accepted guidelines on drug prescribing and individualising drug therapy in neonatal intensive care units (NICUs) (4,5). Consequently, this can cause a large variation in drug prescribing patterns. Also, the lack of licensed formulations and limited evidence-based information on dosing and indication of drugs suitable for this population is another challenging factor many prescribers may face (1). Scoping literature reviews are important in this field as there are many studies that reported on medication use in their settings worldwide.

A review on drug use patterns will collate all the relevant prescribing information to understand the differences in prescribing patterns, if they exist, between and within different geographic regions. Hence, the aim of this study was to conduct an up-to-date review of the literature to find out the most frequently prescribed drugs across neonatal units worldwide.

2.2 Methods

2.2.1 Search strategy

I constructed the search strategy with the help of the senior librarian at the University of Nottingham (Ms. Ruth Curtis). The search was checked by two people to ensure its robustness. Three databases, EMBASE, CINAHL, and Medline were searched from their inception to July 2020 without any other limits. A combination of both 'free text' and Medical subject headings 'MeSH terms' was applied for each database separately to attain a comprehensive literature search. The search was based on the following PICo (Population, Interest/intervention, Context) summarised in Table 2.

Table 2. Summary of the PICo used in this review

Population (P)	Interest or intervention (I)	Context (Co)
Neonates, infants or newborns (all gestation age groups)	Drug use or drug utilisation	Neonatal intensive care units

2.2.2 Search terms

Various free-text keywords were created and used to complement the MesH terms. For the population search terms, an infant* or newborn* or neonate* were used and are defined as those who were born during the first 28 days after birth. For the interest/intervention, free-text keywords, a combination of drug use and drug utili?ation was applied. The term util?ation was used to cover both different spellings of this term; utilisation or utilization. The free text keywords for the context or setting free in this review were neonatal intensive care unit* and neonatal unit*. This setting was used as the aim of this review was to provide an updated drug utilisation literature review at the level of neonatal intensive care units only. All the previously mentioned free text keywords were used in addition to the MeSH terms identified in each database separately. The full search strategy is detailed in 9.2 Following the retrieval of the records, titles were reviewed to remove any duplicates before starting to screen the abstracts for inclusion. This was done manually (using Microsoft Excel, Version 15 Microsoft Corporation) by myself.

2.2.3 Inclusion and exclusion criteria

Inclusion criteria: Studies of drug utilisation were included in this review if they fulfilled all the following criteria:

- Included neonates treated in neonatal units
- Provided information on drug use patterns and/or prescriptions patterns
- Provided information on the most frequently prescribed drugs. This includes general or overall, frequently prescribed drugs or pharmacologic groups, off-label and or unlicenced drugs, specific pharmacologic groups

Exclusion criteria: Studies were excluded for the following reasons:

- Conference abstracts with insufficient data on drug utilisation
- Drug utilisation studies not reporting the most frequently prescribed drugs
- Drug use in children (age > 28 days)
- Editorials and review articles
- Maternal drug use studies
- Systematic reviews
- Studies in non-English language that could not be translated
- Unrelated to the review question

2.2.4 Data extraction and analysis

All included studies were tabulated (using Microsoft Excel, Version 15 Microsoft Corporation) to summarise the most frequently prescribed drugs reported in those studies. To ensure completeness, data extraction was performed by two reviewers: myself and Dr Ojha (Clinical Associate Professor of Neonatology, University of Nottingham and the PhD supervisor). The data extracted included the following:

- Location of the study
- Inclusion and exclusion criteria
- Demographics of the included neonates (number, mean gestational age (GA), mean birth weight (BW), gender)
- The number of drugs prescribed per neonate
- Ten most frequently prescribed drugs or pharmacologic groups

Quality assessment of the studies was not performed as there is no appropriate tool for the type of the studies that are included. All studies included in this review were descriptively summarised and presented in tables or figures. Stata SE 16 (64-bit) software was used to summarise some of the data extracted (sample size and duration of the studies). Where the standard deviation (SD) of the number of the drugs received per neonate not available, it was imputed from the available summary statistics (mean, median, interquartile range (IQR), range) and sample size using the process described by Hozo et al. (62). The correlation between proportion of included preterm neonates and number of drugs per neonate was calculated using the Pearson's correlation coefficient test in Stata.

2.3 Results

2.3.1 Search results

The initial search resulted in 715 titles and abstracts. Duplicates were then removed and titles and abstract screened and 92 studies were selected for full text evaluation. Of these, 15 were excluded and a further seven were added (by searching the reference list of other studies). Thus, a total of 84 studies are included in this review (Figure 6).

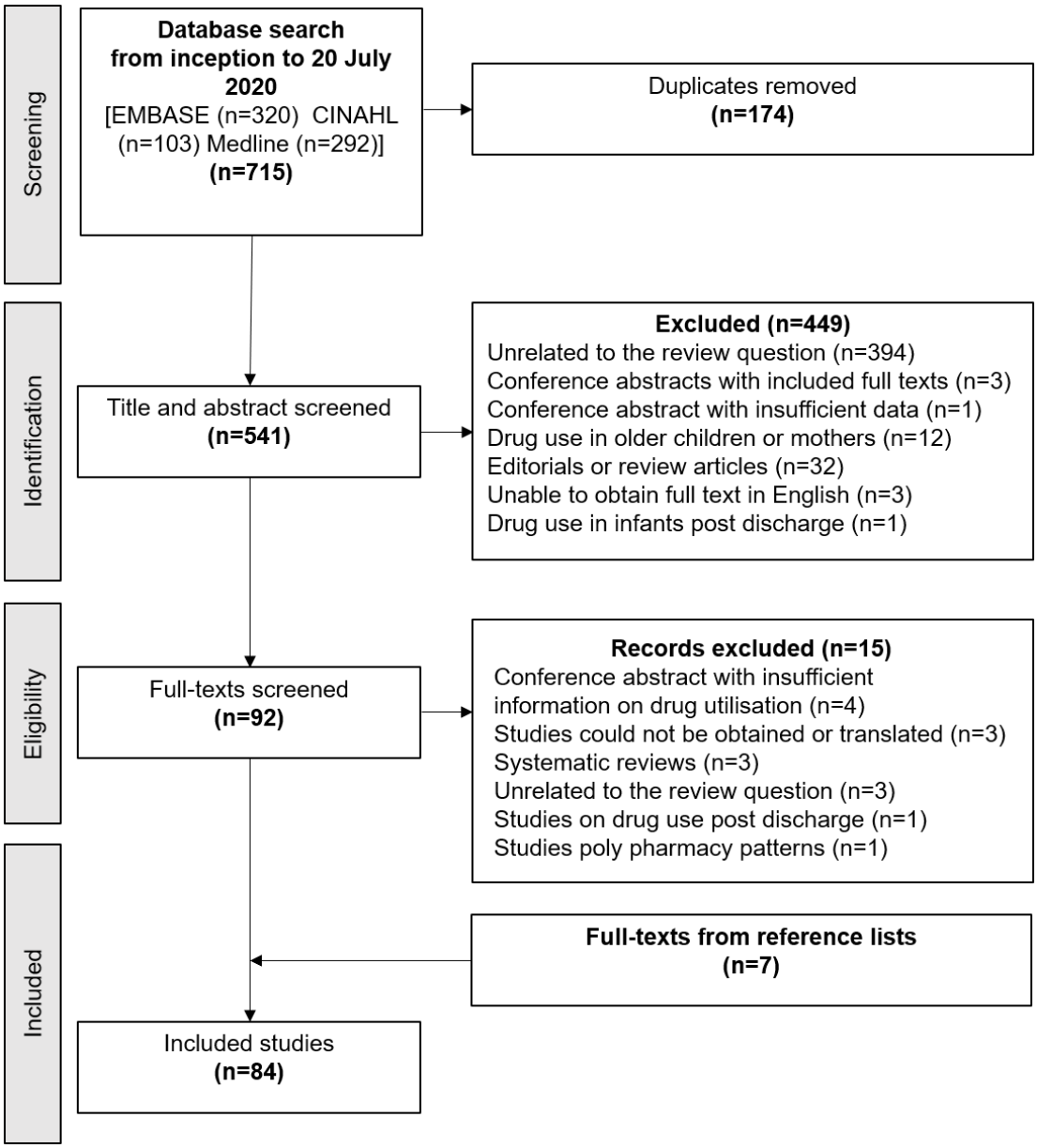


Figure 6. Selection of the studies for inclusion in the review of drug utilisation studies

2.3.2 Drug utilisation studies: An overview

Eighty-four studies included in this review were classified into four groups (Figure 7).

Studies were conducted in 26 different countries across six different continents (Figure 8). India (n=14) and the United States (n=13) accounted for the largest number of drug utilisation studies. There was one study that involved several European countries (21 participated) (63) and one study conducted in Germany and Brazil (64).

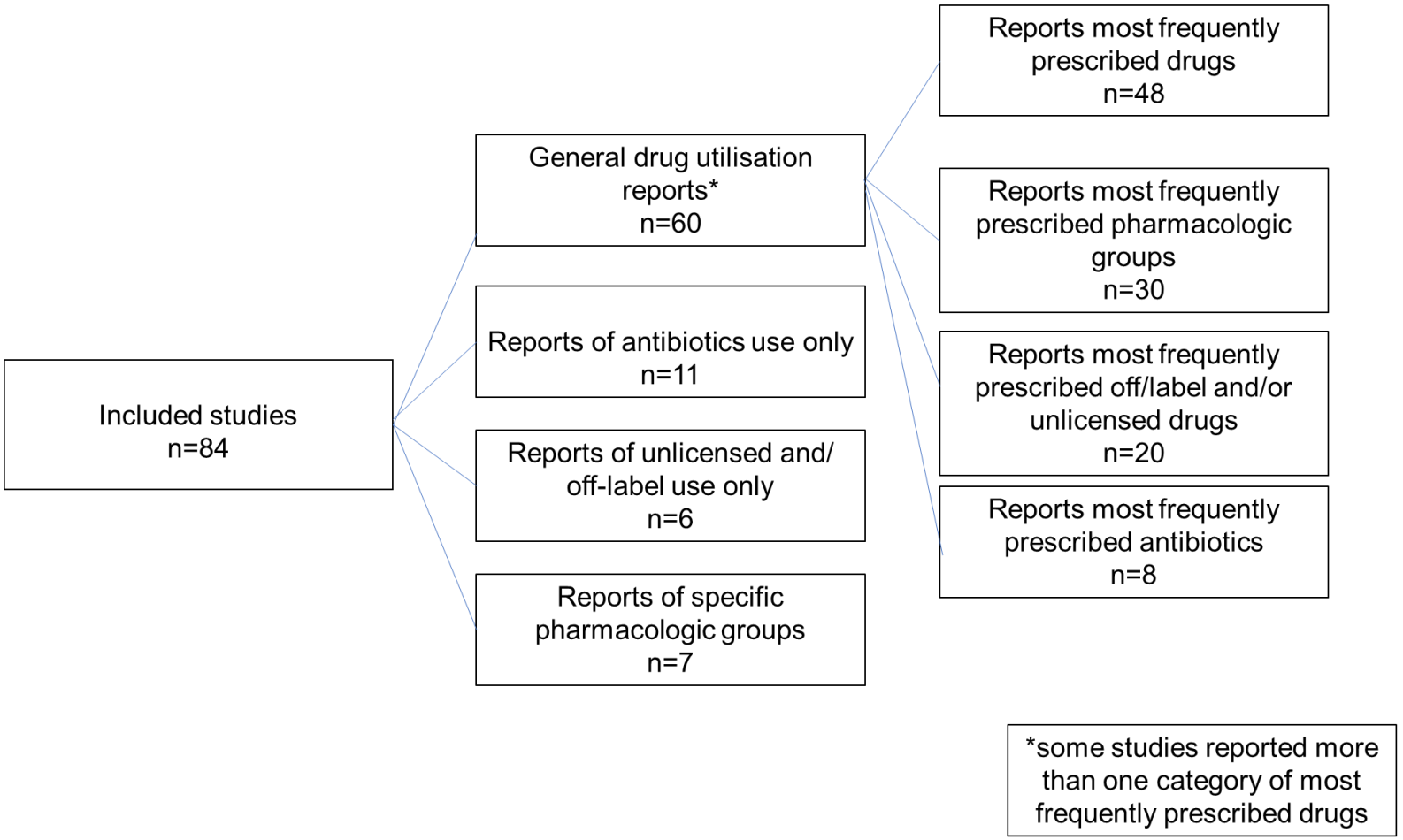


Figure 7. Classification of the studies included in this review

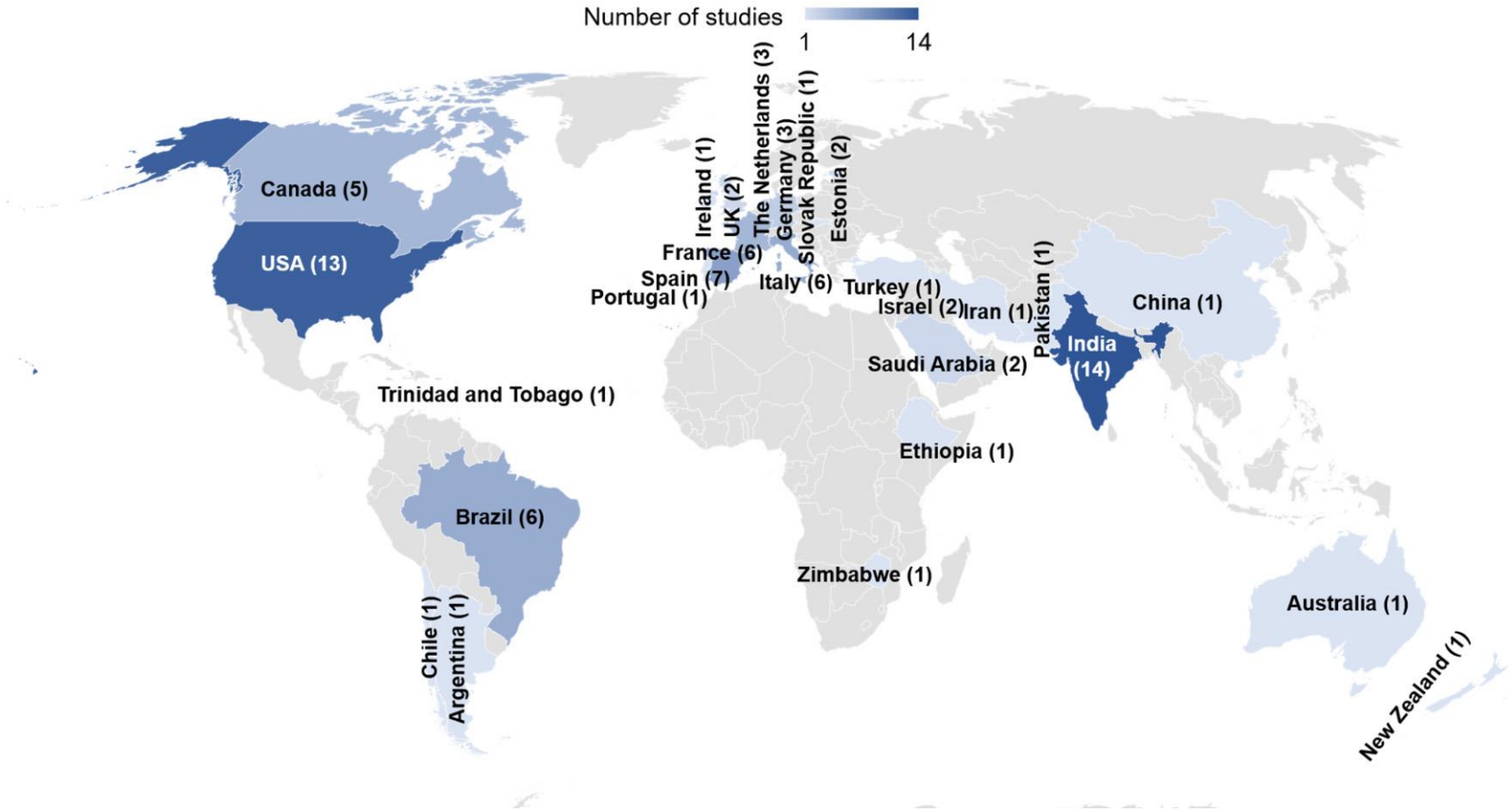


Figure 8. The geographical location of drug utilisation studies included in this review

Table 3 summarises the key demographics of the 84 studies. The studies had a wide range of sample size with a median (IQR) of 220 (113-1491). This reflects the large variation in the duration of the study period (range 1-264, IQR 3-18 months). The retrospective studies utilised large databases with routinely collected data and thus included more neonates and data over a longer span of time. For instance, the two main large studies were conducted in the United States of America (USA) over nine and five year periods by Clark et al. and Hsieh et al. respectively (65,66). There were 52 single centre studies out of 84 included studies.

Table 3. Summary of key demographic data (84 studies)

Demographic data	Median	Range	IQR
Sample size*	220	34-450386	113-1491
Duration of the studies in months **	6	1-264	3-18

*calculated for 77 studies only, 7 studies did not report the sample size
**calculated for 79 studies only, 5 studies did not report the duration of the study period

Figure 9 shows the data of 69 studies that mentioned the sample size and its' duration in months. However, four studies were excluded from this graph due to their large sample size (high outliers) (65–68).

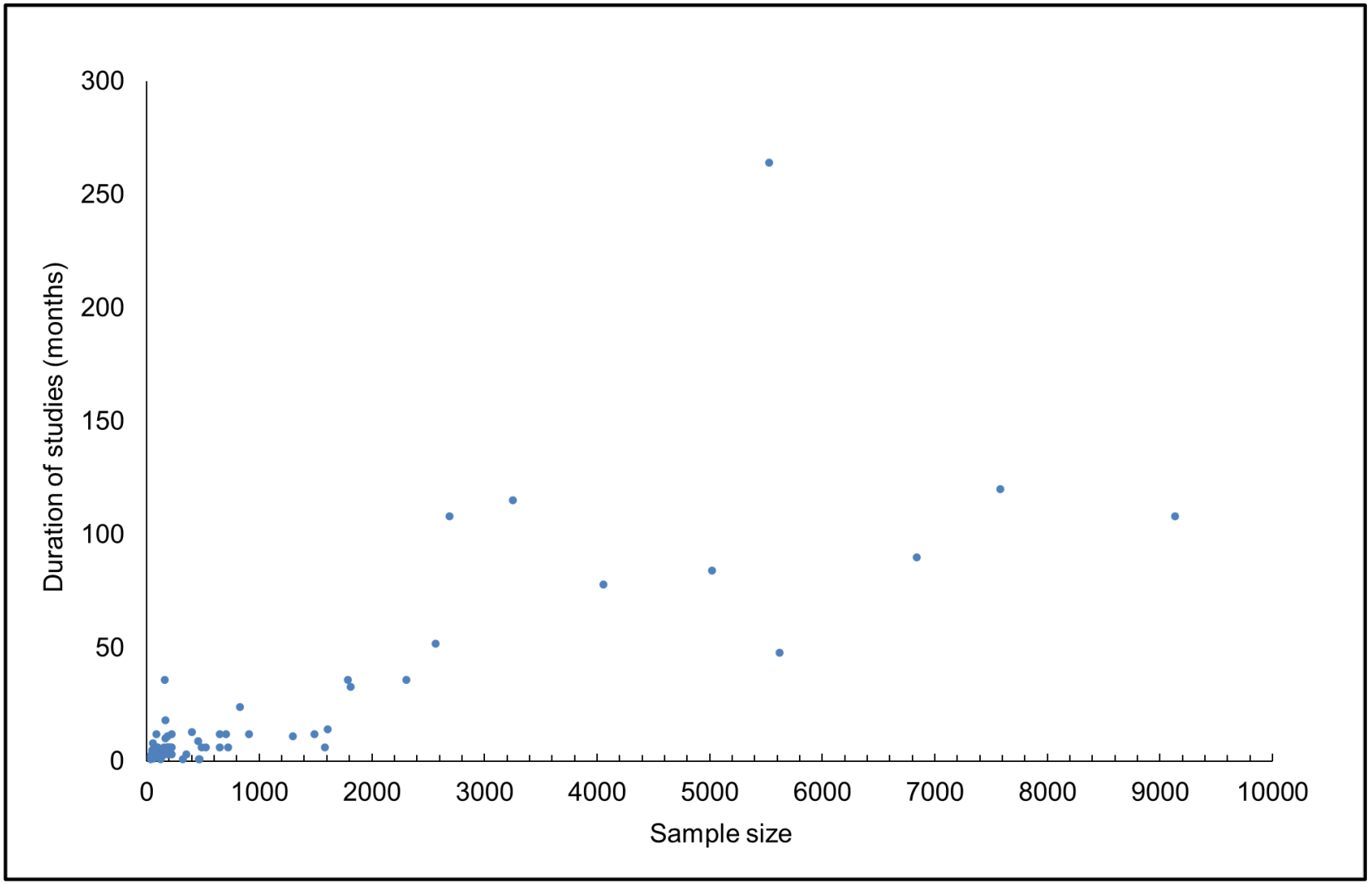


Figure 9. Sample size vs Duration of studies (months) of 69 studies

2.3.2.1 Drug utilisation studies investigating drug use in general

Sixty studies aimed to investigate drug use in the neonatal population and were conducted between 1983 to 2020. The majority of those studies were prospective in their design (43 studies, 73%) (4,5,28,29,63,69–106), with the remaining 17 studies (27%) utilising retrospective data extraction (65,66,68,107–120).

The participants' gender was not reported in 20 of the 60 studies. Where reported, most had more boys than girls (37 of 40 studies). Three studies had equal number of boys and girls.

More than half of the studies (34 of 60, 57%) reported the proportion of prematurity among the participants (Figure 10). Two out of the 34 studies enrolled only preterm neonates. In addition one study by Puia-Dumitrescu et al. reported drugs received by neonates born at gestational age (GA) of 22-24 weeks only (120).

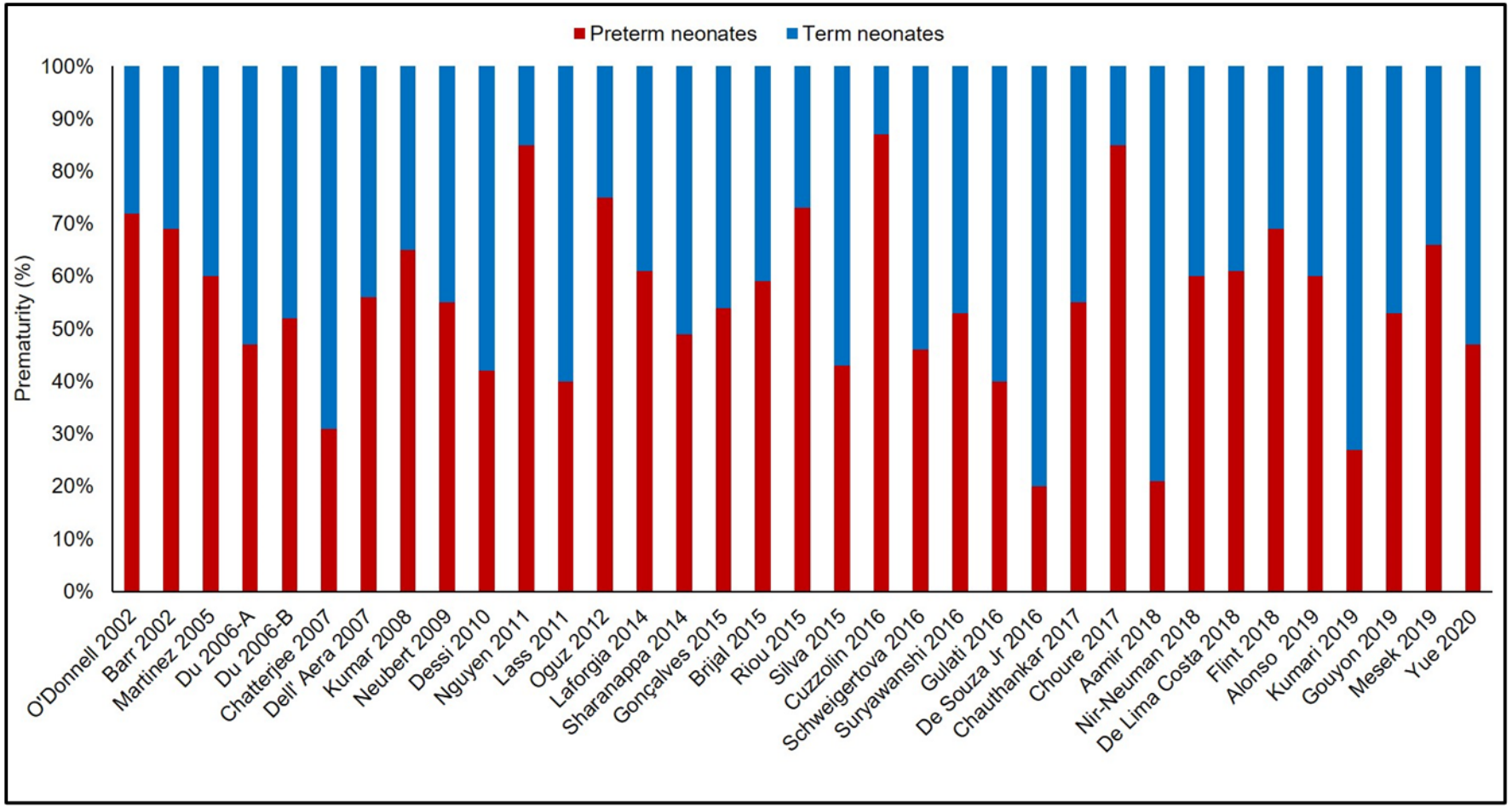


Figure 10. Percentage of preterm neonates among participants in drug utilisation studies in neonates

All the studies had similar inclusion criteria which was based on including all neonates admitted into the neonatal care units who received at least one drug. However, the exclusion criteria varied. The majority of studies excluded certain items from their analyses such vitamin K, intravenous (IV) fluids, total parenteral nutrition (TPN), and fluids to keep the patency of the venous access (e.g. heparin and sodium chloride for flush). The details of inclusion and exclusion for each included study are given in 9.3.

Drug use per neonate: 14 studies out of the 60 studies reported the mean (SD) of the number of drugs prescribed per neonate. Seven studies reported the mean, but provided no information on the SD. The SD for these seven studies were imputed by estimation from the mean, median, range and sample size, where possible (62). However, it is worth noting that this formula has been developed with no assumptions on the distribution of the data. A total of 21 studies with their reported means and reported or imputed standard deviations of the average number of drugs prescribed per neonate in each study and divided by each continent are plotted in Figure 11.

One study by Du et al. is plotted twice (Du-A, and Du-B) as it compared drug use in two different periods and reported different sample sizes and means (109). The pooled mean and the pooled SD from 29 studies out of 60 studies on drug use in general included in this review were 4 (2.4). Those 29 studies include 14 studies that reported the mean (SD) and 15 studies with imputed values of either mean and or SD based on the formula.

The remaining 39 studies were not included in this plot for the following reasons:

- 15 studies reported the median instead of the mean. The medians reported in those studies ranged between 3.5 and 9
- One study by Aranda et al. did not report the sample size (107)
- 17 studies reported neither the mean nor the median
- Six studies reported the mean only without reporting the range. Therefore, the standard deviation could not be estimated using the formula (4,5,72,76,79,117). The means reported in those studies ranged between 1.2 and 11.1

There were 27 studies reporting the maximum number of drugs received by at least one neonate. Kumar et al. reported the highest drug burden with at least one neonate receiving 62 drugs (115), while eight other studies reported that the maximum number of drugs per neonate was $\geq$ 30 in their population.

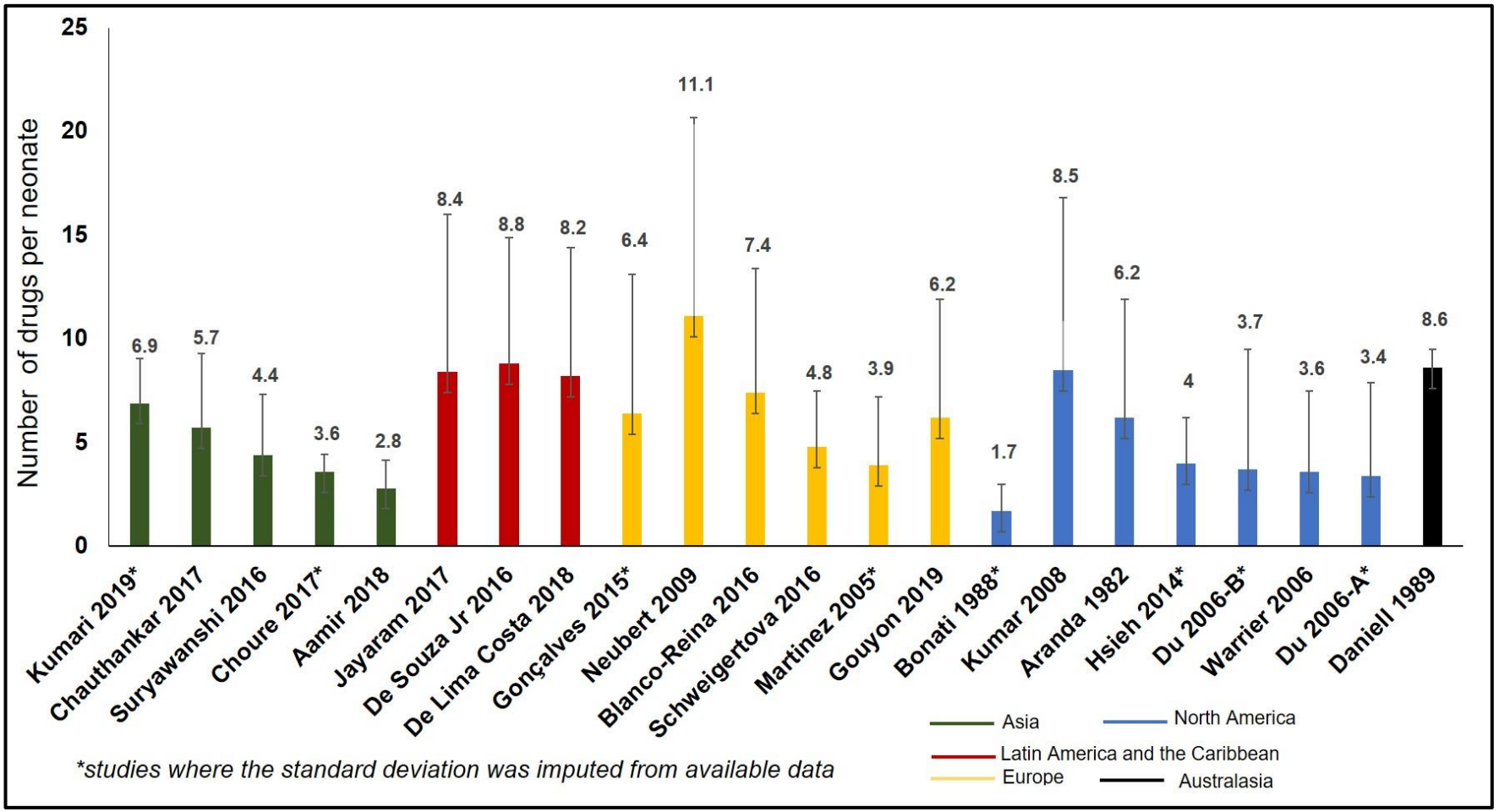


Figure 11. The number of unique drugs prescribed per neonate

2.3.2.1.1 Most frequently prescribed drugs

Among the studies that reported drug use in general, 48 of 60 studies reported the most frequently prescribed drugs. Thirty studies out of the 60 reported the most frequently prescribed pharmacologic groups instead of individual drugs, 20 studies reported most frequently prescribed off-label and/or unlicensed drugs, and eight studies reported most frequently prescribed antibiotics.

All the 48 studies that reported most frequently prescribed drugs have reported at least one antibiotic agent among the ten most frequently prescribed drugs across NICU admissions (Figure 12). Penicillins and gentamicin were among the ten most frequently prescribed drugs in the majority of studies; 41 and 34 studies, respectively. Most studies had either penicillin or gentamicin as the most frequently reported antibiotics in their list except for six studies. Of these, two reported antibiotics (without specifying which antibiotic) (5,78) and the other four had cefotaxime, ceftriaxone, vancomycin, tobramycin, amikacin, cefoperazone-sulbactam and piperacillin-tazobactam amongst their most frequently prescribed drugs (88,104,106,109). Caffeine was among the ten most frequently prescribed drugs cited by 25 studies.

There were 21 studies reporting a drug from other therapeutic class as its most frequently used. These were calcium gluconate (two studies (70,107)), multivitamins (three studies (63,75,96)), vitamin K (seven studies

(4,81,97,101,106,111,121)) caffeine (two studies (80,88)), chlorhexidine powder (one study (89)), theophylline (one study (122)), epinephrine (one study (102)), parenteral nutrition (one study (116)), cholecalciferol (one study (123)), fentanyl (one study (124)) and vitamin D (one study(68)). Of the two studies that reported caffeine as the first most frequently prescribed drug, 86.8% of included neonates in Cuzzolin et al. were preterm (80) while Jong et al. did not report the preterm proportion in their cohort (88).

The following sections detail the most frequently prescribed drugs in each geographic region. The overall summary of the most frequently prescribed drugs per each geographic region is outlined in Table 4.

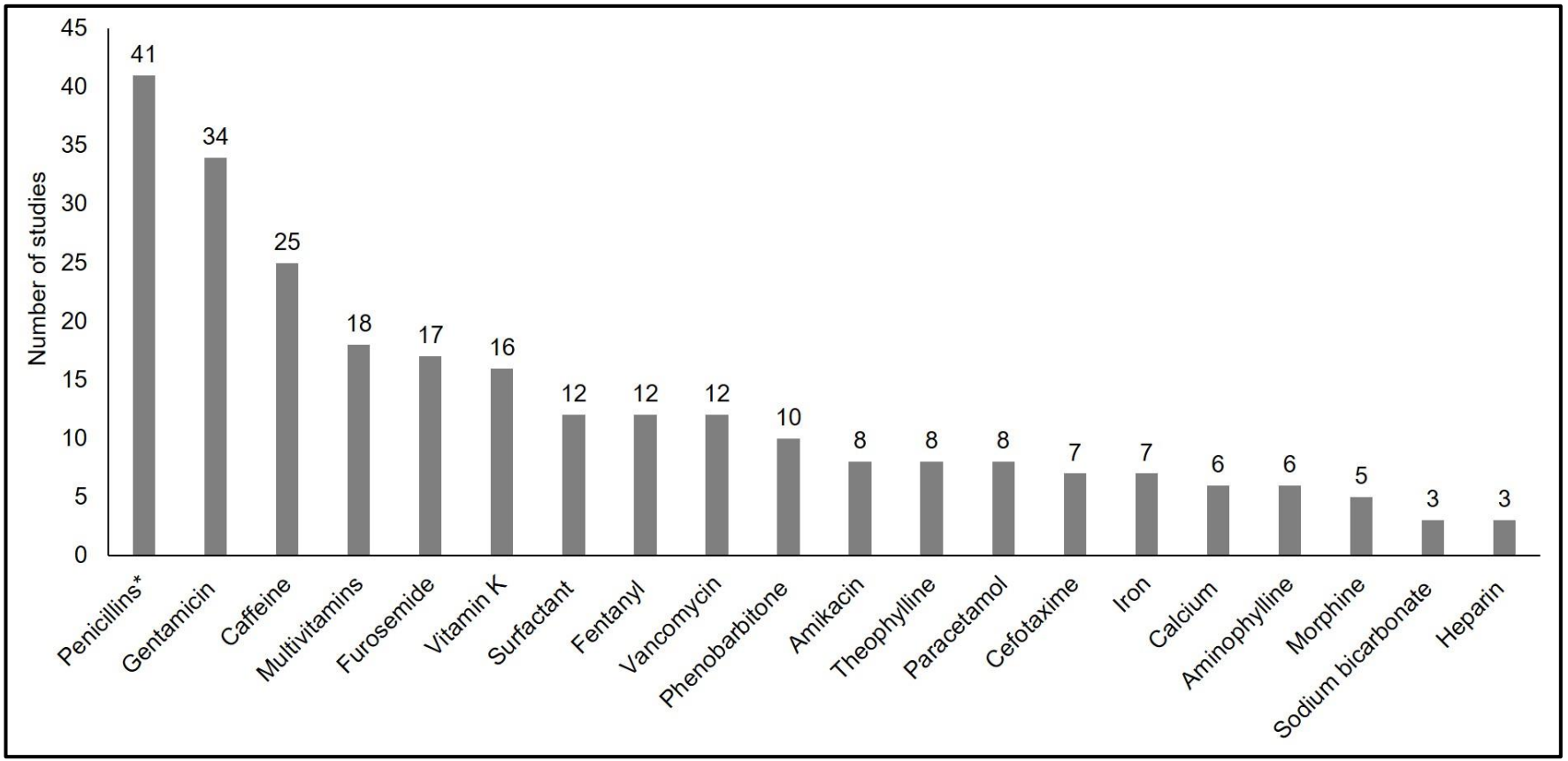


Figure 12. Twenty most frequently prescribed drugs in neonatal units reported by 48 studies (*include:

benzylpenicillin/penicillin/ampicillin/amoxicillin/piperacillin)

Table 4. Overall summary of the most frequently prescribed drugs in each geographic region (48 studies)

Geographic region (number of studies) (ref)	Most frequently prescribed drugs (number of studies citing the drug among the ten most frequently prescribed drugs)
Europe (24 studies) (28,29,63,68,70,74,75,80,83,84,88,89,91,92,95,96,99,101,103,110,111,113,118,122)	Caffeine (18 studies), gentamicin (17 studies), ampicillin (11 studies), furosemide (9 studies), multivitamins (9 studies), vitamin K (11 studies), benzylpenicillin (8 studies), amikacin (6 studies), morphine (5 studies), paracetamol (6 studies)
North America (ten studies) (65,66,71,102,107,109,115,116,119,120)	Ampicillin (8 studies), gentamicin (8 studies), furosemide (6 studies), surfactant (6 studies), penicillin (5 studies), vancomycin (6 studies), caffeine citrate (6 studies), cefotaxime (4 studies), dopamine (5 studies), calcium gluconate (4 studies)
Asia (six studies) (4,5,69,78,104,106)	Phenobarbitone (4 studies), vitamin K (4 studies), amikacin (3 studies), aminophylline (3 studies), ceftriaxone (2 studies), ceftazidime (2 studies), gentamicin (2 studies), phenytoin (2 studies), penicillin/sulbactam (2 studies), caffeine (1 study)
Latin America and Caribbean (four studies) (76,85,108,117)	Fentanyl (4 studies), gentamicin (3 studies), vancomycin (3 studies), multivitamins (3 studies), amikacin (2 studies), ampicillin (2 studies) furosemide (2 studies), aminophylline (2 studies), morphine (1 study), metamizole (1 study)
Middle East (two studies) (73,97)	Gentamicin, ampicillin, amoxicillin and vitamins (reported by both studies)
Australasia (two studies) (81,98)	Vancomycin and gentamicin (reported by both studies)

2.3.2.1.1.1 Frequently prescribed drugs in Europe

Twenty-four studies in Europe have reported the most frequently prescribed drugs in their NICUs, whereas three studies have reported the most frequently prescribed pharmacologic class instead of drugs.

Appendix 9.4 details the ten most frequently prescribed drugs reported by each of those 24 studies. However, some studies have reported less than ten most frequently prescribed drugs; a study by Alonso et al. reported only four frequently prescribed drugs (70).

One study by Girardi et al. compared the frequently prescribed drugs in two different groups of neonates categorised according to their body weights, and therefore it was plotted and reported twice (70). Also, another study by Lass et al. have reported the most frequently prescribed drugs in term and preterm neonates and therefore the results were plotted twice for both groups in this review (92). However, if the same drug was reported in the two groups, it was counted once.

The most frequently prescribed drug in Europe was found to be caffeine or caffeine citrate (18 studies), followed by gentamicin (17 studies) and ampicillin (12 studies).

Two studies were conducted in the UK and both of them reported gentamicin to be the most frequently prescribed drug in neonates followed by benzylpenicillin (28,29).

2.3.2.1.1.2 Frequently prescribed drugs in North America

Ten studies in North America have reported the most frequently prescribed drugs in their NICUs whereas two studies reported the most frequently prescribed pharmacologic class instead of drugs (detailed in 9.5). There were two studies that compared drug use in two different periods and hence the drugs in those studies were counted twice (107,109).

The most frequently reported prescribed drugs in North America were ampicillin and gentamicin, which were reported by nine and eight studies respectively. Aranda et al. (107) reported it in both periods which are included in their study. This was followed by furosemide and surfactants, which were reported by six studies, with also Aranda et al. reporting it twice. A study by Du et al. reported surfactants twice in both periods of the study among the ten most frequently prescribed drugs.

2.3.2.1.1.3 Frequently prescribed drugs in Asia

Six studies from Asia described the most frequently prescribed drugs whereas five studies reported the most frequently prescribed pharmacologic class instead of drugs (detailed in 9.6). Two studies reported antibiotics without specifying the individual drugs as frequently prescribed drugs. These antibiotics are detailed in section 2.3.3.1.3. Phenobarbitone and vitamin K were reported by most of the studies, five and four studies respectively, followed by amikacin, which was reported by three studies.

Choure et al. have reported ‘others’ as most frequently prescribed drugs without any information on what drugs were included in this category (78) .

2.3.2.1.1.4 Frequently prescribed drugs in Latin America and Caribbean

Four studies from this region reported the most frequently prescribed drugs whereas two studies reported the most frequently prescribed pharmacologic class instead of drugs (detailed in 9.7). Marino et al. compared the drug use in four different groups of neonates characterised according to their BW (117). Fentanyl was the most frequently prescribed drug in Latin America and the Caribbean as reported by all of the studies. This was followed by gentamicin, vancomycin, and multivitamins, which were reported by three studies as amongst the ten most frequently prescribed drugs.

2.3.2.1.1.5 Frequently prescribed drugs in the Middle East

Only two out of the 56 studies were conducted in the Middle East (both in Israel) and they reported the most frequently prescribed drugs in their NICUs (73,97). Gentamicin, ampicillin, amoxicillin and vitamins were among the ten most frequently prescribed drugs reported by both studies.

2.3.2.1.1.6 Frequently prescribed drugs in Australasia

Only two studies were conducted in this continent that reported the most frequently prescribed drugs (80,98). Vancomycin and gentamicin were among the most frequently prescribed drugs in both studies.

2.3.2.1.2 Most frequently prescribed pharmacologic groups

As described earlier, 30 studies out of the 60 included studies reported the frequently prescribed pharmacologic groups in their NICUs using different methods in their classification. Most used the World Health Organisation-Anatomical Therapeutic Chemical (WHO-ATC) classification system (19 of 30 studies, 63%). Four studies listed the pharmacologic class of the drugs. One study by Kumar et al. has classified the pharmacologic groups based on the most frequent indication and the physiologic effects of the drug (115). The remaining six studies have not stated their classification method.

Among the studies that used the WHO-ATC system, anti-microbials for systemic use were the most frequently prescribed pharmacologic group in the majority (14 studies, 81%), followed by agents for gastro-intestinal (GI) and metabolism (four studies), and agents for the central nervous system (one study). Among the four studies that listed the pharmacological groups according to their pharmacologic class, three studies reported that antimicrobials were the most frequently prescribed group and one study by Ashwin et al. identified that penicillins were the most frequently prescribed pharmacologic group. A study by Kumar et al. reported that the GI agents were the most frequently prescribed pharmacologic group (115).

2.3.3 Drug utilisation studies investigating antibiotics only

Characteristics of the studies: 11 studies aimed to evaluate antibiotic use only in their neonatal units (64,125–134). The studies varied in their design between prospective (seven studies) (125,126,128,130,131,133,134), retrospective (two studies) (64,129), and two studies used both prospective and retrospective study design (127,132). Enrolled neonates ranged between 84 to 5,619. The inclusion and exclusion criteria of those studies are detailed in 9.8.

2.3.3.1 Most frequently prescribed antibiotics

Seven of the 11 studies reported on the most frequently prescribed antibiotics. In addition, several antibiotics appeared in the list of the most frequently prescribed drugs that did not focus on antibiotics only. In total, 59 studies reported the most frequently prescribed antibiotics used in their NICUs and their data are presented per each continent.

2.3.3.1.1 Most frequently prescribed antibiotics in Europe

Twenty-three studies in Europe have cited antibiotics among their most frequently prescribed drugs. Each study reported more than one antibiotic, and hence they are all counted accordingly. The most frequently prescribed antibiotics in Europe are gentamicin (17 studies) followed by ampicillin (12 studies) (Figure 13).

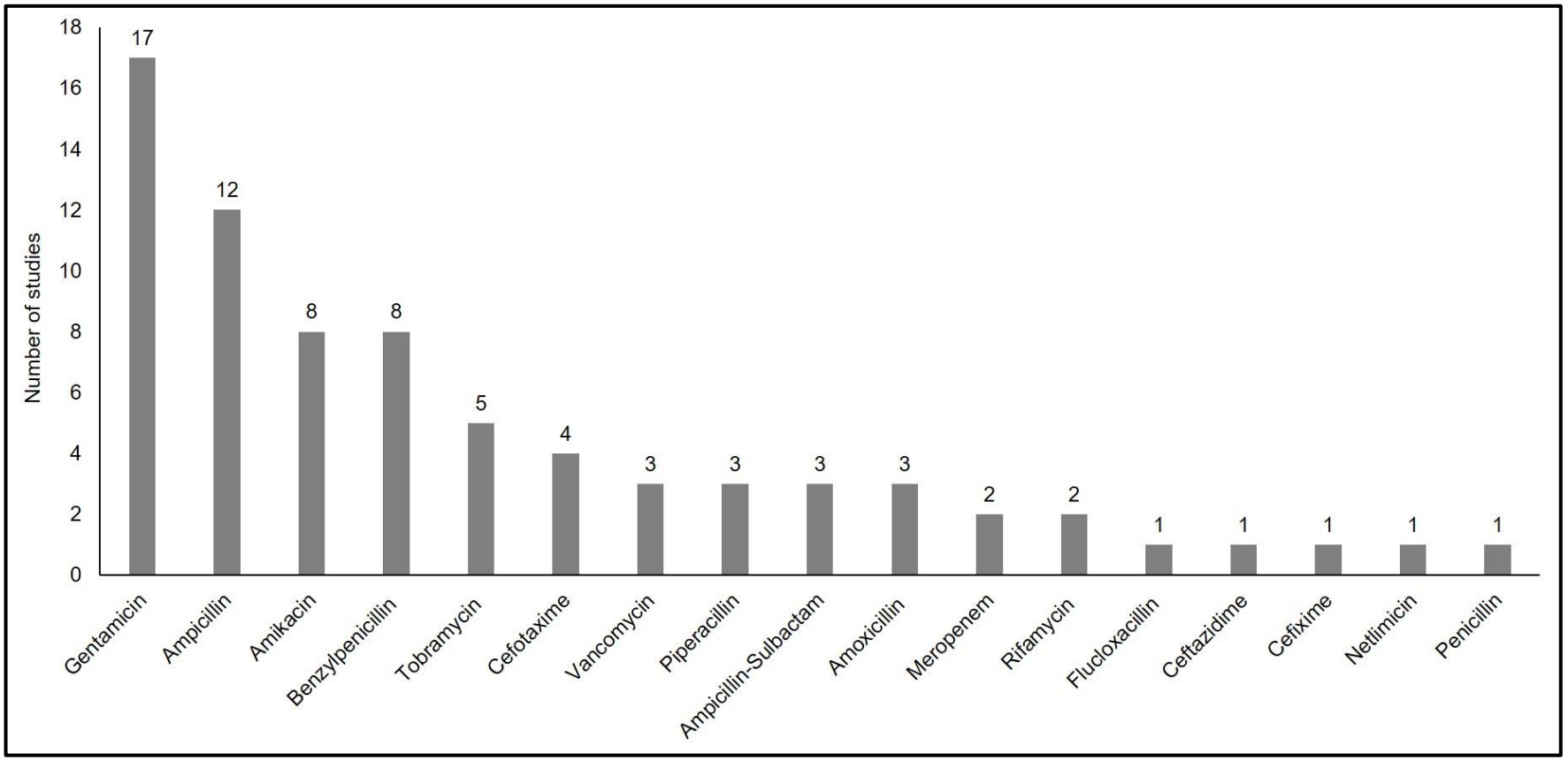


Figure 13. Most frequently prescribed antibiotics in Europe (cited as one of the 10 most frequently prescribed drug in those studies)

2.3.3.1.2 Most frequently prescribed antibiotics in North America

Twelve studies in North America reported the most frequently prescribed antibiotics in their settings. Two studies by Aranda et al. and Du et al. have investigated drug use pattern in two different periods and reported the same antibiotics in both periods (Figure 14).

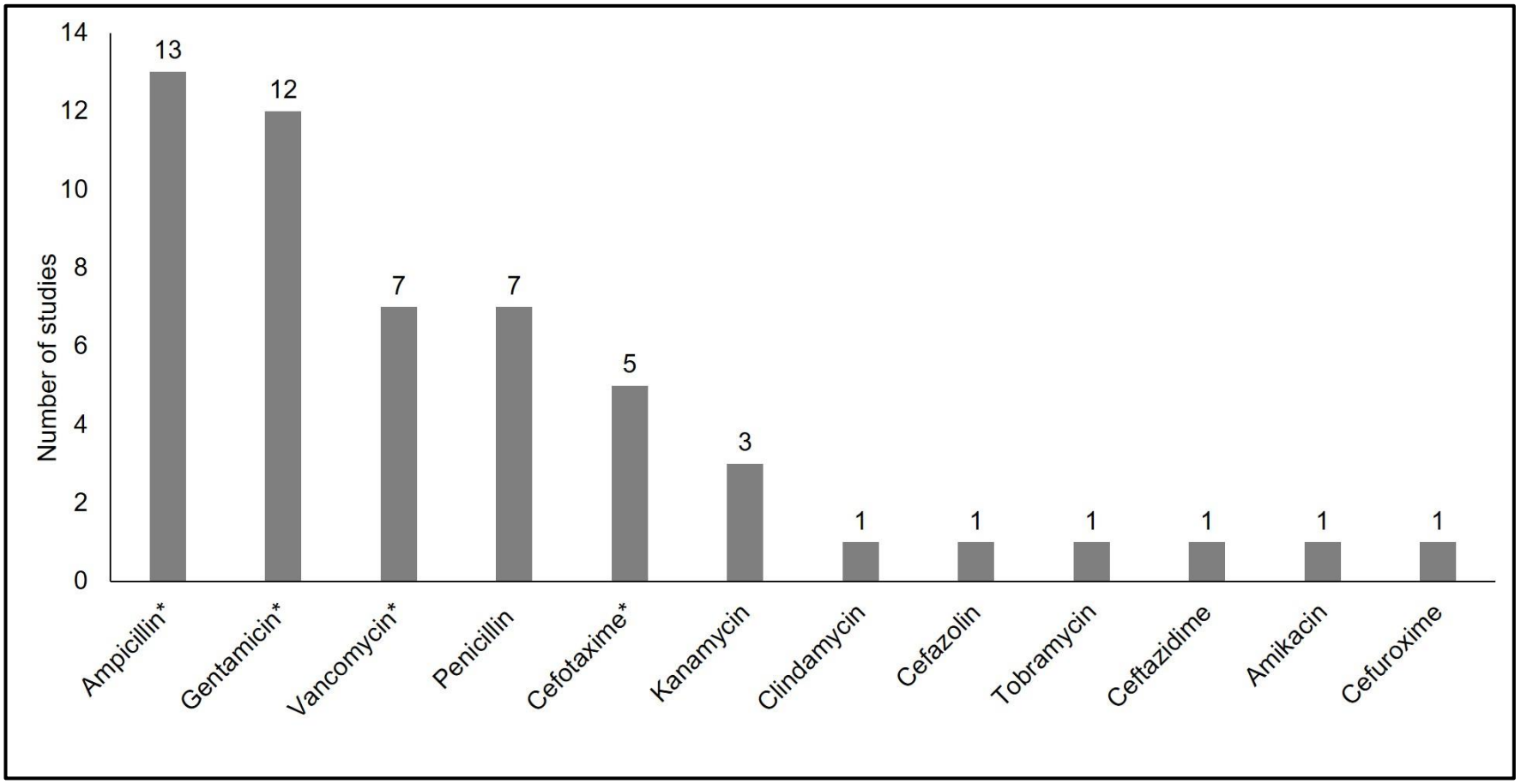


Figure 14. Most frequently prescribed antibiotics in North America (cited as one of the 10 most frequently prescribed drug in those studies; *cited twice by the same study in two different periods)

2.3.3.1.3 Most frequently prescribed antibiotics in Asia

Eleven studies in Asia reported the most frequently prescribed antibiotics. One study out of those 11 have reported the most frequently prescribed antibiotics in the participating units by their broad pharmacological groups instead of individual names of the antibiotics. This study was conducted in two units at two different hospitals and reported that aminoglycosides were among the most frequently prescribed antibiotics in both units (130). Amikacin was reported by most of the studies (nine studies) followed by cefotaxime (eight studies) and gentamicin (six studies) (Figure 15). The single study from China (106) reported the use of cefoperazone-sulbactam, and piperacillin-tazobactam as the most frequently used for all gestational age groups.

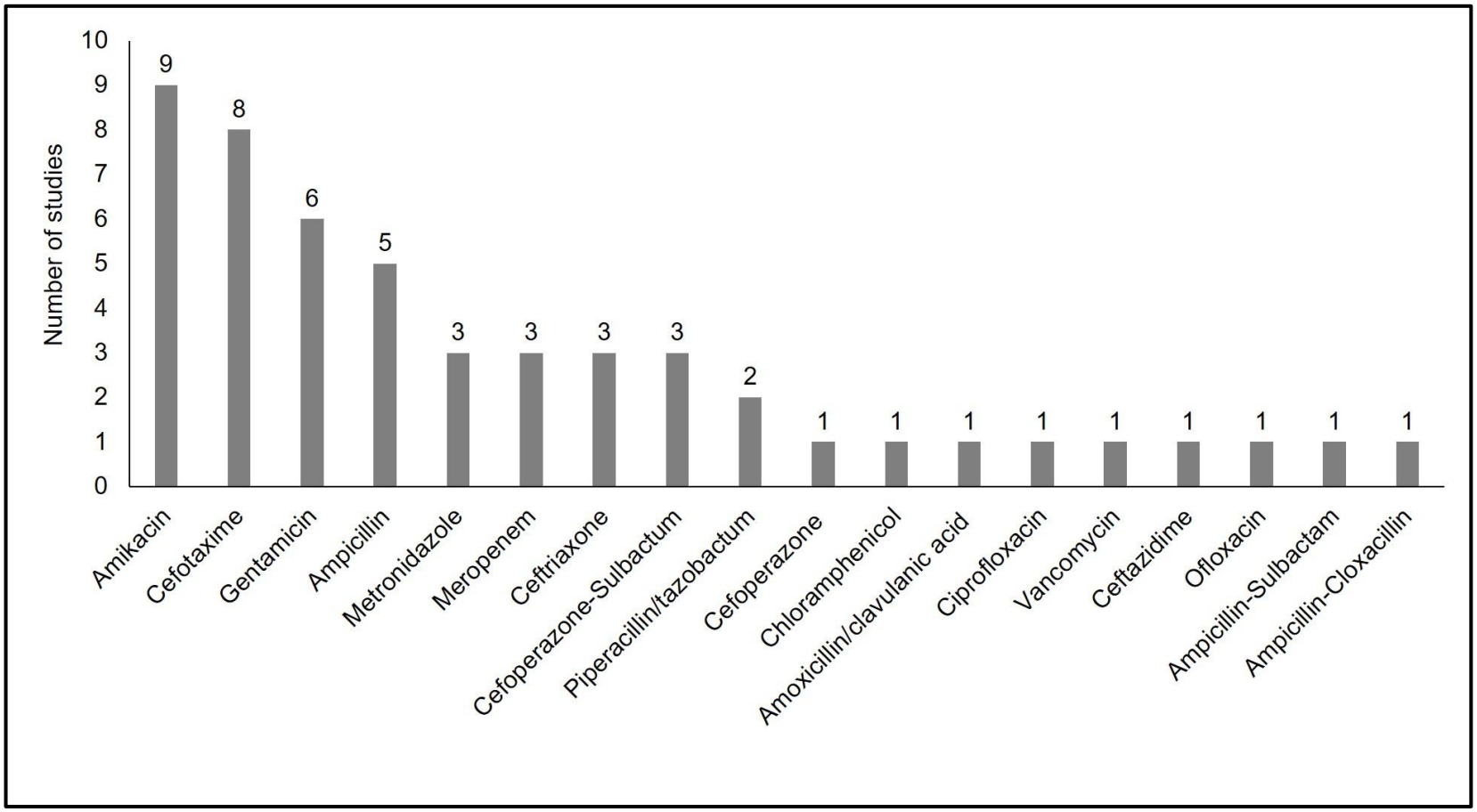


Figure 15. Most frequently prescribed antibiotics in Asia (cited as one of the 10 most frequently prescribed drug in those studies)

2.3.3.1.4 Most frequently prescribed antibiotics in Latin America and Caribbean

Seven studies in this continent reported the most frequently prescribed antibiotics. The data from the study conducted by Marino et al. is counted once in this review if the same drug was reported more than once. The most frequently prescribed antibiotics were gentamicin, ampicillin and vancomycin (all reported by four studies) (Figure 16).

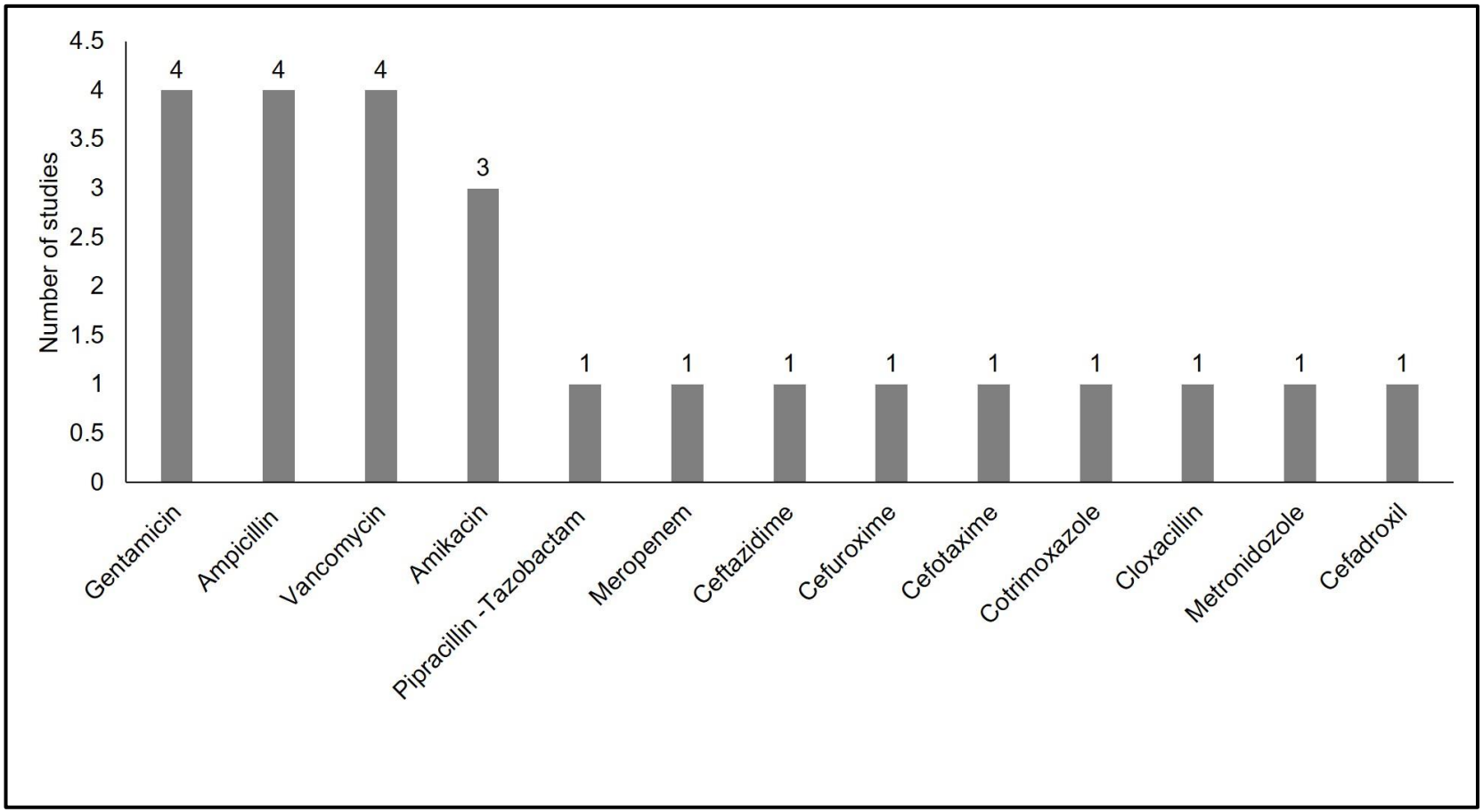


Figure 16. Most frequently prescribed antibiotics in Latin America and Caribbean (cited as one of the 10 most frequently prescribed drug in those studies)

2.3.3.1.5 Most frequently prescribed antibiotics in other regions

The Middle East: Two studies conducted in Israel reported antibiotics among their frequently prescribed drugs in their NICUs (73,97). Both studies cited gentamicin, ampicillin, and amoxicillin among the ten frequently prescribed drugs. The recent study by Nir-Neuman et al. (97) has reported meropenem in addition to the previously mentioned antibiotics.

Australasia: Two studies in Australasia reported the most frequently prescribed antibiotics and have included gentamicin, vancomycin, ampicillin and benzylpenicillin in both lists (80,98).

Africa: One study in Zimbabwe by Chimhini et al. reported gentamicin, amoxicillin and ceftriaxone as the top three most frequently prescribed antibiotics (132).

2.3.4 Drug utilisation studies investigating off-label and or unlicensed drugs only

Characteristics of the studies: Six studies aimed to evaluate only off-label and/or unlicensed drugs use across NICUs (135–140) (detailed in 9.9). Three studies were retrospective (136,138,139), and three were prospective (135,137,140). Number of included neonates ranged from 38 to 910. The percentage of preterm neonates was 53.9% in one study by Kouti et al. (136), whereas three studies reported more term neonates in the included population (137,139,140). The remaining two studies have not stated the percentage of neonatal prematurity in their included population (135,138).

Most frequently prescribed off-label and /or unlicensed drugs: 20 studies that assessed drug utilisation, in general, have reported also most frequently prescribed off-label and/or unlicensed drugs. In total, the number of studies reporting most frequently prescribed off-label and or unlicensed drugs in this review is 26 studies. The studies varied between listing most frequently prescribed off label drugs only or most frequently prescribed both off-label and unlicensed (Table 5). Most of the studies (17 studies, 65%) have listed both the most frequently prescribed off label and/or unlicensed drugs.

Table 5. Studies reporting the most frequent unlicensed and/or off-label drugs

Category	Studies		
	n	%	References
Frequently prescribed off-label drugs only	9	35	(69,77,80,87,111,135,135,137,138)
Both frequently prescribed off-label and or unlicensed drugs	17	65	(29,70,82,83,87–89,91,92,96–98,101,103,136,139,140)

Some studies have not distinguished whether the most frequently prescribed drugs were off-label or unlicensed. Therefore, the results presented here are extracted from studies that clearly reported the most frequently prescribed off-label or unlicensed drugs. Table 6 and Table 7 summarise the most frequently prescribed off-label and unlicensed drugs, respectively.

Table 6. Five most frequently prescribed off-label drugs (15 studies)

Study ID	Country	Reference in classification	Five most frequently prescribed off-label drugs
Aamir 2018 (69)	Pakistan	Not stated	Ampicillin, cefotaxime, phenobarbitone, ceftazidime, amikacin
Chauthankar 2017 (77)	India	British National Formulary for Children (2011-2012) and Neofax (2011)	Antibiotics (meropenem), NSAIDs (paracetamol and ibuprofen), corticosteroids (hydrocortisone)
Jain 2014 (listed pharmacologic groups) (135)	India	British National Formulary of drugs, 2005 version and Neofax 2008 (for doses)	Anti-infectives, anti-convulsants, circulatory agents, pulmonology agents, gastro-intestinal agents
Jayaram 2017 (used WHO-ATC) (87)	India	National Formulary of India (4th edition, 2011)	Anti-infectives, agents for respiratory, agents for central nervous system, alimentary agents and metabolism, cardiovascular agents
Mazhar 2018 (used WHO-ATC) (137)	Saudi Arabia	Saudi FDA approval for use in neonates by using the product monograph	Anti-infectives, alimentary agents and metabolism, agents for the central nervous system, cardiovascular agents
Nir-Neuman 2018 (97)	Israel	Drug summary brochure	Ampicillin, gentamicin, aminophylline, phytomenadione, glycerin

Doherty 2010 (138)	Canada	Health Canada-approved product monographs in the CPS in a Canadian pediatric hospital	Gentamicin, fentanyl, acetaminophen, vancomycin, enoxaparin
Kumar 2008 (115)	USA	FDA (for parenteral medication)	Fentanyl, erythropoietin, dopamine, midazolam, hydrocortisone
Alonso 2019 (70)	Spain	SPC approved by Spanish and European Medicine Agency	Fentanyl, vitamin E, cefazoline, ranitidine, paracetamol
Casan 2017 (139)	Spain	SPC approved by Spanish and European Medicine Agency	Ampicillin, gentamicin, paracetamol, cholecalciferol, amikacin
Cuzzolin 2016 (80)	Italy	Not stated	Ampicillin, fluconazole, gentamicin, fentanyl, ampicillin-salubactam
Flint 2018 (111)	The Netherlands	SPC	Heparin, fentanyl, propofol, dopamine, phenobarbital
Riou 2015 (101)	France	SPC of French formulary (Theriaque 2013)	Calcium folinate, amikacin sulphate, ferrous fumarate, rifamycin, sodium chloride
De Lima Costa 2018 (82)	Brazil	FDA criteria https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm	Fentanyl, gentamicin, aminophylline, furosemide, meropenem
Gidey 2020 (140)	Ethiopia	European Medicine Agency electronic medicine compendium	Antibiotics (ampicillin, vancomycin), NSAIDs, medicines for seziure

CPS, Canadian Compendium of Pharmaceuticals and Specialties; FDA, Food and drug administration; SPC, Summary of product characteristics

Table 7. Five most frequently prescribed unlicensed drugs (six studies)

Study ID	Country	Reference in classification	Five most frequently prescribed unlicensed drugs
Alonso 2019 (70)	Spain	SPC approved by Spanish and European Medicine Agency	Caffeine, spironolactone, phosphate, ranitidine, morphine
Casan 2017 (139)	Spain	SPC approved by Spanish and European Medicine Agency	Caffeine citrate, hydrocortisone, morphine, phenobarbital, Flecainide
Riou 2015 (101)	France	SPC of French formulary (Theriaque, 2013)	Glucose monohydrate, norepinephrine, ketamine hydrochloride, glucose phosphate, phenobarbital
De lima costa 2018 (82)	Brazil	FDA criteria https://www.accessdata.fda.gov/scripts/cder/daf/ index.cfm	Caffeine, phenobarbital, furosemide,
Nir-Neuman 2018 (97)	Israel	Drug's information leaflet approved in the Ministry of Health's drug registry	Vitamin A, furosemide, sodium chloride, phenobarbital, naloxone
Gidey 2020 (140)	Ethiopia	European Medicine Agency electronic medicine compendium	Paracetamol, phenobarbital, aminophylline

FDA, Food and drug administration; SPC, Summary of product characteristics

2.3.5 Drug utilisation investigating specific pharmacologic groups

2.3.5.1 Characteristics of the studies

Seven studies evaluated drug use on specific pharmacological groups (detailed in 9.10). Three studies evaluated the use of sedatives, analgesics and narcotics in their NICUs (67,141,142). One prospective study evaluated the use of anti-epileptics (143), and one study (published as a conference abstract) evaluated the use of cardiovascular agents (144). One study have evaluated the drugs used in neonates diagnosed with Bronchopulmonary dysplasia (BPD) (145). One study have evaluated the use of only IV drugs in neonates (146).

2.3.5.2 Analgesics and sedatives

Three studies investigated the use of analgesics and sedatives in the neonatal population and reported that fentanyl, morphine, midazolam and paracetamol were among the five most frequently prescribed analgesics and sedatives (67,141,142).

2.3.5.3 Anti-convulsants

A study by Ahmad et al. evaluated the changing pattern of anti-convulsants over time, from 2005 to 2014, in 341 NICUs (9,134 neonates) in the USA (143). This retrospective study found that phenobarbital was the most frequently prescribed drug from 2005 to 2014 (96.3% - 99.4%). This was followed by phenytoin (11.6% - 13.8 %) from 2005 to 2012, and levetiracetam (14.3%) was prescribed more than phenytoin (11%) from 2013 to 2014.

2.3.5.4 Cardiovascular agents

A study by Hallik et al. evaluated the use of cardiovascular agents across 89 different European NICUs and reported that inotropes (dopamine followed by dobutamine and adrenaline), diuretics and indomethacin/ibuprofen were the most frequently prescribed cardiovascular agents (144).

2.3.5.5 Drugs used in Bronchopulmonary dysplasia (BPD)

A retrospective study by Bamat et al. that involved multicentre (43 NICUs, 3252 neonates) in the United States aimed to explore the most frequently used drugs among neonates with symptomatic BPD. This study reported sodium chloride followed by furosemide and potassium chloride as the top three drugs used in BPD (145).

2.3.5.6 Intravenous drugs

A prospective survey by De Basagoiti et al. conducted over one month in nine Spanish NICUs with an aim of exploring the most frequently prescribed IV drugs (146). This study reported the most frequently used IV drugs by their pharmacological class and found that anti-infectives followed by cardiovascular drugs and drugs used in central nervous system were the most frequently prescribed IV drugs.

2.3.5.7 Drug utilisation in high- and middle-income regions

This section compares the use of analgesics, anti-convulsants, and surfactants use between high- and middle-income regions.

Use of analgesia: 27 studies in this review cited one or more analgesics among the ten most frequently prescribed drugs in their NICUs (Figure 17) (29,66–69,74,76,78,80,89,98,101,102,108–111,113,115,117,118,120,124,141,142,147,148). In high income regions (Europe, North America, Middle east, Australasia), the most frequently prescribed analgesic was fentanyl, followed by morphine and paracetamol. In middle income regions (Asia, Latin America), the most frequently prescribed drug was fentanyl, followed by paracetamol.

Use of anti-epileptics: 11 studies (4,5,69,76,78,104,108,117,124) reported the use of one or more anti-epileptic agents among the ten most frequently prescribed drugs in their NICUs (Figure 18). In both high- and middle-income regions, phenobarbital was the most frequently prescribed anti-convulsant.

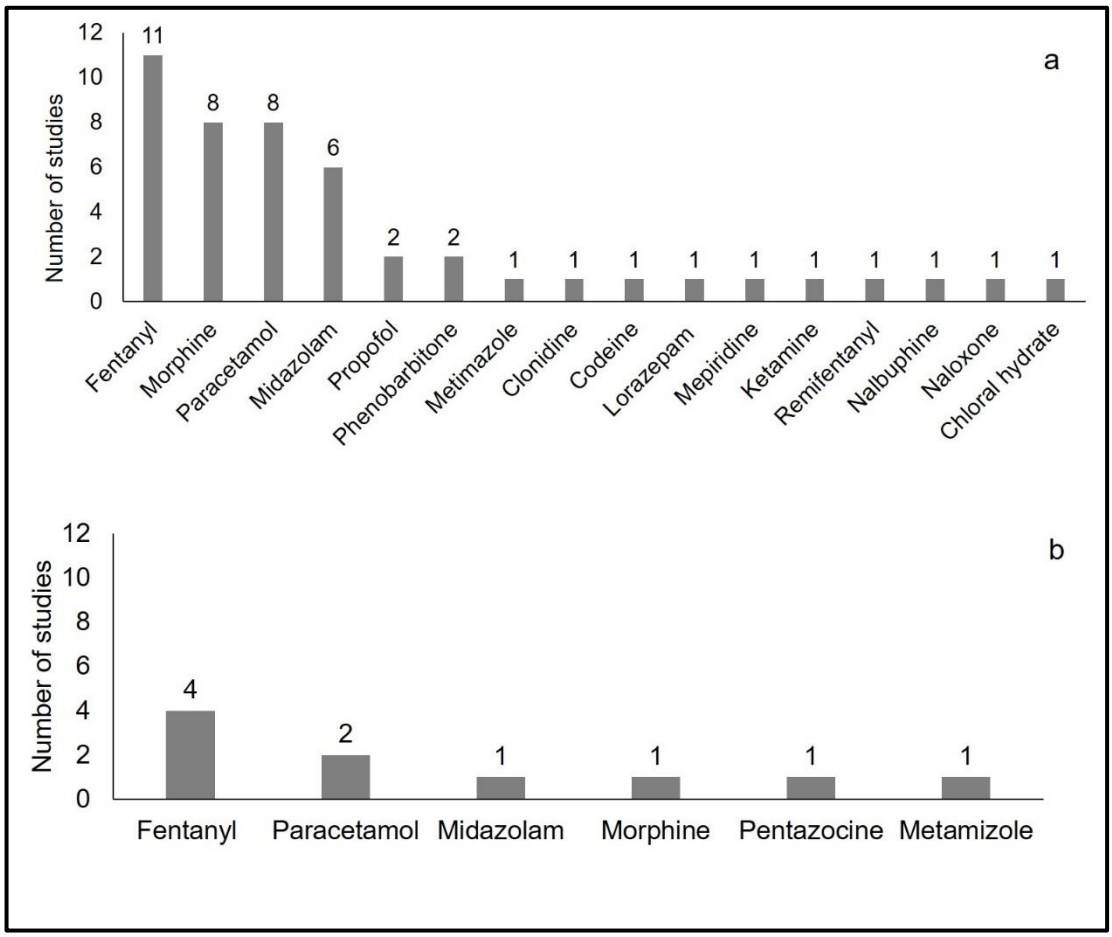


Figure 17. Most frequently prescribed analgesics in a. high income regions b. middle income regions (cited as one of the 10 most frequently prescribed drug in those studies)

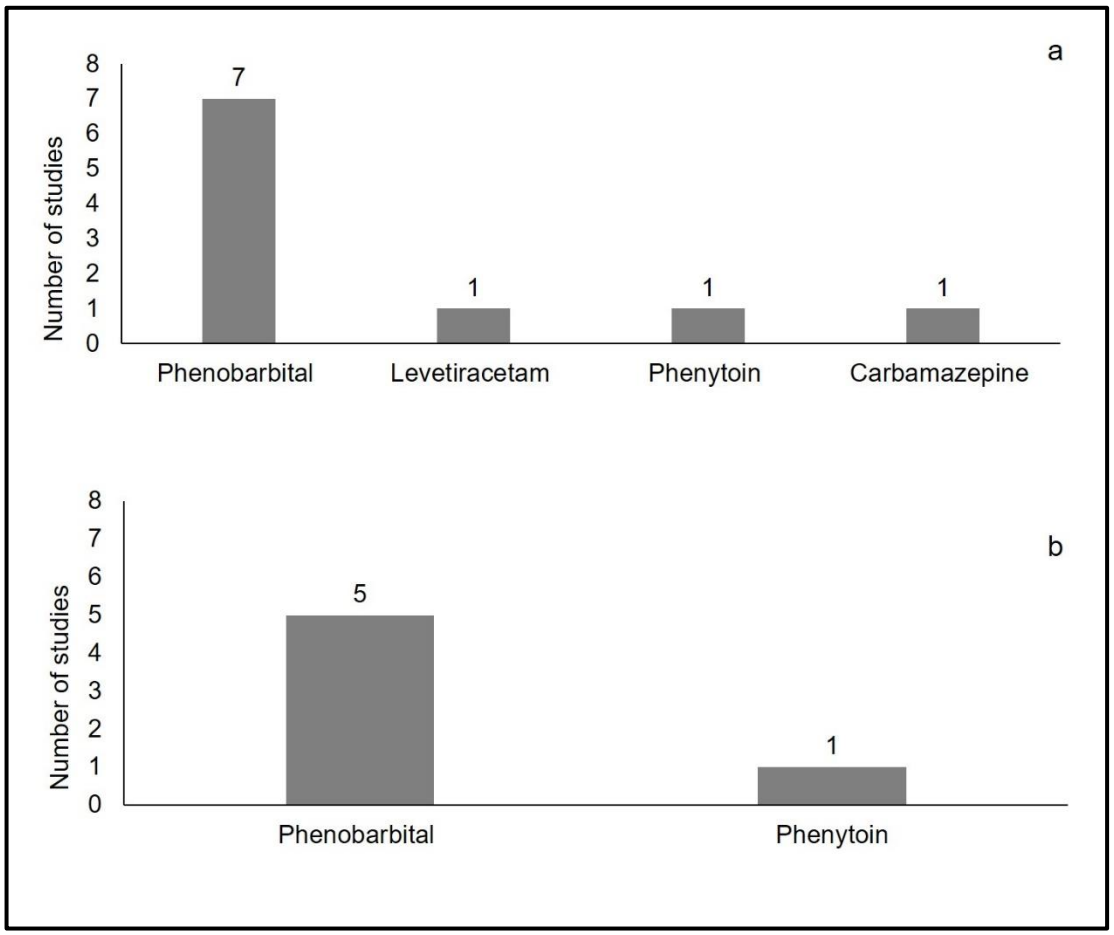


Figure 18. Most frequently prescribed anti-convulsants in a. high income regions b. middle income region (cited as one of the 10 most frequently prescribed drug in those studies)

Use of surfactants: 12 studies (65,66,91,93,95,109–111,113,113,119,120) in high income regions reported different types of surfactants among the ten most frequently prescribed drugs in their NICUs (Figure 19). However, only one study, Marino et al. (117), conducted in Brazil reported pulmonary surfactants as one of their ten most frequently prescribed drugs. This study has reported pulmonary surfactants in four different groups of neonates divided according to their BW and surfactants were reported as the most frequently prescribed drugs in neonates with BW < 2500 g.

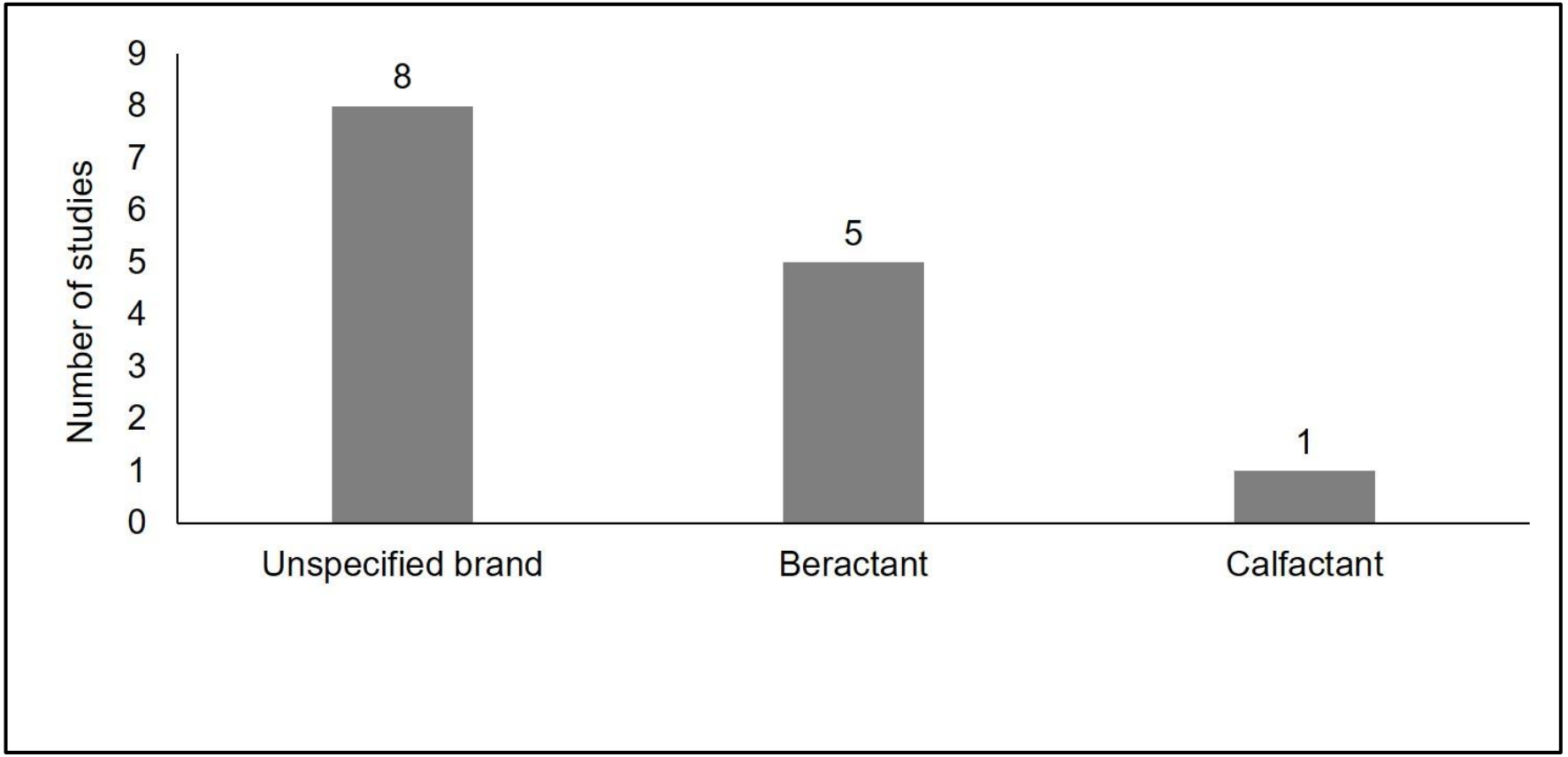


Figure 19. Use of surfactants in high income region (cited as one of the 10 most frequently prescribed drug in those studies)

2.4 Discussion and conclusion

To date, this is the most comprehensive review of the literature that provides widespread and updated information on the most frequently prescribed drugs across various NICUs worldwide, with a comparison between different geographic regions.

2.4.1 Comparison with other reviews

This review has added 35 studies to the previous systematic reviews and their dates of publication ranged from 1983 to the most recent study in 2020.

Availability of resources is a major determinant in provision of neonatal care. This is evident in the wide disparities in survival of neonates, especially preterm neonates between different regions of the world. The United Nations Inter-agency Group for Child Mortality Estimation reported that in 2017 the annual neonatal mortality rate (NMR) was highest in west and central Africa, at 30.2 deaths per 1000 livebirths and in south Asia (which included India) at 26.9 per 1000 livebirths and lowest in the high-income countries, 3.0 per 1000 livebirths. Together, south Asia and sub-Saharan Africa accounted for 79% of the total burden of neonatal deaths (149). With such disparities, it is important to study the differences in all aspects of care between different regions of the world. In this review I have investigated any reported differences in drug utilisation patterns.

When looking at drug utilisation studies globally, this review has captured studies from most parts of the world with India, which has the highest number of preterm births, contributing the largest number of the studies followed by

the USA. There have been WHO-led concern that the WHO South-East Asia region, which includes India, is likely to be the most at risk part of the world for the emergence of resistant to microorganisms (150).

In terms of the methodologies of the included studies, they remained limited due to lack of information to assess the rational use of drugs such as dose, indication or duration of use. Most studies were restricted to a single centre and included a limited sample size. However, larger studies such as those from the Paediatrix Medical group in the USA (65,66) are powered by their electronic patient records. Such records may enable further large-scale evaluations of drug utilization; however, this requires efforts to improve electronic patients records to appropriately assess the rational prescribing in neonatal medicine. Such improvement should be directed towards use of standardized nomenclature and categorization of drugs, collection of data on indications, dosage, adverse effects and medication errors.

2.4.2 Drug use in general

Half of the studies (27 studies) that investigated drug use in general were conducted in 11 European countries. In addition to those 11 European countries, a collaborative study presented in this review was performed which involved several European countries (21 participated) (63).

None of the previous systematic reviews have summarised the sample size, the duration of studies, or proportion of premature neonates in the included cohorts. In this current review, the median (range, IQR) sample size of neonates in 77 studies that reported the sample size was 220 (34-450386, 113-1491). This huge variation can be attributed to the study designs

(prospective vs. retrospective) and the study duration, which can affect the number of neonates enrolled. There were 17 single centre studies (out of 84 studies) with less than one hundred neonates included that may limit a firm conclusion with regard to the drug utilisation in such settings. The larger studies that included many thousands of neonates were enabled by retrospective analyses of routinely collected clinical data from large healthcare providers in the United States (65). In the UK, a critical review by Foster and Young assessed the usefulness of secondary data (i.e. routinely collected patient data and stored electronically) for research purposes on a neonatal level (151). This critical review highlighted the possibility at present of using secondary data for research purposes in the UK due to the existence of the National Health Service (NHS), which holds thousands of electronic neonatal records collected over a long period of time. Black et al. pointed out the usefulness of such data in several research areas such as identifying the development and causes of certain diseases, assessment of the healthcare interventions, and trends in the use of healthcare. The benefit of such data can be manifested in service planning and operational management of a healthcare system as added by Higgins et al. However, one should take into account several issues concerning parents' consent, use of patient-identifiable data, and the accuracy and security of electronic records when using such data in research (151).

The population included in the studies within this review are quite heterogeneous. Most studies include all neonatal unit admissions with varied proportion of preterm neonates. More than half of the studies reported the percentage of included neonates who were born prematurely (34 studies).

Twenty-one out of those studies (64%) reported that more than half of the participants were preterm, with a range of 52%-87% of NICUs admissions included in the study. One would expect a higher number of drugs used in preterm neonates as reported by individual studies (77,82,87,115,121,124). The studies; however, did not directly report the number of drugs per patient for term vs. preterm neonates.

The pooled mean (SD) of the number of drugs per neonate from 29 studies was 4 (2.4) unique drugs per patient. The highest mean was reported by Neubert et al. as 11.1 unique drugs per patient (95). As discussed by the authors, the inclusion of high proportion of preterm and very preterm neonates (69%) and the specialisation of the neonatal unit may have contributed to the high number of drugs prescribed per neonates when compared to other studies. Another possible explanation for this may be the greater availability of medicines in the healthcare setting of this study, as it was conducted in a high-income country. Also, the inclusion of drugs given routinely in the delivery room prior to neonates being transferred to the unit were collected retrospectively and that could increase the number of drugs prescribed. Unlike some studies which have excluded the routinely used drugs at the delivery room (108,109,119), Neubert et al. retrospectively collected this data and included it in their analysis.

2.4.3 Frequently prescribed drugs

Overall, penicillins and gentamicin were among the ten most frequently cited drugs in the majority of the studies. These results support the data from previous systematic reviews (9,10). This was not unexpected as most

neonates admitted for intensive care are treated for presumed infections, and often penicillins and aminoglycosides are the first line antibiotics used.

In most regions, ampicillin and gentamicin were among the ten most frequently prescribed drugs in their neonatal units. There is an exception; in Asia, amikacin and cefotaxime were among the ten most frequently prescribed drugs in their neonatal units. Few studies reported drugs other than an antibiotic as the one in most common usage e.g. caffeine featured at the top of the list in two studies. This can be attributed to the high proportion of preterm neonates in the study; however, this was confirmed by only one study captured in this review (80) where 87% of included neonates were born preterm. Variations in which drugs were excluded from analysis in each study accounts for some other drugs which were not antibiotics appearing as the most frequently prescribed, such as parenteral nutrition, vitamin K and multivitamins which, due to their ubiquitous use, were excluded from most studies.

The current review found limited studies conducted in the Middle East region that cited most frequently prescribed drugs in their neonatal units with only two studies were found, both in Israel (73,97). Both studies were also prospective and reported that gentamicin and ampicillin were among the five most frequently prescribed drugs in their centres. The limited data on drug use is a matter of concern, especially in a vulnerable population such as neonates. The need to investigate the drug use pattern in such regions is important to explore where the main misuse, if any, of drugs exists. Also, it

will identify existing gaps and whether adherence to guidelines is implemented.

Surfactants are recommended by the WHO for ventilated and intubated neonates with respiratory distress syndrome (152). However, in the low- and middle-income regions, lack of human or material resources may hinder the use of those agents compared to countries in high income regions. This is supported by this review as seven studies in high income regions cited surfactants as one of the ten most frequently prescribed drugs, whereas only one study conducted in a middle-income region cited the use of surfactants as frequently prescribed drugs.

2.4.4 Antibiotic use

This review has reported the most frequently prescribed antibiotics in 59 studies that ranked the use of antibiotics in their NICUs. Overall, the use of antibiotics was similar in Europe, North America and Latin America, with ampicillin and gentamicin to be among the most frequently prescribed antibiotics. This finding broadly supports the work of a previous systematic review by Rosli et al. that concluded ampicillins and aminoglycosides were the commonest antibiotic groups reported by the included studies (10). This is again is not an unexpected finding as the burden of infections remains high; neonatal sepsis or meningitis accounted for 6.8% neonatal death globally in 2015 (153). High risk of death and poor outcomes in survivors warrants the reliance on empirical antibiotic usage based on the sensitive but nonspecific clinical diagnosis of possible infections, particularly in preterm neonates, and the antibiotics given to clinically well neonates born with risk-

factors for early-onset sepsis. Unfortunately, the selective pressure exerted by this widespread use is driving antimicrobial antibiotic resistance. The wide use of antibiotics in the neonatal population is mainly to manage neonatal sepsis as either a prophylactic or treatment measure. However, an observed difference between these findings and Asia was found in this review. Many neonates in hospitals in south Asia are now treated with carbapenems as a first-line therapy for sepsis or presumed sepsis (154). This was reflected in this review, with the more frequent appearance of antibiotics such as third generation cephalosporins (cefotaxime, ceftriaxone) and meropenem, and tazobactam in studies from Asia and Latin America. Cefotaxime was cited as the most frequently prescribed antibiotic instead of penicillins in studies conducted in Asia, followed by amikacin. Cefotaxime can also be used in the management of neonatal sepsis due to its broad-spectrum cover for both gram positive and negative organisms. Cephalosporins are mainly eliminated via the kidneys with their clearance and half-life being dependent on neonates' development. The half-life of cefotaxime and ceftazidime decreases with the increase in gestational and postnatal age with an opposite trend of the clearance of those agents (155). This warrants careful monitoring when it comes to deciding the dosage regimen for neonates. Data from South Asia reflect a high burden on neonatal sepsis and a distinct pathogen profile with predominance of Gram-negative organisms and lower prevalence of group B streptococci as compared to high income countries (156). In this review of neonatal sepsis in South Asia, Chaurasia et al. reported that 50–88% of common isolates from health facilities are resistant

to first-line antibiotics ampicillin and gentamicin and often to third-generation cephalosporins such as cefotaxime.

One unanticipated finding was that ceftriaxone appeared among the ten most frequently cited drugs in three studies in Asia (69,104,134). Ceftriaxone was also cited among the ten most frequently prescribed antibiotics in an African NICU in Zimbabwe (132). Ceftriaxone has been associated with several concerns about its safety use in neonates. This antibiotic is highly protein bound with an ability of displacing bilirubin from its albumin binding sites, resulting in accumulation of bilirubin in brain tissues, and consequently kernicterus in neonates (155). Furthermore, the FDA has issued a warning in 2007 restricting its use in neonates, especially when used concomitantly with calcium-containing IV products (157). This is because this combination has been associated with life threatening cardiopulmonary adverse drug reactions due to the precipitation of calcium salts in the lungs and kidney (158).

Another interesting finding seen in antibiotics use in Asia is the combination of cefoperazone-sulbactum, which was cited by two studies in India among their most frequently prescribed antibiotics (5,134) and in one recent study in China (106). This antibiotic is a combination of B-lactam antibiotic and b-lactamase inhibitor and it is used for nosocomial sepsis caused by multi-drug resistant pathogens in NICUs (159). This combination is not routinely used in the neonatal population due to the limited data on its use in neonates. A study by Ovali et al. was the first study to show the effectiveness of this combination to be used as an alternative to carbapenems in the management

of nosocomial sepsis in NICUs without any apparent adverse effects (159). However, the emergence of this agent among the frequently prescribed drugs may suggest the emergence of antibiotic resistance, which warrants further evaluation and application of strategies to improve antibiotic prescribing.

To date, there is a lack of standard guidelines for empiric choice of antibiotics in neonatal sepsis, especially late onset sepsis. This is evident as the last published Cochrane review in 2005 concluded inadequacy of randomised trials for the empiric choice of antibiotic for late onset sepsis (160,161). This can explain the variety of antibiotics regimens used for neonatal sepsis worldwide and even in NICUs within the same country. Broad spectrum antibiotics are often being prescribed by neonatologists, as it is difficult to differentiate signs of preterm sepsis from those of prematurity (160). This is also compounded by the fact that clinical and laboratory findings (such as C-reactive protein and white blood cells count) are not sensitive during the first hours following birth (105). Therefore, these reasons can be attributed to the high rate of antibiotic use which can accelerate resistance, especially with broad spectrum antibiotics. Overuse of antibiotics, especially in early neonatal life, can distort the gut microbiota which is pivotal for the developmental of the immune system and digestive function, leading to dysbacteriosis (162). A recent systematic review was conducted with the aim of investigating the effect of antibiotic therapy in neonates on gut microbiota and/or antibiotic resistance (162). This systematic review included 48 studies (three RCTs and 45 observational studies) and concluded that prolonged antibiotic therapy was associated with reduced gut microbial diversity (i.e.

disrupts the microbiota) and increased antibiotic resistance. Antibiotic use pattern in China is distinctively different from any other setting around the globe. A recent Lancet global health commentary has reported that China is accounted for the lowest antibiotic use (7.8%) among 56 countries (23,572 patients) that participated in a global study that describe paediatric patterns of WHO's Access, Watch, and Reserve classification of antibiotics (113). The pattern of antibiotic use in China is different when compared to other countries due to several reasons. First, gentamicin is banned in China for children who are below 8 years, unlike many countries in which it is used for gram negative bacteria in children and neonates. Another reason is the limited access of penicillin in China due to their policy of skin testing prior to penicillin use and the unavailability of those agents in many hospitals in China. A final reason is the high willingness of physicians to prescribe macrolide and third generation cephalosporins in China based on a latest survey on knowledge, attitude, and practice of antibacterial agents among Chinese paediatricians (113). The search in the present review have yielded one recent study conducted in a Chinese NICU (106) that supported this difference in drug use pattern in China. This study concluded that the three most frequently prescribed drugs were vitamin K1, hepatitis B vaccine, and cefoperazone-sulbactum. Authors suggest that this is driven by the high levels of ampicillin resistance and prohibition of gentamicin use due to the high risk of hearing loss in the population.

2.4.5 Lack of evidence for antiepileptic use in neonates

There is insufficient evidence from literature supporting the use of anti-epileptics in neonates. Only two RCTs were found to assess pharmacotherapy of anti-epileptics and were reported by a Cochrane review published in 2004 (163). With regards to this current review, four studies in Asia have cited phenobarbitone among the ten most frequently prescribed drugs in their NICUs. Phenobarbitone remains the mainstay in the management of neonatal seizures as cited in the literature (143,164). A recent large retrospective cohort study in the USA by Ahmad et al. was conducted with the aim of investigating the change of antiepileptic use over time (143). This study concluded that phenobarbitone was used in 98% of the cohort, with a minor decrease overtime compared to phenytoin use, which decreased significantly from the period 2005 to 2014. This downward trend was met with an opposing trend in levetiracetam use during the same period. A possible explanation for the recent increase in levetiracetam use is the favourable safety profile in several studies compared to phenobarbitone (165). Levetiracetam is currently suggested to be possibly used as a second-line agent following phenobarbital due to its efficacy and safety, but evidence is still lacking with regards to its use as monotherapy or a first-line agent.

The fact that phenobarbitone appears to be cited among the ten most frequently prescribed drugs in the majority of the studies in Asia indicates the prevalence of neonatal seizures in this region. The four studies that were conducted in Asia have reported that perinatal asphyxia was found to be one of the common morbidities and mortalities of the included neonates

(4,69,78,104). Annually, three million neonatal deaths are due to prematurity, asphyxia and sepsis on a global scale (166). Perinatal asphyxia is a major cause of neonatal mortality in Asian countries. This was evident in a study that analysed the causes of 3,772 neonatal deaths in Nepal, Bangladesh, Malawi and India between 2001 and 2011 (167). This study has found that more than one third of neonatal deaths in urban India were attributed to asphyxia. Perinatal asphyxia could trigger seizures in neonates, which can eventually lead to the use of anti-epileptic drugs. Hence, this could explain the frequent use of phenobarbitone compared to other drugs. Furthermore, phenobarbitone and other first-generation antiepileptics (e.g. phenytoin) are readily accessed in low- and middle-income countries due to their lower cost compared to the higher cost newer generation anti-epileptic drugs (e.g. levetiracetam) which explains the high use of first generation anti-epileptic drugs in Asia (168).

2.4.6 Strengths and limitations

This is the most updated review to provide comprehensive data on the most frequently prescribed drugs, from 1983 to July 2020, in different regions. It included all studies without any restriction on language or search dates. The robust search strategy that was constructed with a senior clinical librarian has added another strength to this review. The data extraction, which was done by two reviewers, is considered another strength that ensures completion of the extracted data. This review has summarised the overall drug use in neonates worldwide in terms of the geographic location, the included sample size, duration of the studies, average drug use per neonate, and the most frequently prescribed drugs of all of the studies that aimed to evaluate drug use in general. Unlike the systematic review by Rosli et al. (10), the high number of the studies yielded in this review would provide a thorough picture of drug use across the globe and in different geographic regions.

The analysis of data extracted from the included studies is limited by the heterogeneity of the included populations, variations in study designs and different methods of reporting the findings. One source of weakness in this review is excluding two studies in German as one could not be obtained (169), and the other one was received as a scanned copy which hindered its translation to English (170). Due to the lack of uniformity among the included studies in terms of the labelling and licensing definitions, the identification of the most frequently prescribed off-label and/or unlicensed drugs was not feasible, which added another limitation to this review and hence they were reported descriptively per each study.

2.4.7 Conclusion

Despite the descriptive nature of this systematic review, it provides valuable insight into the frequently used drugs across different NICUs worldwide. Globally, the pattern of drug use across neonatal units is similar, especially in Europe, with antibiotics being the most frequently prescribed drugs. The high usage of antibiotics is still an ongoing concern that needs to be tackled to rationalise the use of those agents worldwide, especially with the introduction of combined antibiotics, which has led towards the emergence of resistance in some countries. This review also highlighted the lack of details such as paucity on information of indication, dose, duration of use or adverse effects calling for improvement in data collection and analysis of drug utilisation data when conducted on a neonatal level. Such research is important, particularly when conducted collaboratively across national and continental boundaries to improve rational use of medicine in neonates.

In the UK, there is a need for larger updated studies on drug use in neonates due to the limitations of previously conducted studies. A further study with more focus on drug use in neonatal units at a national level will provide a better description of the most frequently prescribed drugs and the current practice in the UK.

CHAPTER 3 DRUG UTILISATION PATTERNS IN NEONATAL UNITS IN ENGLAND AND WALES

3.1 Introduction

Assessing the rational process behind drug therapy is the fundamental goal of drug utilisation research, which involves either quantitative or qualitative methods. Quantitative methods aim to measure prescribing, dispensing, or the consumption of medicines in a population using primary or secondary data sources (171). As very little was found in the previous review chapter regarding the question of the pattern of drug utilisation in neonatal units in the UK, the present study was designed to fill the gaps and extend the body of literature. This chapter describes a retrospective pharmaco-epidemiological study in England and Wales over a long period of time and on a national level using prospectively collected data stored in the National Neonatal Research Database (NNRD).

3.2 Study design

This is a retrospective pharmaco-epidemiological study to explore the utilisation of drugs across neonatal units in England and Wales over eight years (2010 to 2017). The study uses a database of routinely-recorded, prospectively collected data (NNRD), which is approved by the National Research Ethics Service in the UK to permit the use of de-identified data for research (REC Number: 16/1093). A description of the database is detailed in section 3.4.

3.2.1 Ethical approval process

This study was registered prospectively at ClinicalTrials.gov (NCT03773289). The protocol for this study was approved by the Health Research Authority (HRA) following a favourable opinion from the Yorkshire & The Humber – Leeds East Research Ethics Committee and Health and Care Research Wales (IRAS project ID: 248088, REC reference: 18/YH/0209; Date of approval: 25 May 2018) (attached in 9.11).

3.3 Aim and objectives

The overall aim of this study was to investigate historic pattern of drug utilisation in neonatal units in England and Wales.

- Objective 1: What are the most frequently prescribed drugs?
- Objective 2: Have prescribing patterns changed from 2010 to 2017?
- Objective 3: Are there any variations in prescribing according to gestational age and birth weight and treatment location?
- Post-hoc objective: Are there any differences in antibiotic prescribing according to gestational age group?

3.4 Methods

3.4.1 Overview of the data used in this study

3.4.1.1 Sources of neonatal data in the UK

The routine collection of neonatal data in the UK started in 1990 through a study called The Neonatal Survey, which has become a resource for providing clinical information on neonates (172). However, the data provided by this survey covers some regions of England only (Leicestershire & Rutland, Derbyshire, Nottinghamshire, Lincolnshire, South Yorkshire, South Humberside and Northamptonshire). In addition, the reports produced by The Neonatal Survey do not provide drug records from the collaborating neonatal units.

Another electronic platform that is used in the UK is the Hospital Episode Statistics (HES) database. HES is a database of all admissions, Acute care and Emergency (A and E) attendances, and outpatient appointments in the National Health Service (NHS) hospitals in England only. This database was established in 1989 with an aim of recording every episode of admission in England and the care delivered (173). This database contains key clinical information (diagnoses and operations), patient information (age groups, gender, and ethnicity), administrative information (dates and methods of admission and discharge), and finally, geographical information (treating centre and area of living) (174). However, it does not capture any information regarding drug treatment in neonates.

Since the main aim of this study was to identify the most frequently prescribed drugs in the neonatal population and investigate patterns of drug use over time, the use of both the Neonatal Survey and HES were not appropriate. The NNRD, established in 2007 by the Neonatal Data Analysis Unit (NDAU), is an approved research database which can be used to meet the aim and objectives of this study.

3.4.1.2 NNRD and justification for its use in this study

Neonatal clinical data are entered daily into a national electronic platform by healthcare professionals providing care to neonates across the UK. This platform is known as Badger.net, which holds neonatal electronic health records of all admissions to NHS neonatal units and is managed by an authorised hosting company, Clevermed Ltd (Level 6, Edinburgh Quay, 133 Fountainbridge, Edinburgh, EH3 9QG, www.clevermed.com). Since the establishment of the NDAU in 2007, based at the Chelsea and Westminster Hospital campus of Imperial College London, the collection of electronic neonatal data for research and quality assessment was facilitated (175). Neonatal Data Analysis Unit (NDAU) extract data quarterly from all NHS neonatal units, combine it, and undertake initial data management and cleaning to produce the NNRD.

At present, the NNRD holds data on around one million neonates and ten million days of care (176). The database includes a variable where names of individual drugs prescribed to neonates are entered daily. In addition, there are other data items which capture drug use, such as drugs used in resuscitation at birth, surfactant at delivery, and drugs given for specific

conditions, such as for patent ductus arteriosus (PDA). Therefore, the NNRD was selected for its ability to provide a detailed insight into drug use across neonatal units in the UK and fulfil the aim and objectives of this study, as it is currently considered the only national neonatal database providing clinical information on neonates admitted at different neonatal unit levels and their drug use across the UK. For this study, all data on neonatal unit admissions over an eight-year period (01 January 2010 to 31 December 2017) in England and Wales was utilised for the purpose of analysis. However, the data from Scotland and Northern Ireland were not included. This is because a different ethics process was required and Northern Ireland do not use the Badger.net. Therefore, I have focused on data from England and Wales only.

3.4.1.3 Dataset used in this study and statistical software

Data in the NNRD are broadly organised in two files – Episode data and Daily data – and were extracted by NDAU and provided to us in this form. Episode data represent an admission to a neonatal care unit. Each row in the episode data corresponds to one admission (i.e. one episode of care in a single unit regardless of how many days a neonate stays at the unit). A neonate may have several episodes of care if they are transferred between units. Daily data represent a day of care for a neonate and each row in the daily data file corresponds to one day of care. Figure 20 and Figure 21 detail the variables requested from NDAU to be extracted from NNRD.

All data management and statistical analysis were carried out using Stata SE 16 (64-bit) (Stata Corp. College Station, TX, USA) for Windows 2010 Enterprise Edition (Microsoft Corporation, Seattle, USA).

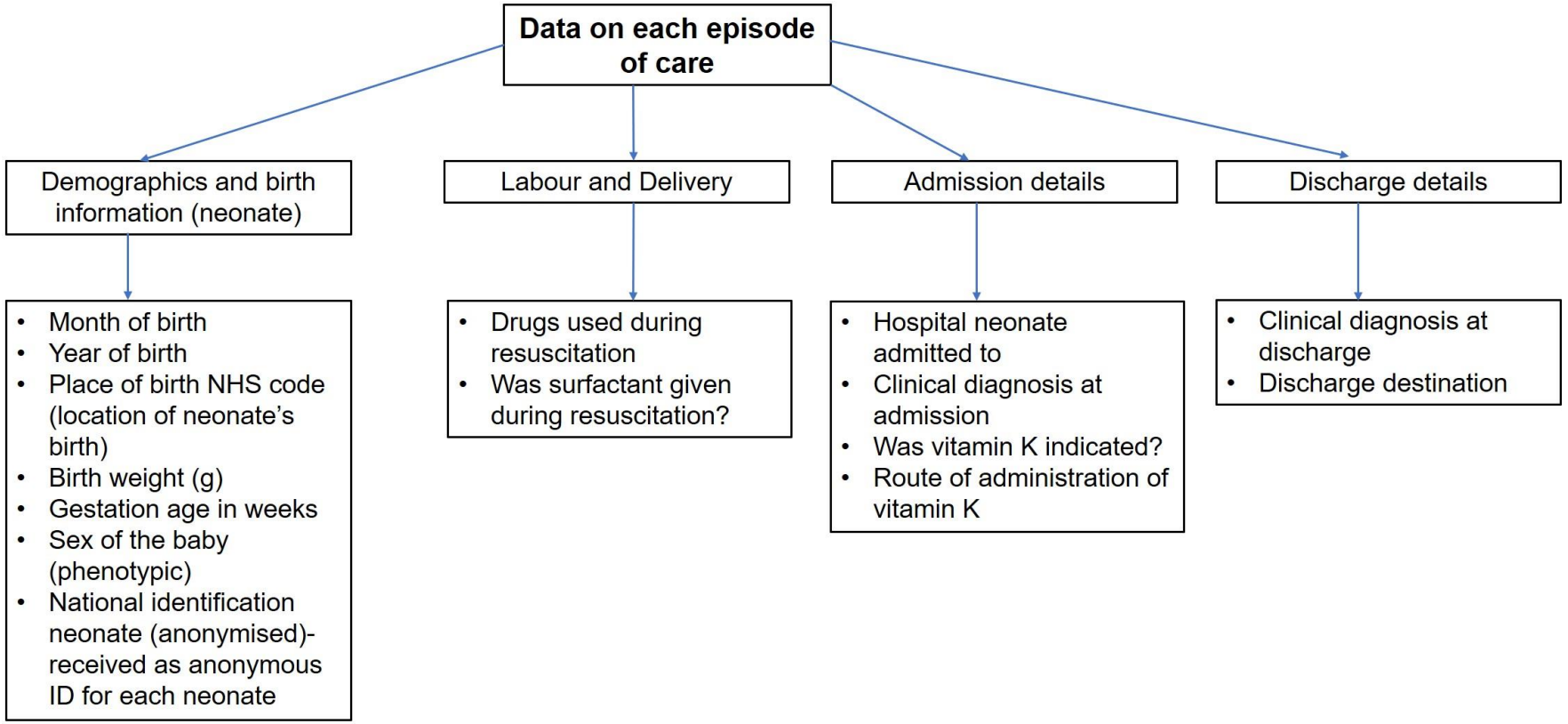
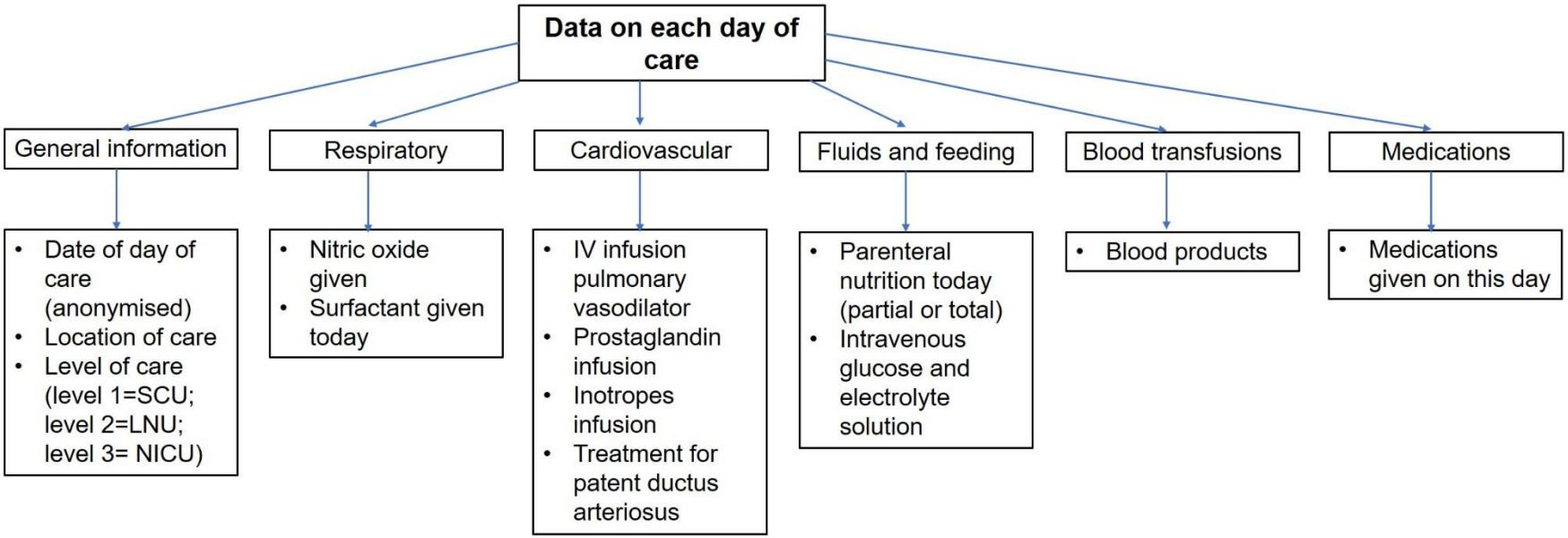


Figure 20. Variables extracted from the NNRD Episode file



SCU, Special care unit; LNU, Local neonatal unit; NICU, Neonatal intensive care unit

Figure 21. Variables extracted from the NNRD Daily data file

3.4.2 Study population

All neonates admitted to a neonatal unit in England or Wales from 01 January 2010 to 31 December 2017 were eligible for inclusion. Neonates with the following criteria were excluded:

- Neonates with missing or contradictory information in their demographic data (gestational age (GA), birth weight (BW), gender, month of birth)
- Neonates admitted to a non-neonatal unit
- Neonates with missing episodes at the start or in the middle of their care
- Neonates whose first admission is not within the study period
- Neonates with GA < 22 weeks or > 44 weeks
- Neonates with extreme BW for GA Z-scores (detailed in section 3.4.3.4)

WHO definitions were adopted to categorise neonates according to different GA groups and BW groups (13,177) (Table 8).

Table 8. Definitions of gestational age and birth weight categories according to WHO

Gestational age category	Birth weight category
Term: born at ≥ 37 weeks	Normal birth weight: born ≥ 2500 g
Moderate to late preterm: born between 32-36 weeks	Low birth weight (LBW): born < 2499 g
Very preterm: born between 28-31 weeks	Very low birth weight (VLBW): born < 1500 g
Extremely preterm: born at < 28 weeks	Extremely low birth weight (ELBW): born < 1000 g

3.4.3 Overview of data management

A summary of the steps taken to derive the final study dataset for the purpose of analysis is provided in Figure 22, followed by a detailed explanation.

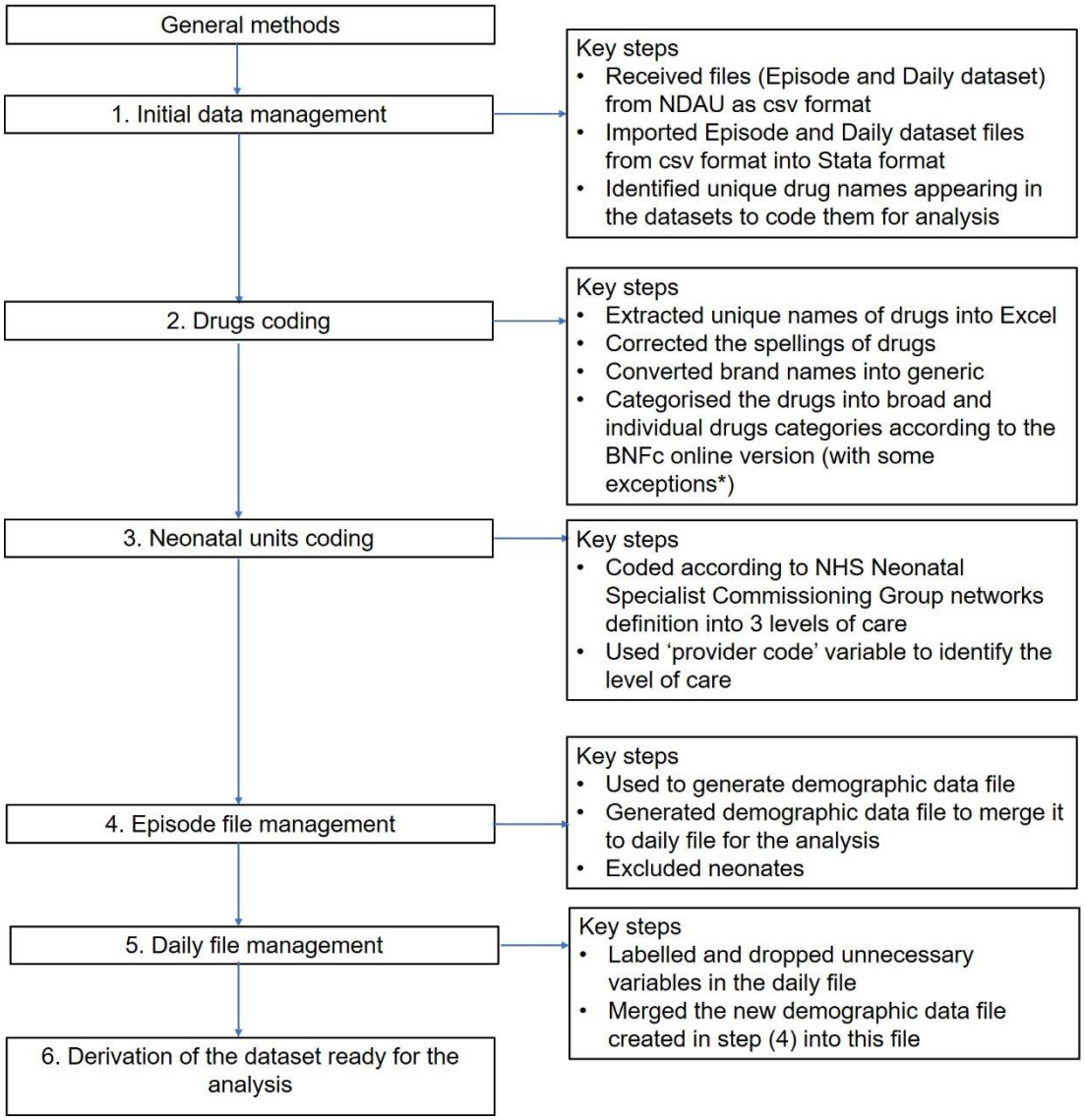


Figure 22. Summary of the key steps in data management

3.4.3.1 Initial data management

Episode and Daily data were received from NDAU as two separate.csv files, and an anonymised identification number (anon-id) was used to enable linkage between the two files. Some of the variables were coded as ‘integers’ (i.e. numbers) while others were coded as ‘strings’ (i.e. text). The initial data management was supported by my supervisor Dr Lisa Szatkowski (Associate Professor in Medical Statistics, School of Medicine, University of Nottingham) using her computer as initial data processing required a computer with sufficient processing power to be able to open the extremely large files. This process involved importing the .csv dataset into Stata and saving it in a Stata format. Both Episode and Daily datasets were then divided into 20 smaller files of approximately equal numbers of neonates. This was done as I was not able to run the analysis on one complete file on my computer due to lack of adequate processing power. It was therefore necessary for me to perform the key steps of analysis on one Episode/Daily data file and then repeat it on the subsequent 19 files before combining results.

3.4.3.2 Drugs coding

Drug data entered in the NNRD data are in text format with different spellings and alternate names (generic/brand). For example, amoxicillin appears as two different spellings, ‘amoxicillin’ and ‘amoxycillin’, and paracetamol is entered using the brand name ‘calpol’ as well as the generic ‘paracetamol’. Hence, it was essential to harmonise and code drugs before starting the analysis. As a first step, every single drug entry in the Daily data file was identified and extracted. The number of unique drugs identified from the raw data was 659. These were extracted and copied to an Excel file to start the process of coding. This process involved three different steps applied as necessary (Figure 23).

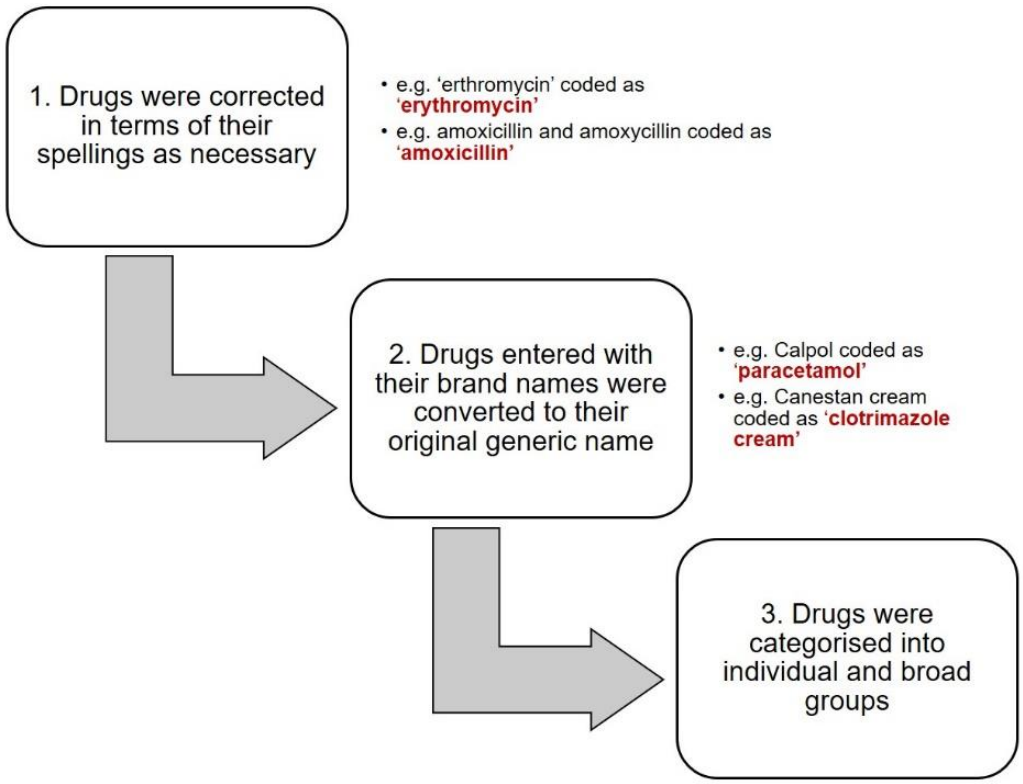


Figure 23. Stepwise drugs coding process

In the first step, all drug entries were corrected in terms of their spelling. Secondly, drugs entered using brand name entries were converted to their generic names. Following those two steps, the drugs were then categorised according to two main categories for the purpose of analyses:

- **Broad group category:** Drugs were renamed according to their broader category and their primary use in the neonatal population
- **Individual category:** Drugs were renamed according to their original scientific/generic name with appropriate UK spellings

I performed the initial cleaning and categorisation which was subsequently checked by my supervisor Dr Ojha. The British National Formulary for Children (BNF-C, September 2018 update) and specific product characteristics (www.medicines.org.uk) were used as a reference for categorisation. Some examples of the drug cleaning and categorisation are shown in Table 9.

Table 9. Examples of coding and categorising drugs

Drug entry (as presented in original dataset)	Broad group	Individual drug
ibuprofen	Agents used in patent ductus arteriosus	Ibuprofen
indometacin		Indomethacin
indometacin (indomethacin)		
indomethacin		
morphine - oral	Analgesics	Morphine (oral)
oral morphine		
oral morphine - level 1		
oral morphine - level 3		
oral morphine - level 4		
oramorph		
oromorph		

Some drugs were not categorised according to the references stated above, but instead according to their use as reported in the literature. An example of this is oral sucrose which is effective as an analgesic for procedural pain in neonates (178). Another example is paracetamol, which can be used in neonates as an analgesic but more recently shown to be effective in PDA management (179). However, paracetamol was classified as analgesic as it was not clear at this stage from the data if it was used for PDA or as an analgesic. The broad pharmacological groups of the drugs are listed in Figure 24 whereas the full drug list with their codes and categories along with the corresponding references is detailed in 9.12.

CVD, cardiovascular; F&E, fluids and electrolytes; GI, gastro-intestinal; PH, pulmonary hypertension; PDA, patent ductus arteriosus; PGs, prostaglandins

Figure 24. Broad pharmacological group categories

3.4.3.3 Neonatal units coding

The neonatal unit providing each episode of care was coded according to their level (level one, two, or three) as defined by the NHS Neonatal Specialist Commissioning Group network's definition of different neonatal levels of care (180,181) and British Association of Perinatal Medicine (BAPM) categories of care (24) .

These are:

- Level one: SCU (special care unit) for initial and short-term care for neonates born at GA > 32 weeks
- Level two: LNU (local neonatal unit) for high dependency care for neonates born between 28-32 weeks
- Level three: NICU (neonatal intensive care unit) for complex care for neonates born at GA < 28 weeks

One unit was identified as a non-neonatal unit and coded as level 0 of care after checking with NDAU. All neonates labelled with admission to this unit were excluded from the study.

3.4.3.4 Episode file management

The Episode file contains information on basic characteristics of neonates' demographics, such as GA in weeks, BW in grams, month and year of birth, gender of the baby, and the place of birth. The Episode data file was therefore used as the key file to create a new dataset of demographic data for each neonate, which was later merged into the Daily file to enable analyses.

Before merging, an initial attempt was made to ensure that the data in the Episode file were consistent and there were no duplicates, conflicts, or missing records in any entry of the demographic variables. A summary of the steps followed to ensure completeness of data in the Episode data file is presented in Figure 25.

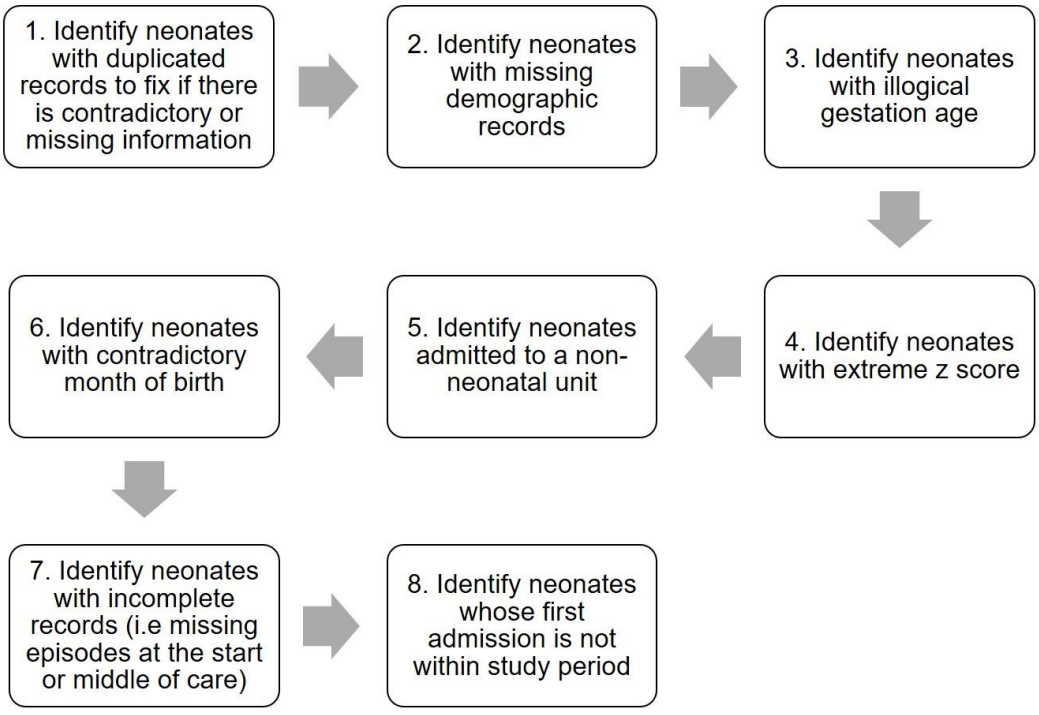


Figure 25. Steps followed to ensure completeness and consistency in demographic variables in the Episode data file

Neonates with GA < 22 weeks or > 44 weeks were marked to be excluded. Neonates with extreme BW for GA Z scores were also identified for exclusion. A Z score is a standard deviation (SD) score that allows a comparison of a child to the reference population (182). In this study, Z scores were calculated to exclude neonates with a BW for GA Z score greater or less than 4 SD as performed in the recent published study using the same database wherein neonates with incongruous BW were also excluded (27). Z scores were calculated using the 'Zanthro' function in Stata to generate the acceptable BW bounds, based on the UK-WHO growth charts-neonatal and infant close monitoring (NCIM) (183). Appendix 9.13 details the calculated ±4 SD Z score bounds for boys and girls for each week of GA at birth (184). Weight data in UK reference charts are available from 23 weeks' gestation only. Since there are no reference BW data for neonates at 22 weeks of gestation, BW records for neonates born at this gestation were examined manually and compared to the ±4 SD bounds for neonates born at GA of 23 weeks. This manual inspection concluded that the BW of all neonates born at 22 weeks' gestation fell within the acceptable weight range for neonates born at 23 weeks and so these neonates were not marked for exclusion.

3.4.3.5 Daily file management

Management of the Daily data file included simple ‘housekeeping’ tasks such as labelling variables and dropping variables not needed at this point in order to reduce the data file size.

3.4.3.6 Derivation of the final study dataset

At this stage, the clean Daily data file and the demographic data file were merged. Figures for the number of neonates excluded, both in total and according to each specific exclusion criterion, were created.

3.4.4 Specific methods for each objective

3.4.4.1 Objective 1: What are the most frequently prescribed drugs?

For this objective, the following steps were undertaken:

1. Merged the newly created demographic data file to the Daily data file using the anonymous Identification number (anon_id) variable to link individuals and excluded neonates based on the previously mentioned list.
2. Dropped any irrelevant variables from the data file to reduce its size and speed the analysis process.
3. Created a new variable for each individual drug and group of drugs, coded as ‘one’ if the drug/group was prescribed on each day of care and coded as ‘zero’ if it was not prescribed.

4. For each neonate, created a binary variable indicating whether each individual drug or group of drugs was prescribed at least once during their care.
5. For each neonate, created a continuous variable counting the number of days each individual drug or group of drugs was prescribed during their care.

I have tabulated two scenarios below from the data analysing the prescribing of analgesics (as an example) to explain the function of the created variables (Figure 26). Intravenous (IV) morphine and paracetamol are two examples that were coded as analgesics in those presented scenarios. The anon_id was removed and replaced by ‘a’ and ‘b’ for the purpose of confidentiality.

number of episodes for each neonate

length of hospital stay in days

shows each drug received on the day of care

created to code analgesics either 1=received, 0=not received

created to code all row=0 or 1 if they received/not an analgesic

created to code the rows with the number of days an analgesic was received

anon_id	episode number baby	total days	drugs day	analgesics	analgesics_baby	analgesics_baby_days
a	1	8	dinoprostone (prostaglandin e2), benzylpenicillin, gentamicin, nystatin	0	0	0
a	1	8	dinoprostone (prostaglandin e2), benzylpenicillin, gentamicin, nystatin	0	0	0
a	2	8		0	0	0
a	2	8		0	0	0
a	2	8		0	0	0
a	2	8		0	0	0
a	2	8		0	0	0
a	2	8		0	0	0
b	1	6	benzyl penicillin, cefotaxime, iv morphine, phenobarbitone - loading dose	1	1	4
b	2	6	cefotaxime, iv morphine, amoxicillin, paracetamol	1	1	4
b	2	6	cefotaxime, amoxicillin	0	1	4
b	2	6	cefotaxime, amoxicillin	0	1	4
b	2	6	cefotaxime, iv morphine, amoxicillin, paracetamol	1	1	4
b	2	6	benzyl penicillin, cefotaxime, iv morphine	1	1	4

Figure 26. Variables created to identify drug prescribing

3.4.4.1.1 Mean number of drugs and proportion of drugs free days

A secondary aim was to quantify the mean number of drugs per neonate and the proportion of drug free days. To achieve this, for each neonate I created a variable counting the total number of different individual drugs prescribed, and a variable counting the number of days when no drugs were prescribed.

3.4.4.1.2 Drugs excluded from the analyses

In line with other drug utilisation studies, some drugs and other substances were excluded from the analyses. These include IV fluids to prevent clotting of vascular lines (heparin sodium, sodium chloride for flush), standard IV replacement solutions (electrolytes, glucose), parenteral nutrition solutions, milk formula, and all types of vitamins and topical dermatological agents that contain combined antibiotics and/or corticosteroids. Also, some substances were classified as unrecognised as they could not be identified and were excluded from the analysis (detailed in 9.14).

3.4.4.1.3 The total days of use of drugs

This was calculated by multiplying the number of neonates who were prescribed a particular drug at least once during their neonatal stay by the average number of days of exposure. The drugs were then ranked based on the total number of days of use from the highest number of days of use to the lowest and the results of the top ten drugs are presented.

3.4.4.2 Objective 2: Have prescribing patterns changed over time?

The methods used to answer the three parts of this objective build on those described above and are detailed below.

3.4.4.2.1 Changes over time in which drugs are most frequently used relative to other drugs

For this, I have taken the ten most frequently prescribed drugs identified from objective 1 and analysed them by year of admission using the absolute number and proportion of neonates who have been prescribed each individual drug at least once from 2010 to 2017.

3.4.4.2.2 Changes over time in the average number of days that neonates are given particular drugs

Again, the ten most frequently prescribed drugs were identified as per the first objective. Then, the absolute numbers and proportion of neonates prescribed those drugs at least once were tabulated by year of admission from 2010 to 2017 to illustrate the change in prescribing patterns. In addition, the median, range and interquartile range for the number of days each drug was prescribed were calculated by year of admission from 2010 to 2017, and this was also repeated for each GA group.

3.4.4.2.3 Changes in drug use over time for the entire cohort and for very and extremely preterm neonates

In order to explore the change in drug use over time for the full cohort (i.e. neonates of all GA), the percentage of neonates who were prescribed a particular drug at least once in a particular year (e.g. 2010) among all neonates who were admitted in that year (e.g. 2010) was calculated. This was repeated for each year in the study period (from 2010 to 2017). Following this step, the minimum, maximum, and range of the percentage of neonates who received the drug at least once in each study year was determined. These ranges were ranked from the largest to the smallest value (detailed in 9.15). However, only the data on drugs with a range of greater than one percent were extracted to attain a manageable number of drugs to describe in more detail. This cut off was chosen for the full cohort. Following this, the percentages of neonates prescribed the drugs at least once from 2010 to 2017 were plotted.

Similarly, the change in drug use over time was investigated among very and extremely preterm neonates separately. As the ranges of the percentages of neonates who received the drug at least once in these subgroups were larger, a higher percentage cut off was selected to attain a manageable number of drugs to describe in more detail for these two cohorts. For very preterm neonates, drugs that had a range of more than 3% (detailed in 9.16) and for extremely preterm neonates, drugs that had a range of more than 5% (detailed in 9.17) are presented. All the calculations were done using Microsoft Excel (version 16, 64 bit).

In this analysis, research drugs were excluded as the change in the use of those drugs over time is related to the start and the end of each trial, and hence will not provide a meaningful interpretation of the change in their use over time. Those drugs are detailed in 9.12.

3.4.4.3 Objective 3: Are there any variations in prescribing according to gestational age and birth weight of neonates and treatment location?

For this objective, the analyses carried out for objective 1 were repeated for sub-groups of the study population defined by GA groups, BW group and unit level, using the group definitions listed in Table 8 and Section 3.4.3.3.

For the analyses at unit level, only those neonates who received all their neonatal care in one unit were included. Neonates who were treated in more than one unit were excluded, as were any neonates where the care level of the treating unit could not be identified.

3.4.4.4 Post-hoc objective: Are there any differences in antibiotic prescribing for each gestational age group?

This objective focuses on four questions; the methods for each are detailed below. Initially, a general coding of the antibiotics was undertaken similar to that described in objective 1 (step 4), but this was done only for the group of antibiotics. After that, the following analysis steps were undertaken for each question.

3.4.4.4.1 How many different antibiotics are prescribed per neonate during their hospital stay?

A binary variable was created for each individual antibiotic where each row, representing a day of care, was coded as ‘one’ if a neonate was prescribed that antibiotic on that day. Then, by generating a variable called total antibiotics (total abx), the number of different antibiotics that were prescribed per neonate who were prescribed antibiotics at least once during their hospital stay was calculated.

3.4.4.4.2 How many days of antibiotics are prescribed per neonate?

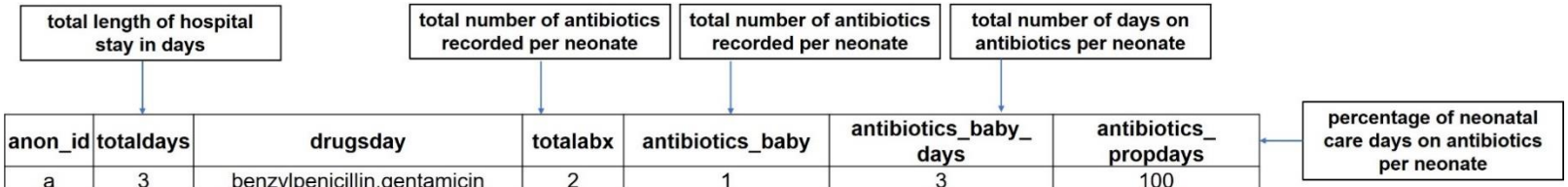
The number of days on which neonates were prescribed antibiotics was analysed by first generating a binary variable (antibiotics_baby) identifying neonates who were prescribed antibiotics on at least one day. Another variable was created (antibiotics_baby_days) to count the number of days antibiotics were prescribed per baby.

3.4.4.4.3 On what percentage of neonatal care days are antibiotics prescribed amongst neonates who have been prescribed antibiotics for at least one day?

This percentage was calculated for each neonate by dividing the number of days where antibiotics were prescribed by the total number of days of care. Figure 27 depicts two scenarios extracted from the dataset to illustrate the function of the above-mentioned variables used to identify antibiotics prescribing.

3.4.4.4.4 How many courses of antibiotics were prescribed, where antibiotics were prescribed for at least 5 days continuously?

For this analysis, a course of antibiotics was defined as five consecutive days of prescribing per neonate. A gap of at least two days was required between courses to call them different courses of antibiotics. The total number of courses of antibiotics prescribed, overall and in each GA, group was counted.



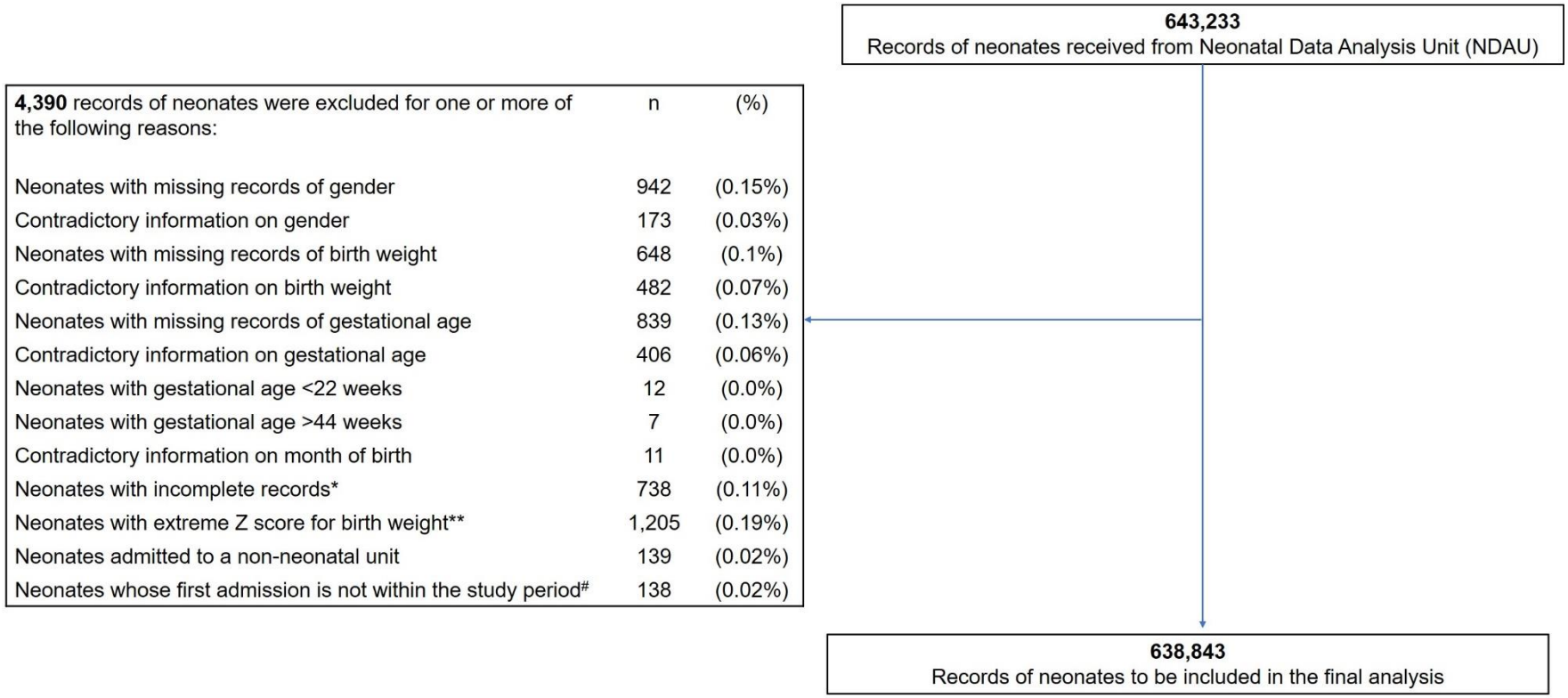
anon_id	totaldays	drugsday	totalabx	antibiotics_baby	antibiotics_baby_days	antibiotics_propdays
a	3	benzylpenicillin,gentamicin	2	1	3	100
a	3	benzylpenicillin,gentamicin	2	1	3	100
a	3	benzylpenicillin,gentamicin	2	1	3	100
b	16	benzylpenicillin,gentamicin, vitamin k, phenobarbitone-loading dose, morphine, suxamethonium,morphine infusion	4	1	12	75
b	16	benzylpenicillin, phenobarbitone-loading dose, morphine infusion, cefotaxime	4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75
b	16	morphine infusion, cefotaxime, vancomycin	4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75
b	16	benzylpenicillin,gentamicin,vitamin k, phenobarbitone-loading dose, morphine, suxamethonium,morphine infusion	4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75
b	16		4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75
b	16		4	1	12	75
b	16		4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75
b	16		4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75
b	16	cefotaxime,vancomycin	4	1	12	75

Figure 27. Variables created to identify antibiotic prescribing

3.5 Results

3.5.1 Derivation of the study dataset for the analyses

The total number of neonates for whom records were received from NDAU was 643,233. Of these, a total of 4,390 (0.7%) neonates were excluded from analysis for one or more reasons (Figure 28).



4,390 records of neonates were excluded for one or more of the following reasons:	n	(%)
Neonates with missing records of gender	942	(0.15%)
Contradictory information on gender	173	(0.03%)
Neonates with missing records of birth weight	648	(0.1%)
Contradictory information on birth weight	482	(0.07%)
Neonates with missing records of gestational age	839	(0.13%)
Contradictory information on gestational age	406	(0.06%)
Neonates with gestational age <22 weeks	12	(0.0%)
Neonates with gestational age >44 weeks	7	(0.0%)
Contradictory information on month of birth	11	(0.0%)
Neonates with incomplete records*	738	(0.11%)
Neonates with extreme Z score for birth weight**	1,205	(0.19%)
Neonates admitted to a non-neonatal unit	139	(0.02%)
Neonates whose first admission is not within the study period#	138	(0.02%)

* Neonates with a missing episode at the start or in the middle of their care
**Neonates with a birth weight Z score greater than 4 SD or less than -4 SD
Study period: defined from January 2010 to December 2017

Figure 28. Number of neonates excluded from the analyses

For the analysis at unit level (objective 3), 52,566 (8%) neonates were excluded where they were treated in more than one unit or because the level of care could not be identified (Figure 29). 586,277 neonates were therefore included in the analyses of drug use by unit level.

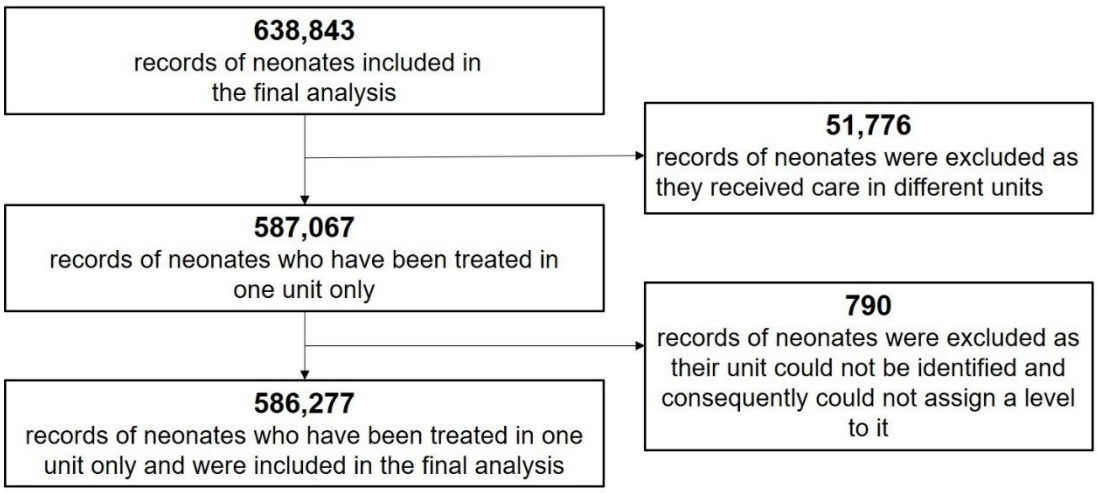


Figure 29. Derivation of neonatal record for the inclusion of analysis by unit level

3.5.2 Population characteristics

After exclusions, a total of 638,843 neonates admitted to 187 neonatal units across England and Wales from January 2010 to December 2017 were included in the study (Table 10). 44% of neonates (n=283,553) were female and 59% were born at term (n=379,410).

A histogram was done to inspect the normality of the data sets and mean/median were chosen for normal/skewed distribution, respectively. Following the inspection of the histogram it was clearly not normally distributed data set in terms of the GA, BW, and length of hospital stay. Therefore, median (IQR) was chosen to summarise these variables.

The median (IQR) GA in weeks and median (IQR) BW in grams were 37 weeks (35-40) and 2890 (2168-3500), respectively. The median length of neonatal unit stay was five days (IQR 3-13). As expected, length of stay was longer for neonates born the most premature. 66% of neonates were discharged to home and 1% (n=8,666) died. Mortality was highest among extremely preterm neonates, 22% (n=4,234) of whom died.

Appendix 9.18 describes the demographic characteristics of neonates by BW category.

Table 10. Characteristics of the study population, overall and by gestational age group

Demographic comparison		All gestational age groups	Extremely preterm (< 28 weeks)	Very preterm (28-31 weeks)	Moderate to late preterm (32-36 weeks)	Term (≥ 37 weeks)
Number of neonates n (%)		638,843 (99.3)	19,159 (3)	42,106 (7)	198,168 (31)	379,410 (59)
Gestational age (weeks) median (IQR)		37 (35-40)	26 (24-27)	30 (29-31)	35 (33-36)	39 (38-40)
Birth weight (grams) median (IQR)		2890 (2168-3500)	814 (677-965)	1375 (1160-1590)	2240 (1910-2595)	3362 (2955-3760)
Female n (%)		283,553 (44)	8,739 (46)	19,148 (46)	90,540 (46)	165,126 (44)
Length of hospital stay in days median (IQR)		5 (3-13)	85 (60-109)	43 (33-57)	11 (5-18)	3 (2-6)
Discharge destination n (%)	**Home**	419,671 (66)	13,481 (70)	39,209 (93)	153,996 (77)	212,985 (56)
	Died	8,666 (1)	4,234 (22)	1,347 (3)	1,255 (1)	1,830 (1)
	Ward	192,766 (30)	387 (2)	525 (2)	39,469 (20)	152,385 (40)
	Transfer	16,022 (3)	968 (5)	943 (2)	3,140 (2)	10,974 (3)
	Missing	1,715 (<0.01)	89 (1)	82 (<0.01)	308 (<0.01)	1,236 (<0.01)

IQR, interquartile range; SD, standard deviation

3.5.2.1 Characteristics of the study population based on receiving treatment in one neonatal unit

Of the population included, 44% (n= 255,738) of neonates were admitted to NICUs, followed by 42% (n=248,108) to LNUs and 14% (n=82,431) to SCUs. The median (IQR) of the GA in weeks and BW in grams were 38 weeks (35-40) and 2960 g (2270-3530), respectively. The median length of neonatal unit stay was approximately the same for all three levels of care (Table 11).

Table 11. Characteristics of neonates who received care in only one neonatal unit

		All neonatal units	Level 1 neonatal units (SCU)	Level 2 neonatal units (LNU)	Level 3 neonatal units (NICU)
Number of neonates n (%)		586,277	82,431 (14)	248,108 (42)	255,738 (44)
Gestational age (weeks) median (IQR)		38 (35-40)	38 (35-40)	38 (35-40)	38 (35-40)
Gestational age group (n)		586,277	82,431	248,108	255,738
	Term n (%)	366,252 (62)	51, 016 (62)	151,310 (61)	163,926 (64)
	Moderate to late preterm n (%)	181,875 (31)	28,919 (35)	81,410 (33)	71,546 (28)
	Very preterm n (%)	29,093 (5)	2,256 (3)	13,591 (5)	13,246 (5)
	Extremely preterm n (%)	9,057 (2)	240 (0.3)	1,797 (1)	7,020 (3)
Birth weight (grams) median (IQR)		2960 (2270-3530)	2975 (2320-3550)	2940 (2246-3522)	2960 (2280-3525)
Female n (%)		260,174 (44)	36,045 (44)	109,741 (44)	114,388 (45)
Length of hospital stay (days) median (IQR)		4 (2-10)	5 (3-10)	5 (3-11)	4 (2-10)
Discharge destination n (%)	**Home**	374,475 (64)	51,379 (62)	159,598 (64)	163,498 (64)
	Died	6,366 (1)	317 (0)	1,324 (1)	4,725 (2)
	Ward	190,448 (33)	29,407 (36)	83,110 (34)	77,931 (31)
	Transfer	13,441 (2)	1,244 (2)	3,901 (1)	8,296 (3)
	Missing	1,547 (0)	84 (0)	175 (0)	1,288 (0)

SCU, special care unit; LNU, local care unit; NICU, neonatal intensive care unit; IQR, interquartile range; SD, standard deviation

3.5.2.2 Characteristics of the study population based on drug prescribing

Of the population included, 30% of neonates were not prescribed any drug (not including the excluded drugs) during their neonatal stay (Table 12). As expected, neonates who have not been prescribed any drugs had higher GA and BW compared to those who had drugs during their neonatal stay. Also, the median length of neonatal unit stay of neonates who did not have any drugs was three days (IQR 2-5), which was lower than those who had the drugs (median 7, IQR 3-18) ($p<0.001$).

Further analyses was done to extract the diagnosis at the admission of neonates who have not been prescribed any drugs (Table 13). Across all the cohort, 22% (n=137,578) of neonates had no entries of any diagnosis at admission. Whereas 39% (n=74,698) of neonates who have not prescribed any drugs had no entries of diagnosis at admission. At least 13% of neonates who have not prescribed any drugs were diagnosed with prematurity, followed by hypoglycaemia (10%), and 'other' (10%). Some entries were excluded from the list of diagnosis as they were signs and symptoms (1%, n=2,730), unclear entries (2%, n=4,036), entries related to social issues and delivery (3%, n=6,610), or maternal related conditions (5%, n=10,140).

Table 12. Characteristics of the study population based on drugs prescribing

Demographic comparison		Prescribed drugs	Not prescribed drugs	P value for difference between groups
Number of neonates n (%)		445,322 (70%)	193,521 (30%)	-
Gestational age (weeks) median (IQR)		37 (34-40)	38 (36-40)	P<0.001*
Birth weight (grams) mean (SD)		2732 (966)	2998 (740)	P<0.001**
Female n (%)		189,692 (43%)	93,861 (49%)	P<0.001***
Length of neonatal stay in days median (IQR)		7 (3-18)	3 (2-5)	P<0.001*
Discharge destination n (%)	**Home**	298,375 (67%)	121,296 (63%)	P<0.001***
	Died	7,955 (2%)	711 (0.4%)	
	Ward	125,532 (28%)	67,234 (35%)	
	Transfer	13,023 (3%)	3,002 (1%)	
	Missing	427 (0.1%)	1,278 (0.6%)	

*Mann-Whitney test; **Two sample t-test; ***Pearson Chi-square test

Table 13. Diagnosis at admission of neonates who were not prescribed any drugs

Conditions based on diagnosis at admission variable	Neonates with no drug prescriptions (n=193,521)	
	n	(%)
Prematurity	25,368	13
Hypoglycaemia	20,212	10
Other*	18,540	10
Neonatal jaundice	14,943	8
Intrauterine growth restriction	13,622	7
Respiratory diseases	12,110	6
Syndrome of infant of mother with gestational diabetes	9,536	5
Feeding issues	9,113	5
Hypothermia or disturbances in temperature regulation of new-born	6,761	4
Low birth weight	6,386	3
Risk of infections	5,807	3
Weight loss	5,056	3
Infections**	4,737	3
Birth asphyxia	4,429	2
Congenital malformation	4,145	2
Neonatal abstinence syndrome	2,650	1
CVD and all related heart defects conditions	2,363	1
Unspecified conditions	1,988	1
Disorders of fluid, electrolyte and acid-base balance	1,808	1
Cleft lip and cleft palate	1,226	1

Perinatal haematological disorders	1,025	1
Fetal macrosomia	823	0.4
Fetus affected by maternal condition	751	0.4
Neonatal aspiration syndromes	676	0.4
Confirmed or suspected major trisomy (Down's, Edward's, Patau's)	566	0.3
Haemolytic disease of fetus and new-born	478	0.3
Birth trauma	439	0.2
Neonates with birth weight> 4.5 kg	412	0.2
Disturbances of cerebral status of new-born	346	0.2
Abnormal findings (blood, diagnostic imaging)	278	0.1
Diseases of other systems (immune, muscle tone/musculoskeletal, circulatory, genital organs)	253	0.1
Coagulation defects, purpura and other haemorrhagic conditions	181	0.1
Injuries	149	0.1
Neonatal seizures	135	0.1
Other conditions (adrenal, gingiva, pleural, intestine, kidney and ureter, urinary)	128	0.1
Intrauterine hypoxia	115	0.1
Intestinal obstruction	97	0.1
Transitory endocrine and metabolic disorders specific to fetus and new-born	93	0.04
Fetal blood loss	90	0.1
Metabolic disorders***	86	0.04
Diabetes mellitus	76	0.04
Haemolytic anaemias	68	0.04
Cerebro-vascular diseases	63	0.03
Neoplasms (benign, malignant)	60	0.03
Complications (surgical, related to puerperium, labour)	45	0.02

Neonatal haemorrhage	42	0.02
Hernia	39	0.02
Persistent pulmonary hypertension of the newborn	34	0.02
Gastroesophageal reflux disease	31	0.02
Hypotension	28	0.01
Renal failure	27	0.01
Skin related issues	20	0.01
Hydrops fetalis	14	0.01
Hypertensive diseases	13	0.01
Disorders of the nervous system	6	0
Drug toxicity	4	0
Vitamin deficiency	4	0
Retinopathy of prematurity	1	0
Oral candidiasis	1	0
Neonatal death	1	0

CVD, cardiovascular disease

*Other: literally written as ‘other’ without any further details

** include respiratory syncytial virus, suspected sepsis, conjunctivitis, fungal/skin/viral infections, suspected urinary tract infections, gastroenteritis

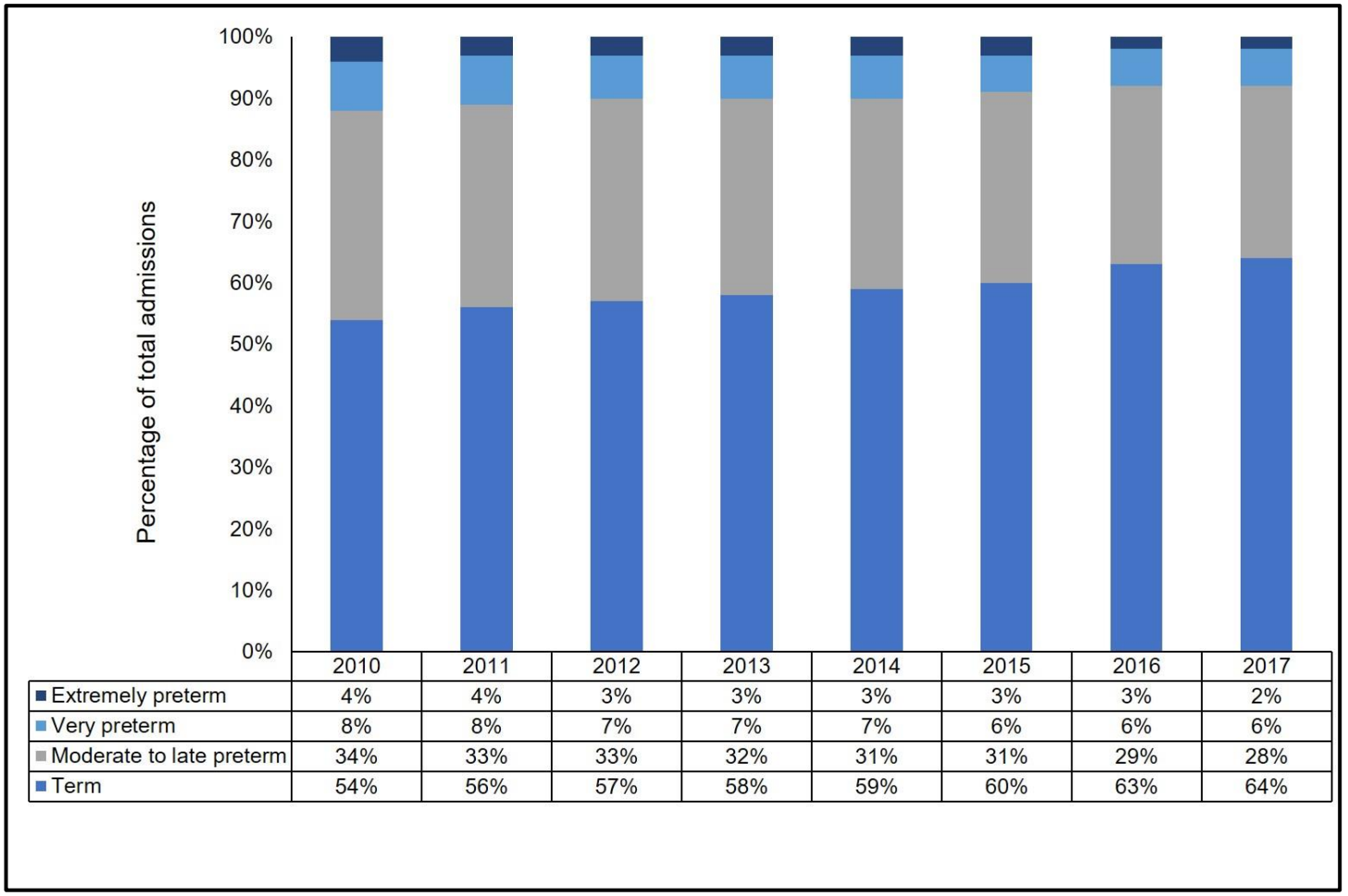
*** include alkalosis, acidosis, hypo/ernatraemia, hypo/erkalaemia, hypochloraemia

3.5.2.3 Admissions per year

Overall, the total number of admissions increased from 60,437 (9% of the total) in 2010 to 99,541 (16% of total) in 2017, which can be attributed to the increase in the number of term admissions (Figure 30). The number of term neonates increased from 32,567 (54% of total admission in the year) in 2010 to 63,760 (64% of total admissions) in 2017. Moderate to late preterm neonates were 34% of the total admission in 2010 (n=20,573) and their percentage reduced to 28% of all admissions (n=27,943) in 2017. There was a slight decrease over time in the percentage of admissions in the year who were born at very preterm (from 8% (n=5,057) in 2010 to 6 % (n=5,437) in 2017). Although the actual number of extremely preterm neonates increased, there was a decrease in their percentage among the total admission for each year from 4% (n=2,240) in 2010 to 2% (n=2,401) in 2017. The number of neonates admitted each year by GA group is detailed in Table 14.

Table 14. Number of neonatal admissions by all and each gestational age group in England and Wales from 2010 to 2017

Admission year	Term		Moderate to late preterm		Very preterm		Extremely preterm		All gestational age	
	n	%	n	%	n	%	n	%	n	%
2010	32,567	9	20,573	10	5,057	12	2,240	12	60,437	10
2011	37,883	10	22,260	11	5,161	12	2,407	13	67,711	10
2012	42,176	11	23,970	12	5,200	12	2,463	13	73,809	12
2013	44,727	12	24,433	12	5,269	13	2,406	13	76,835	12
2014	47,870	13	25,248	13	5,188	12	2,337	12	80,643	13
2015	51,088	13	26,148	13	5,331	13	2,414	13	84,981	13
2016	59,339	16	27,593	14	5,463	13	2,491	13	94,886	15
2017	63,760	17	27,943	14	5,437	13	2,401	13	99,541	16
Total	379,410		198,168		42,106		19,159		638,843	



	2010	2011	2012	2013	2014	2015	2016	2017
Extremely preterm	4%	4%	3%	3%	3%	3%	3%	2%
Very preterm	8%	8%	7%	7%	7%	6%	6%	6%
Moderate to late preterm	34%	33%	33%	32%	31%	31%	29%	28%
Term	54%	56%	57%	58%	59%	60%	63%	64%

Figure 30. Percentage of total admissions to neonatal units by gestational age group at birth in England and Wales (2010-2017)

3.5.3 Results for objective 1: What are the most frequently prescribed drugs in neonatal units in England and Wales

Among the 638,843 included neonates, the most frequently prescribed pharmacological group was antibiotics. 66% (n=423,918) of neonates prescribed at least one antibiotic during their neonatal stay. The second most frequently prescribed group was electrolytes and minerals, prescribed to 26% of neonates. The miscellaneous group of drugs included emollients, ocular lubricants, and wound dressings (detailed in 9.12) was the 10th most frequently prescribed pharmacological group (Figure 31).

The most frequently prescribed drug was benzylpenicillin, prescribed to 56% (n=355,679) of neonates at least once during their neonatal stay, closely followed by gentamicin which was prescribed to 54% (n=347,713) of neonates. Sodium was prescribed to 24% of neonates (n=56,109) at least once during their neonatal stay (Figure 32). The top 50 most frequently prescribed drugs are listed in descending order in 9.19 for all and each GA.

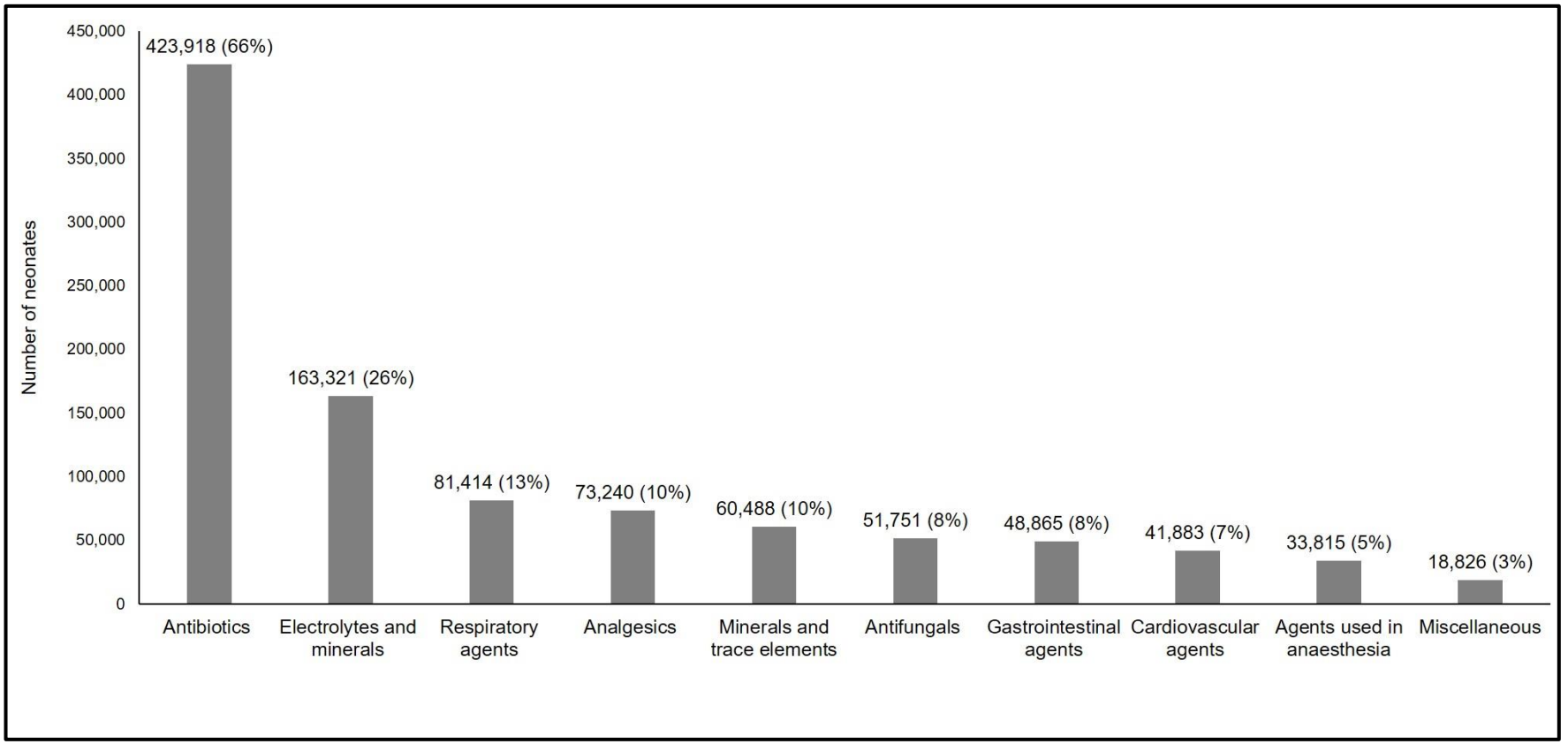


Figure 31. Ten most frequently prescribed pharmacological groups in neonatal units in England and Wales (2010-2017)

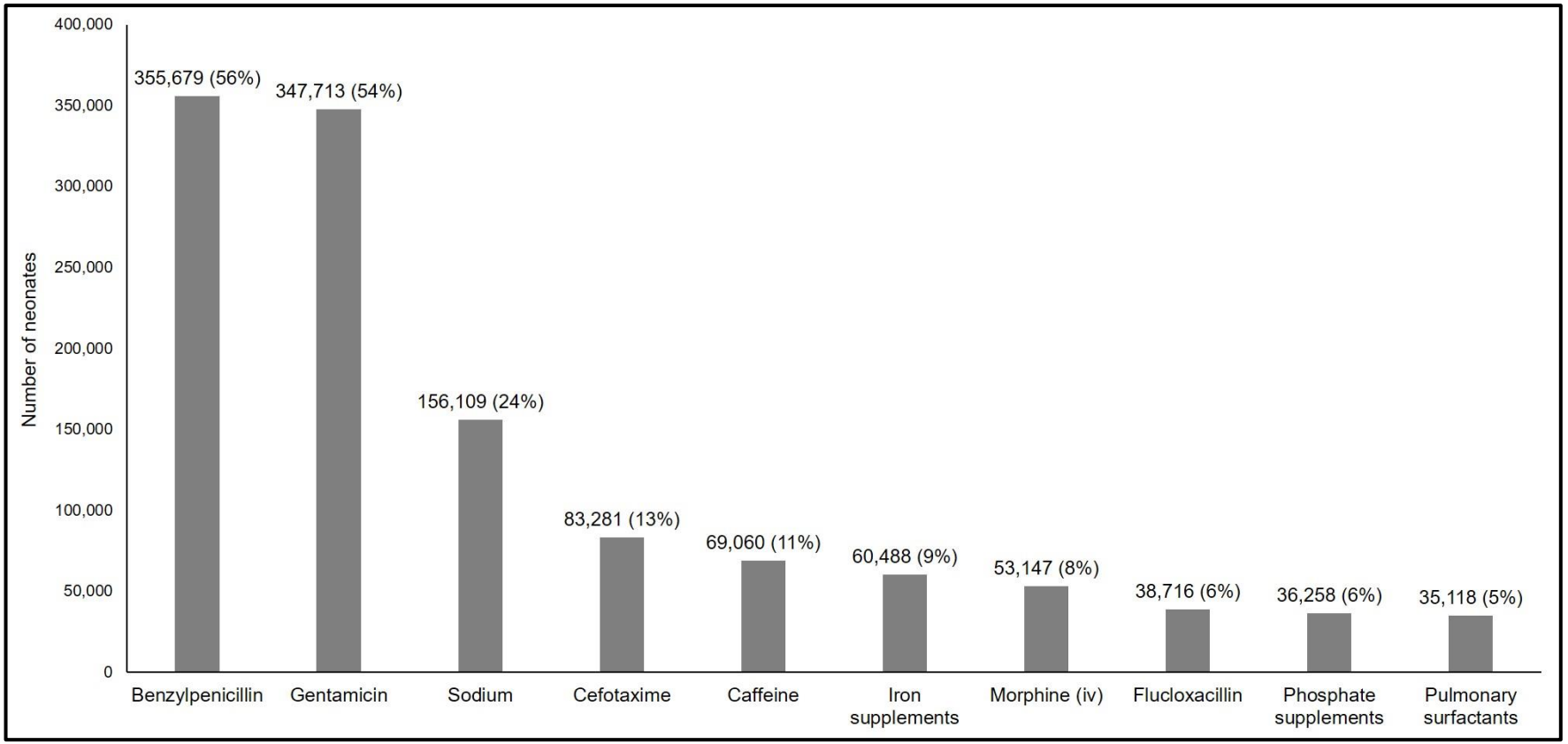


Figure 32. Ten most frequently prescribed individual drugs in neonatal units in England and Wales (2010-2017)

There was a total of 377 different individual drugs prescribed from 2010 to 2017 in neonatal units across England and Wales, after omitting those labelled as excluded drugs. The median (range, IQR) number of drugs prescribed per neonate across neonatal units was 2 (0-69, 0-3). Extremely preterm neonates were prescribed the largest number of drugs and this number decreased with increasing GA (Table 15). The median number of drugs prescribed by neonates was similar for each year of admission (Appendix 9.20).

Overall, half of all days of care were drug free, but there were large differences by GA group (Figure 33). For neonates born extremely preterm, just 3% of days were drug free on average. Moderate to late preterm neonates had the highest proportion of drug free days, 70% on average.

Table 15. Percentage of drug free days across all and each gestational age group

Gestational age groups	All (n=638,843)	Extremely preterm (n=19,159)	Very preterm (n=42,106)	Moderate to late preterm (n=198,168)	Term (n=379,410)
Number of unique drugs per patient median (range, IQR)	2 (0-69,0-3)	17 (0-69,12-25)	8 (0-66,5-11)	2 (0-57,0-3)	2 (0-47,0-3)
Percentage of drug free days median (range, IQR)	50 (0-100,2-100)	3 (0-100,1-10)	10 (0-100,4-36)	70 (0-100,36-100)	40 (0-100,0-100)

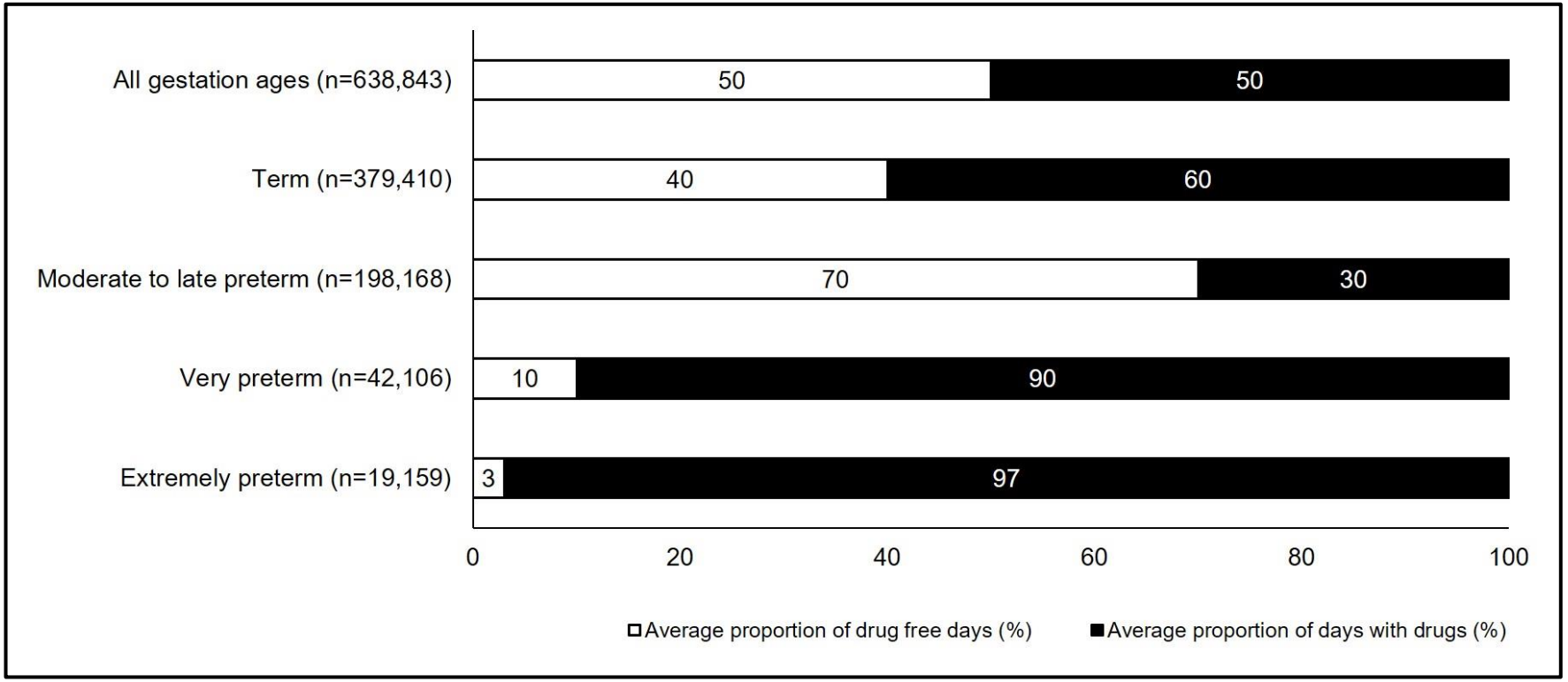


Figure 33. Drug free days (white proportion of the bars represent percentage of total neonatal care days that were drug free)

Caffeine was prescribed to 69,060 neonates at least once and the cumulative number of days of use was 1,381,200. This was followed by benzylpenicillin and gentamicin as they were prescribed for a total 1,067,037 and 1,043,139 days, respectively (Figure 34).

Appendix 9.21 shows the calculated total number of days of use of the top 50 drugs ranked from the highest to lowest number of days of use.

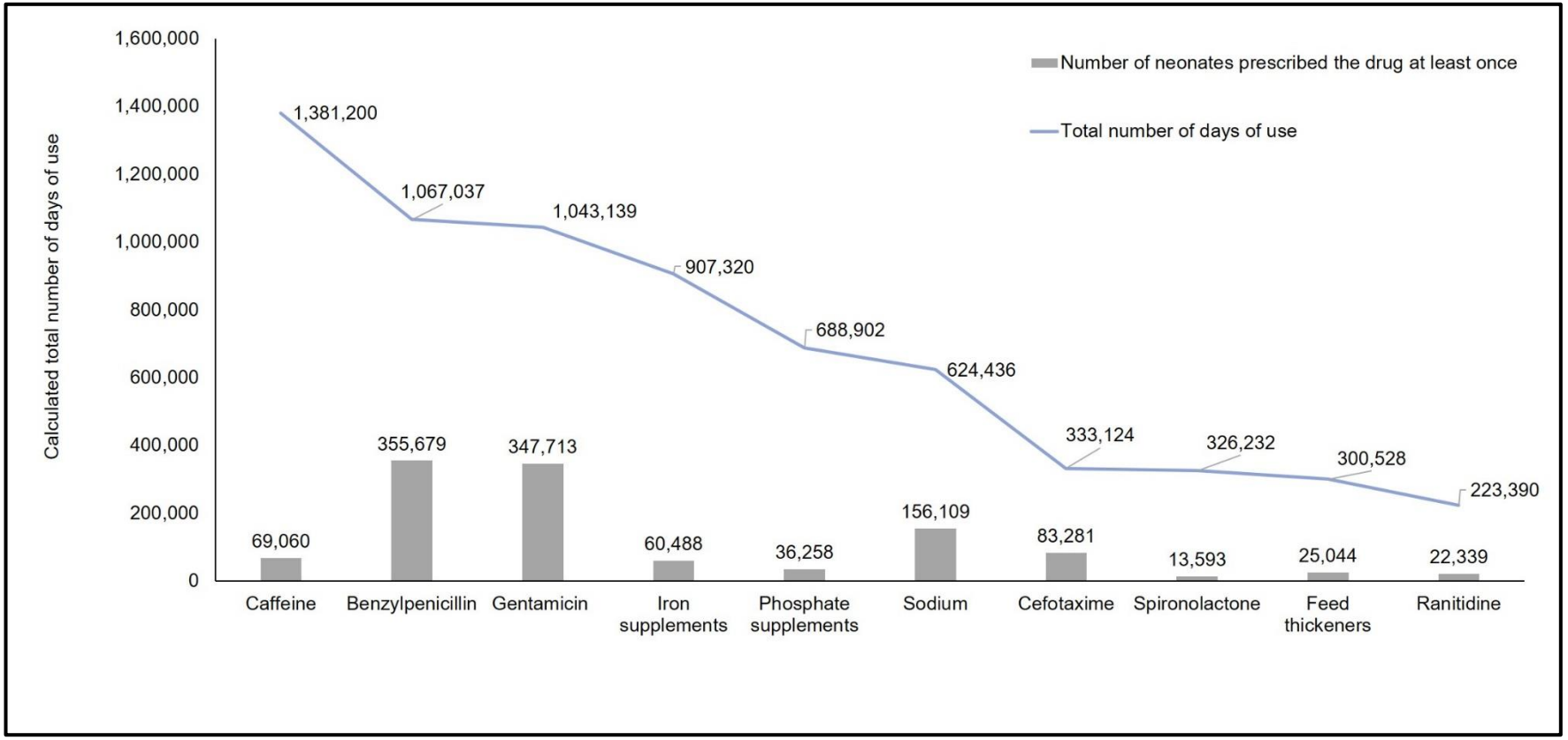


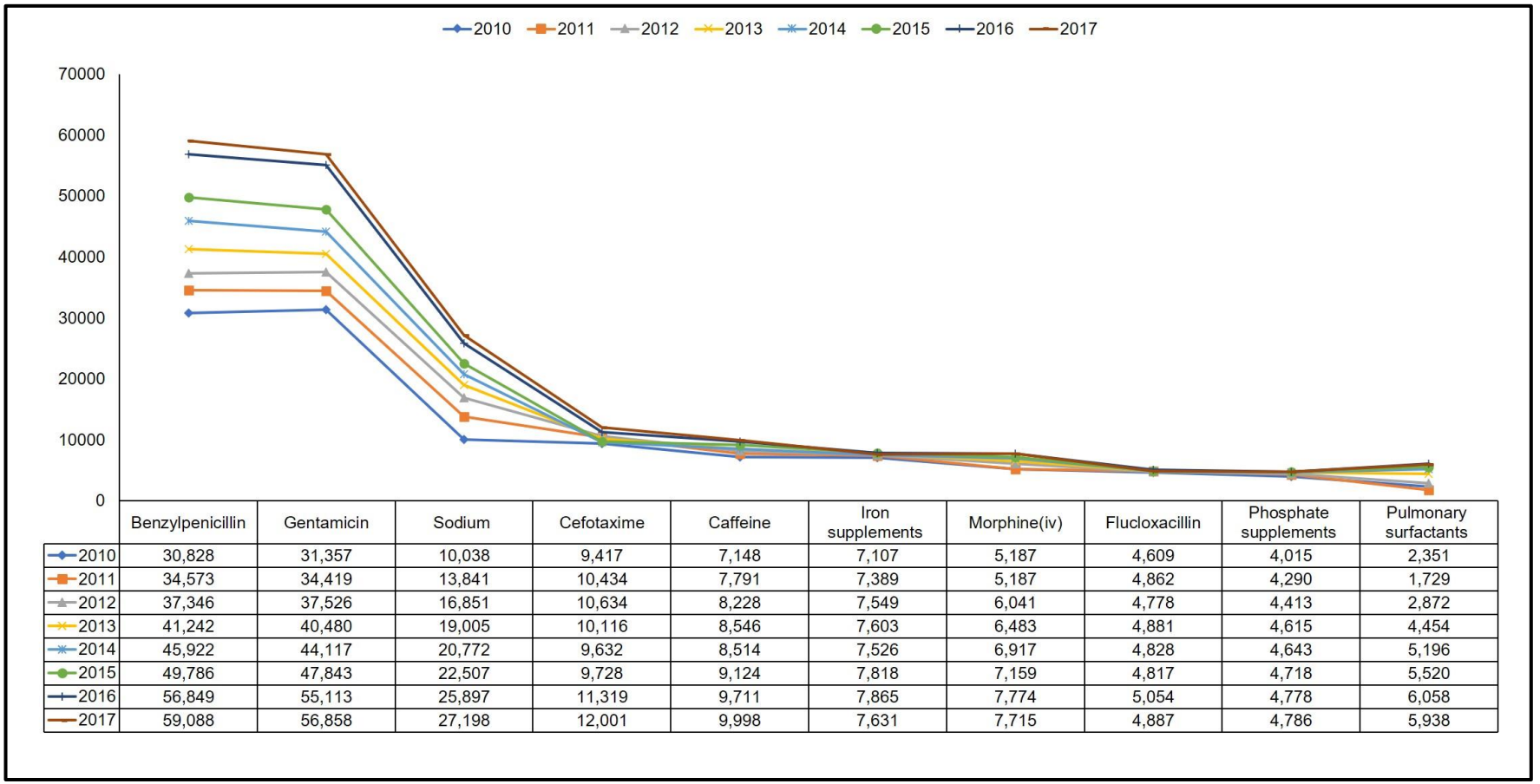
Figure 34. Most frequently prescribed drugs in neonatal units in England and Wales (2010-2017) (measured as the number of days of use of individual drug

3.5.4 Results for objective 2: Have prescribing patterns changed over time?

3.5.4.1 Changes over time in which drugs are most frequently used relative to other drugs

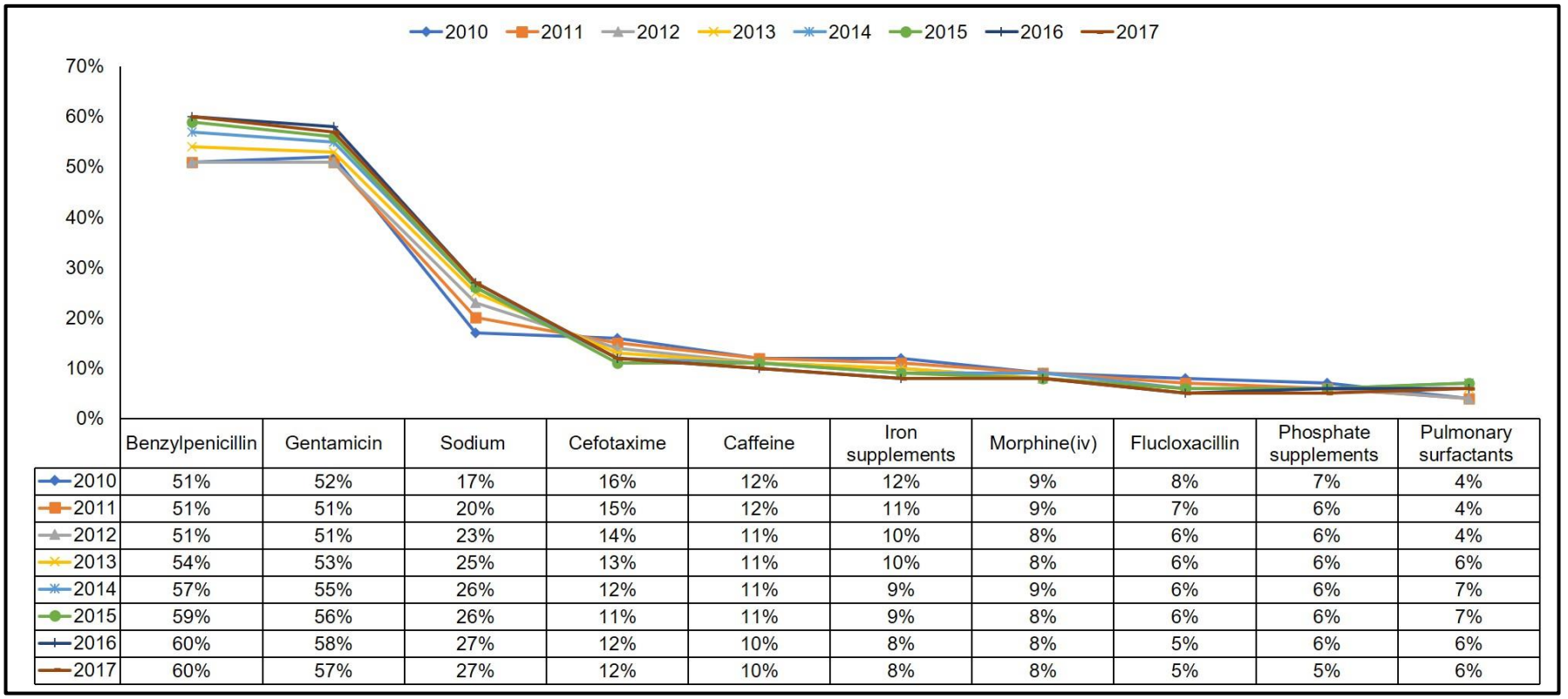
The ten most frequently prescribed drugs identified in section 3.5.3 are here analysed further to investigate changes in the frequency of their prescribing over time.

Figure 35 and Figure 36 show that the number of neonates prescribed benzylpenicillin, gentamicin and pulmonary surfactants at least once, has increased over time. Of the total admissions in each year, the percentage of neonates prescribed benzylpenicillin and gentamicin at least once during their neonatal stay increased from 51% to 60% and from 52% to 57%, respectively from 2010 to 2017 (Figure 36). The percentage of neonates receiving pulmonary surfactants increased from 4% to 6% from 2010 to 2017. The absolute number and percentage of neonates who have been prescribed the remaining seven top ten drugs remained fairly constant over the study period. However, the percentages in Figure 36 are misleading as of the number of term admissions have increased significantly over the years. This inflation can lead to an apparent decrease in the use of drugs that are given only to preterm neonates. Therefore, I have done sub-group analysis for the change in drug use over time in very and extremely preterm neonates' cohort (detailed in 3.5.4.4 and 3.5.4.5).



	Benzylpenicillin	Gentamicin	Sodium	Cefotaxime	Caffeine	Iron supplements	Morphine(iv)	Flucloxacillin	Phosphate supplements	Pulmonary surfactants
2010	30,828	31,357	10,038	9,417	7,148	7,107	5,187	4,609	4,015	2,351
2011	34,573	34,419	13,841	10,434	7,791	7,389	5,187	4,862	4,290	1,729
2012	37,346	37,526	16,851	10,634	8,228	7,549	6,041	4,778	4,413	2,872
2013	41,242	40,480	19,005	10,116	8,546	7,603	6,483	4,881	4,615	4,454
2014	45,922	44,117	20,772	9,632	8,514	7,526	6,917	4,828	4,643	5,196
2015	49,786	47,843	22,507	9,728	9,124	7,818	7,159	4,817	4,718	5,520
2016	56,849	55,113	25,897	11,319	9,711	7,865	7,774	5,054	4,778	6,058
2017	59,088	56,858	27,198	12,001	9,998	7,631	7,715	4,887	4,786	5,938

Figure 35. Absolute numbers of neonates prescribed the most frequently prescribed drugs by year of admission



	Benzylpenicillin	Gentamicin	Sodium	Cefotaxime	Caffeine	Iron supplements	Morphine(iv)	Flucloxacillin	Phosphate supplements	Pulmonary surfactants
2010	51%	52%	17%	16%	12%	12%	9%	8%	7%	4%
2011	51%	51%	20%	15%	12%	11%	9%	7%	6%	4%
2012	51%	51%	23%	14%	11%	10%	8%	6%	6%	4%
2013	54%	53%	25%	13%	11%	10%	8%	6%	6%	6%
2014	57%	55%	26%	12%	11%	9%	9%	6%	6%	7%
2015	59%	56%	26%	11%	11%	9%	8%	6%	6%	7%
2016	60%	58%	27%	12%	10%	8%	8%	5%	6%	6%
2017	60%	57%	27%	12%	10%	8%	8%	5%	5%	6%

Figure 36. Percentage of neonates prescribed the most frequently prescribed drugs by year of admission

3.5.4.2 Changes over time in the average number of days that neonates are given particular drugs

Caffeine and phosphate supplements were prescribed for the highest median number of days compared to other drugs, with a median (IQR) of 20 (9-37) and 15 (6-34) days, respectively (Table 16). Table 17 shows the median number of days of exposure (IQR) for the ten most frequently prescribed individual drugs, for each GA group. The median number of days on which neonates were prescribed these drugs amongst neonates prescribed the drug on at least one day was higher with increasing prematurity. This was found, for example, with gentamicin, in which number of days was higher in extremely preterm neonates compared to term neonates, with a median (IQR) of 8 (4-14) and 3 (2-4) respectively. This was also true for caffeine, in which the number of days of drug exposure decreased from 48 (37-60) to 1 (1-3) in extremely preterm and term neonates, respectively.

Table 16. Number of days of exposure to the most frequently prescribed drugs (by year of admission)

Drug	All (n=638,843)	2010 (n=60,437)	2011 (n=67,711)	2012 (n=73,809)	2013 (n=76,835)	2014 (n=80,643)	2015 (n=84,981)	2016 (n=94,886)	2017 (n=99,541)
Benzyl-penicillin	3 (2-4)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)
Gentamicin	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-4)	3 (2-4)
Sodium	4 (2-8)	5 (2-18)	4 (2-13)	4 (2-10)	4 (2-9)	4 (2-8)	3 (2-7)	3 (2-7)	3 (2-6)
Cefotaxime	4 (2-6)	4 (2-6)	4 (2-6)	4 (2-6)	4 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-5)
Caffeine	20 (9-37)	20 (9-36)	21 (10-37)	20 (9-37)	20 (9-38)	20 (9-37)	20 (9-37)	20 (9-38)	20 (9-37)
Iron supplements	15 (6-34)	15 (6-23)	15 (6-33)	16 (6-34)	15 (6-34)	15 (6-35)	16 (6-35)	16 (6-36)	16 (6-35)
Morphine (IV)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)
Flucloxacillin	4 (3-7)	5 (3-7)	5 (3-7)	5 (3-7)	5 (3-7)	4 (3-7)	4 (3-7)	4 (3-7)	4 (3-7)
Phosphate supplements	19 (9-38)	20 (9-37)	19 (9-36)	20 (9-39)	19 (8-37)	19 (8-37)	19 (9-37)	20 (9-39)	19 (8-39)

n, number of neonates (population size)
Pulmonary surfactants are not reported since they are prescribed as one dose only
All figures are median (interquartile range)

Table 17. Number of days of exposure to the most frequently prescribed drugs (by gestational age groups)

Drug	All gestational age group (n=638,843)	Term (n=379,410)	Moderate to late preterm (n=198,168)	Very preterm (n=42,106)	Extremely preterm (n=19,159)
Benzylpenicillin	3 (2-4)	3 (2-4)	3 (2-4)	4 (3-5)	4 (3-6)
Gentamicin	3 (2-5)	3 (2-4)	3 (2-4)	4 (3-6)	8 (4-14)
Sodium	4 (2-8)	3 (2-4)	3 (2-5)	13 (5-27)	39 (15-63)
Cefotaxime	4 (2-6)	3 (2-5)	3 (2-5)	5 (3-8)	7 (4-12)
Caffeine	20 (9-37)	1 (1-3)	7 (4-10)	22 (14-31)	48 (37-60)
Iron supplements	15 (6-34)	6 (2-14)	5 (2-11)	16 (8-28)	47 (29-67)
Morphine (IV)	3 (2-7)	3 (2-5)	2 (1-4)	3 (1-5)	8 (3-19)
Flucloxacillin	4 (3-7)	3 (2-5)	4 (2-6)	5 (3-7)	7 (4-12)
Phosphate supplements	19 (9-38)	5 (2-11)	8 (5-14)	19 (10-31)	40 (20-61)

n, number of neonates (population size)
All figures are median (interquartile range)

3.5.4.3 Change in drug use in the full cohort (all GA)

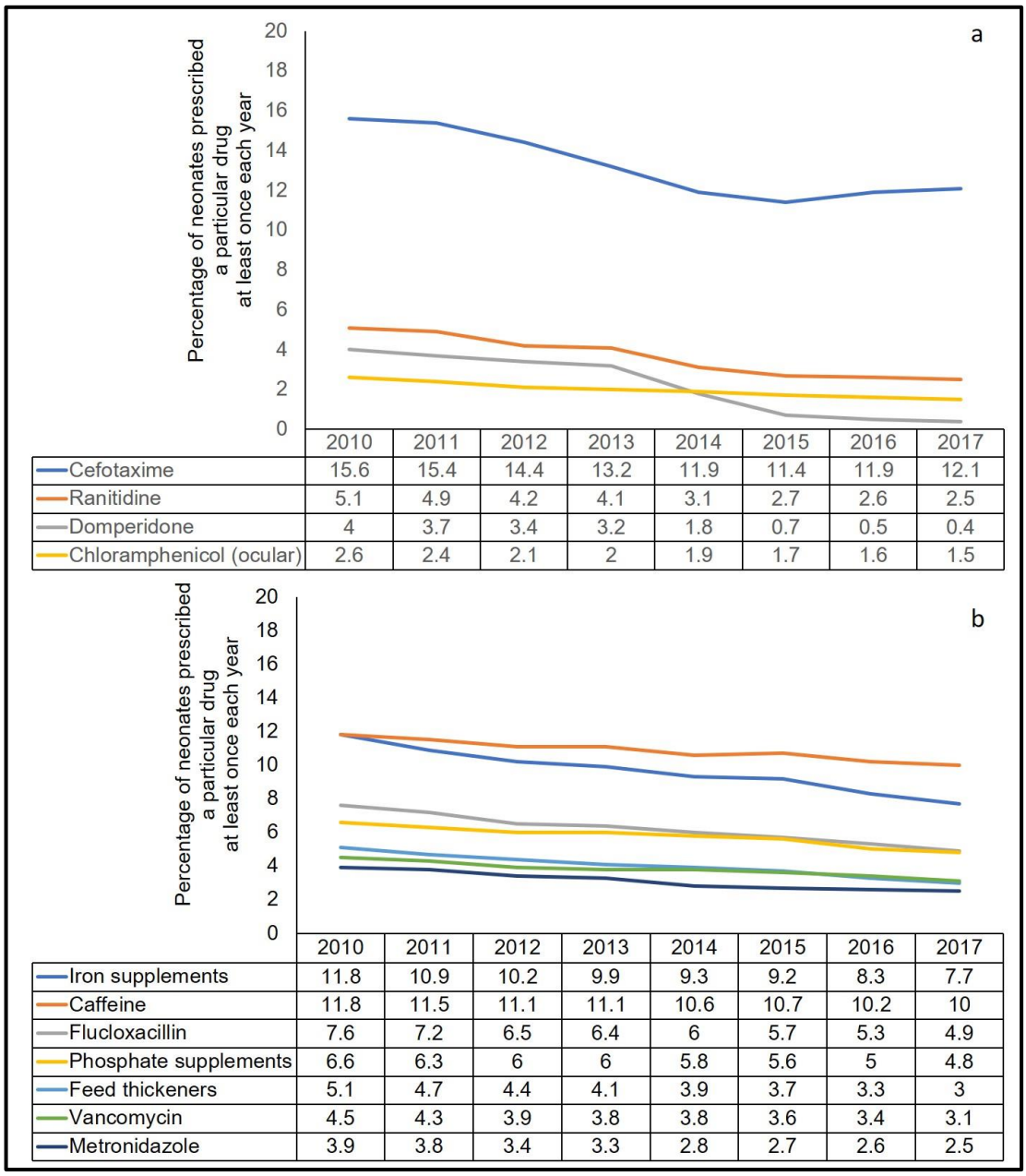
There were 20 drugs that had a calculated range of change in frequency of use between the years in the study period greater than one percent (detailed in 9.15). The percentage of neonates receiving the drug at least once increased for some drugs (n=5) and decreased for others (n=12) while four drugs showed a fluctuation in use over the years (n=3).

Overall decrease: 12 drugs had an overall decrease in their use over the years. This change in use could be attributed to either safety issues or factors related to their use in different neonatal gestational age groups. I have divided them into three groups of drugs: those with a decrease in their use that may be due to safety concerns, those where the decrease may be due to changes in the proportion of admitted neonates over the years based on their GA, and those where the decrease may be associated with lack of evidence of effectiveness.

Safety concerns: the percentage of neonates who have been prescribed cefotaxime, domperidone, ranitidine, and ocular chloramphenicol (Figure 37.a) at least once decreased from 2010 to 2017. This may be related to safety concerns associated with their use in neonates, which is detailed in the discussion. The percentage of neonates who have been prescribed cefotaxime decreased over time in general from 15.6% (9,417 neonates) in 2010 to 12.1 % (12,001 neonates) in 2017, with 3.5% absolute decrease from 2010 to 2017. The percentage of neonates who have been prescribed domperidone at least once decreased from 4% (2,406 neonates) in 2010 to 0.4% (377 neonates) in 2017, i.e. a 3.6 % absolute decrease in use. The

percentage of neonates who have been prescribed ranitidine at least once decreased from 5.1% (3,100 neonates) in 2010 to 2.5 % (2,504 neonates) in 2017, with a 2.6% absolute decrease from 2010 to 2017. Percentage of neonates who have been prescribed ocular chloramphenicol decreased steadily from 2.6% (1,567 neonates) in 2010 to 1.5% (1,525 neonates) in 2017, with 1.1% absolute decrease from 2010 to 2017.

Changes in population composition: The percentage of neonates who have been prescribed flucloxacillin, vancomycin, metronidazole, caffeine, feed thickeners, and supplements (iron, phosphates) at least once have decreased from 2010 to 2017 (Figure 37.b). All these drugs are known to be prescribed to preterm neonates and their decrease in use might be attributed to the change in the population composition of the study cohort, detailed in the discussion.



	2010	2011	2012	2013	2014	2015	2016	2017
Cefotaxime	15.6	15.4	14.4	13.2	11.9	11.4	11.9	12.1
Ranitidine	5.1	4.9	4.2	4.1	3.1	2.7	2.6	2.5
Domperidone	4	3.7	3.4	3.2	1.8	0.7	0.5	0.4
Chloramphenicol (ocular)	2.6	2.4	2.1	2	1.9	1.7	1.6	1.5

	2010	2011	2012	2013	2014	2015	2016	2017
Iron supplements	11.8	10.9	10.2	9.9	9.3	9.2	8.3	7.7
Caffeine	11.8	11.5	11.1	11.1	10.6	10.7	10.2	10
Flucloxacillin	7.6	7.2	6.5	6.4	6	5.7	5.3	4.9
Phosphate supplements	6.6	6.3	6	6	5.8	5.6	5	4.8
Feed thickeners	5.1	4.7	4.4	4.1	3.9	3.7	3.3	3
Vancomycin	4.5	4.3	3.9	3.8	3.8	3.6	3.4	3.1
Metronidazole	3.9	3.8	3.4	3.3	2.8	2.7	2.6	2.5

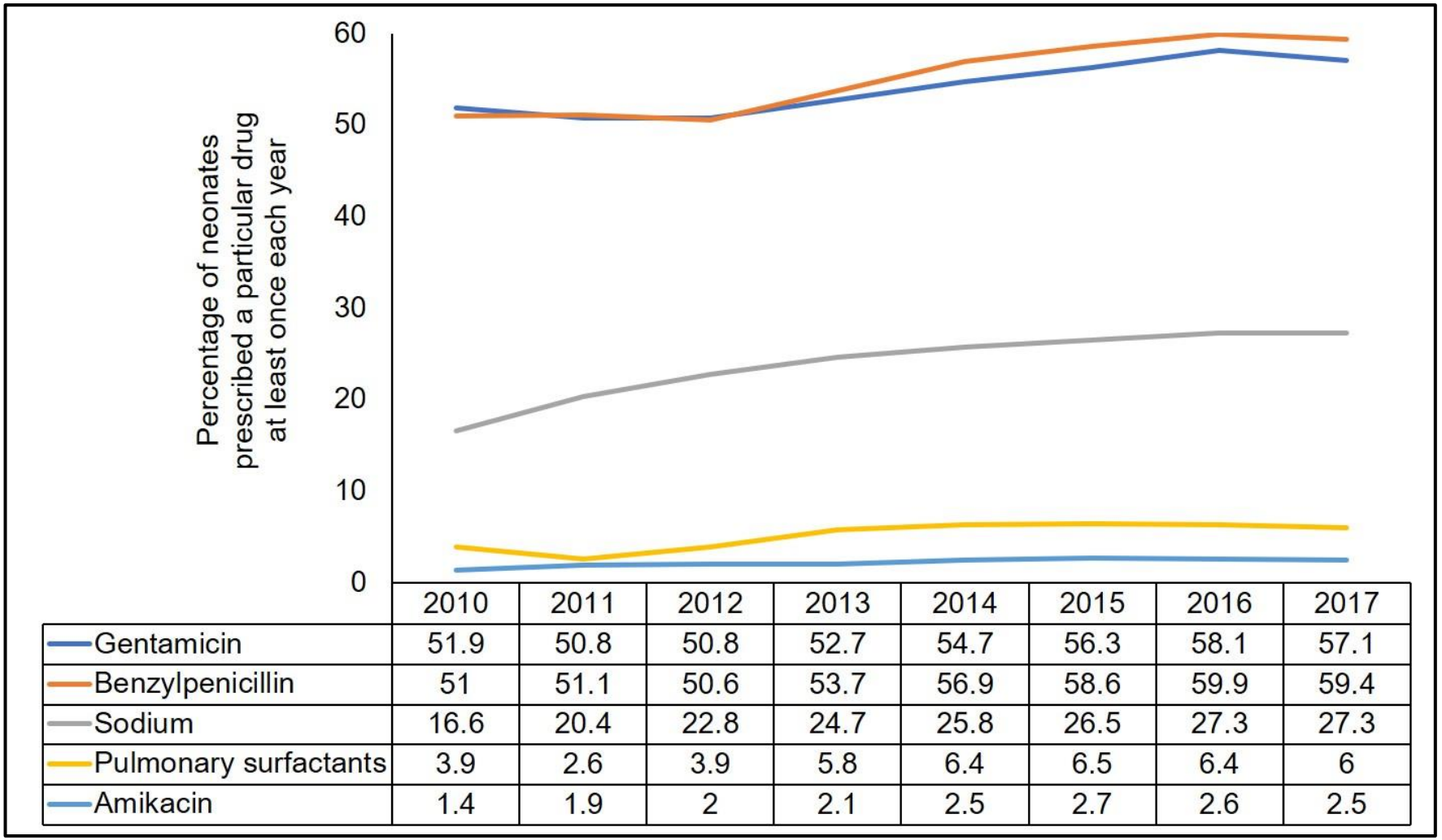
Figure 37. Drugs with an overall decrease in the percentage of neonates receiving it at least once from 2010 to 2017 a. safety concerns b. changes in population

Lack of evidence: The percentage of neonates who have been prescribed topical nystatin at least once decreased from 5.1% (4,096 neonates) in 2014 to 3.9% (3,868 neonates) in 2017, with 1.3% absolute decrease from 2010 to 2017, which might be attributed to the lack of evidence that supports its effectiveness in the neonatal population.

Overall increase: Five drugs were found to have an overall increase in their use over time; sodium, benzylpenicillin, gentamicin, amikacin, and pulmonary surfactants (Figure 38).

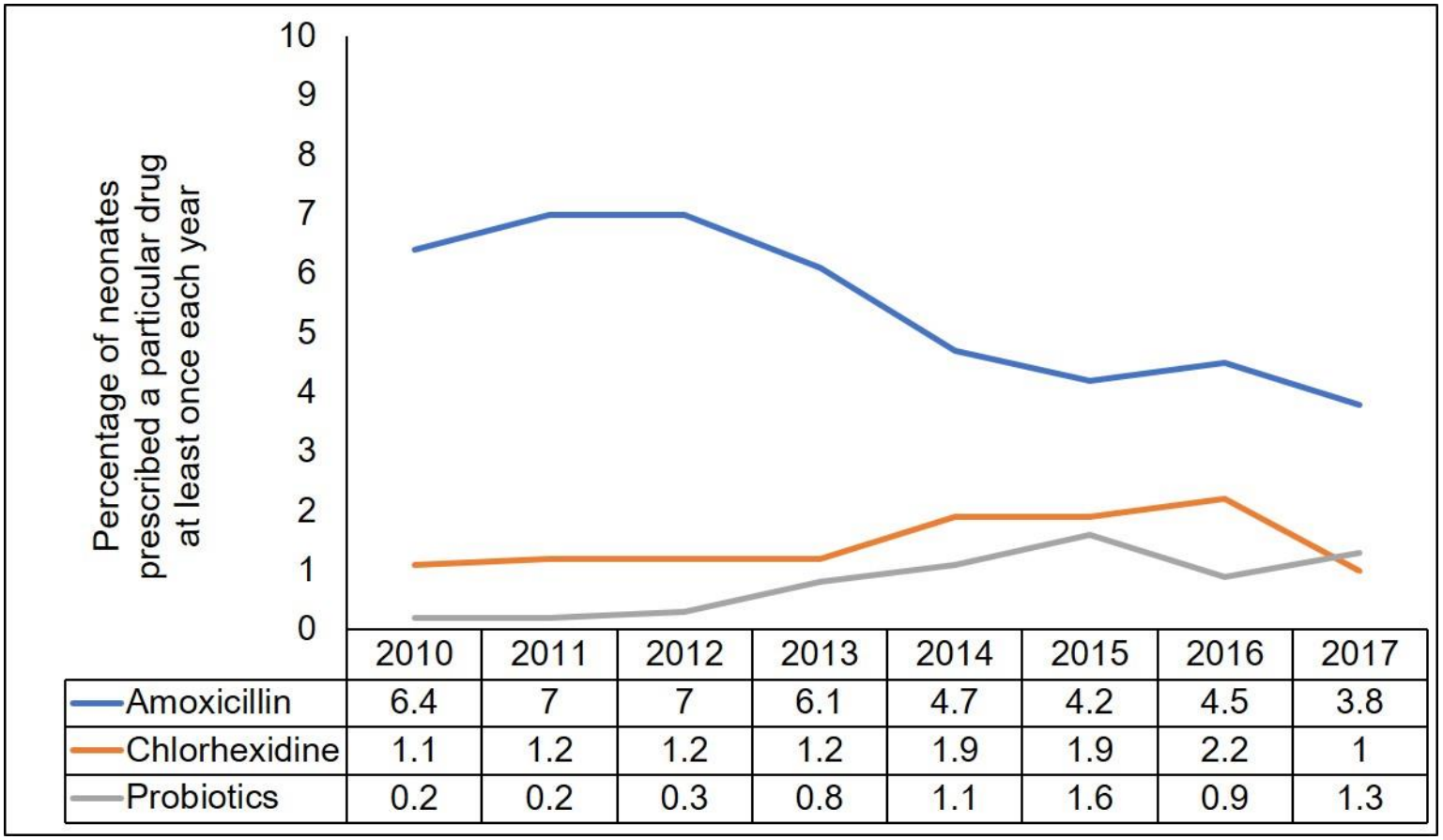
The percentage of neonates who have been prescribed sodium at least once increased from 16.6% (10,038 neonates) in 2010 to 27.3% (27,198 neonates) in 2017, with 10.7% absolute increase from 2010 to 2017. Amongst the antibiotics, benzylpenicillin had the highest percentage of increase over time. The percentage of neonates who have been prescribed benzylpenicillin at least once increased from 51% (30,828 neonates) in 2010 to 59.4% (59,088 neonates) in 2017, with 8.4% absolute increase from 2010 to 2017. With regard to pulmonary surfactants, the percentage of neonates who have been prescribed these agents at least once increased from 3.9% (2,351 neonates) in 2010 to 6% (5,938 neonates) in 2017, with 2.1% absolute increase from 2010 to 2017.

Fluctuated: The percentage of neonates receiving amoxicillin, probiotics, and chlorhexidine at least once fluctuated over time (Figure 39).



	2010	2011	2012	2013	2014	2015	2016	2017
Gentamicin	51.9	50.8	50.8	52.7	54.7	56.3	58.1	57.1
Benzylpenicillin	51	51.1	50.6	53.7	56.9	58.6	59.9	59.4
Sodium	16.6	20.4	22.8	24.7	25.8	26.5	27.3	27.3
Pulmonary surfactants	3.9	2.6	3.9	5.8	6.4	6.5	6.4	6
Amikacin	1.4	1.9	2	2.1	2.5	2.7	2.6	2.5

Figure 38. Drugs with an overall increase in the percentage of neonates receiving it at least once from 2010 to 2017



	2010	2011	2012	2013	2014	2015	2016	2017
Amoxicillin	6.4	7	7	6.1	4.7	4.2	4.5	3.8
Chlorhexidine	1.1	1.2	1.2	1.2	1.9	1.9	2.2	1
Probiotics	0.2	0.2	0.3	0.8	1.1	1.6	0.9	1.3

Figure 39. Drugs fluctuated in the percentage of neonates receiving it at least once from 2010 to 2017

3.5.4.4 Change in drug use among very preterm neonates

There were 26 drugs that had a calculated range value greater than three percent (detailed in 9.16). Some of these drugs had an overall increase in their use (n=10) or an overall decrease in their use (n=1). Others displayed fluctuations in use over the years (n=15). Those with fluctuations in their use are detailed in 9.22.

Overall decrease: Percentage of very preterm neonates who have been prescribed domperidone at least once each admission year was found to be continuously decreased from 17.8% (899 neonates) in 2010 to 2.6% (139 neonates) in 2017, with 15.2% absolute decrease from 2010 to 2017 (Figure 40).

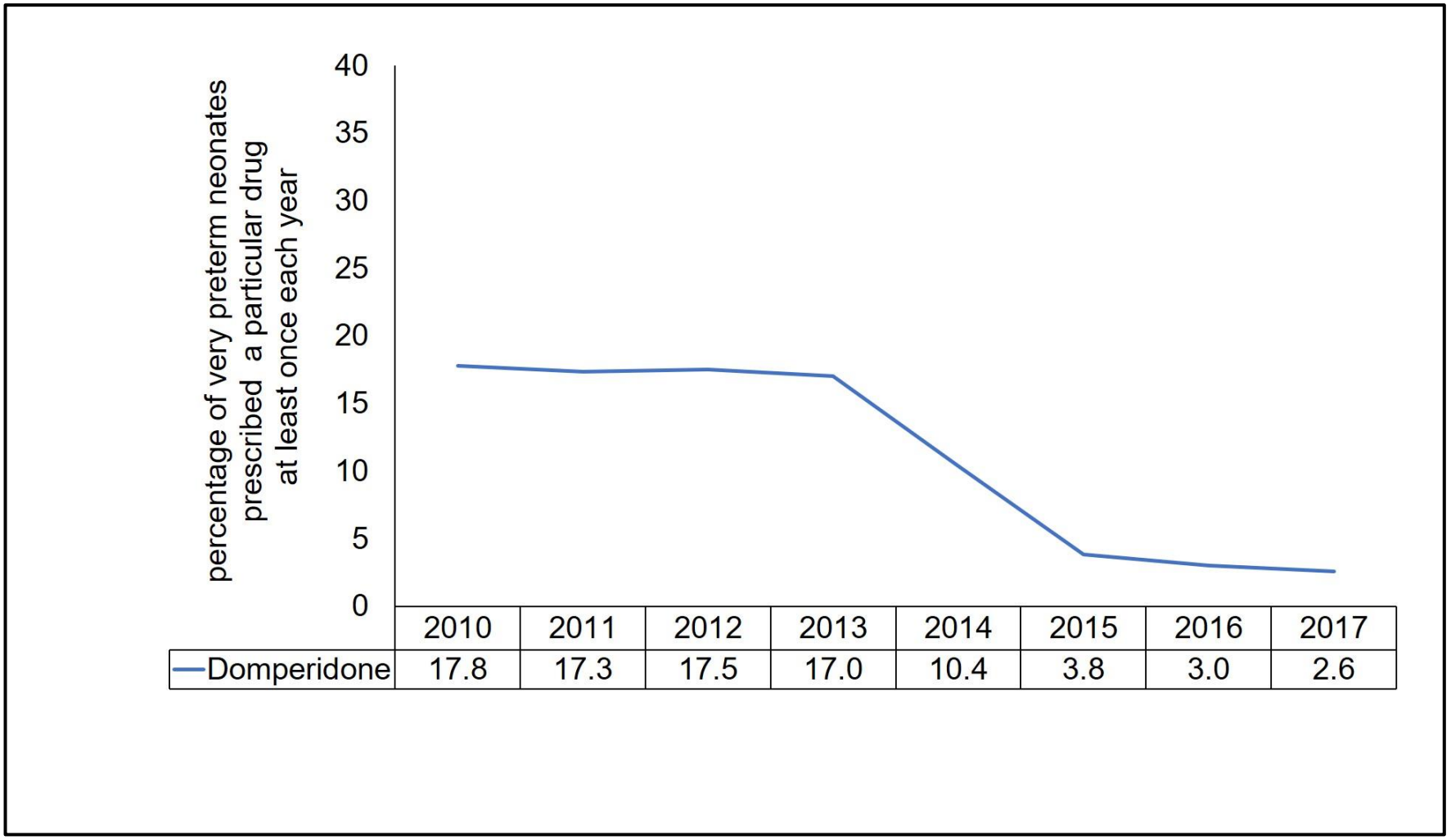
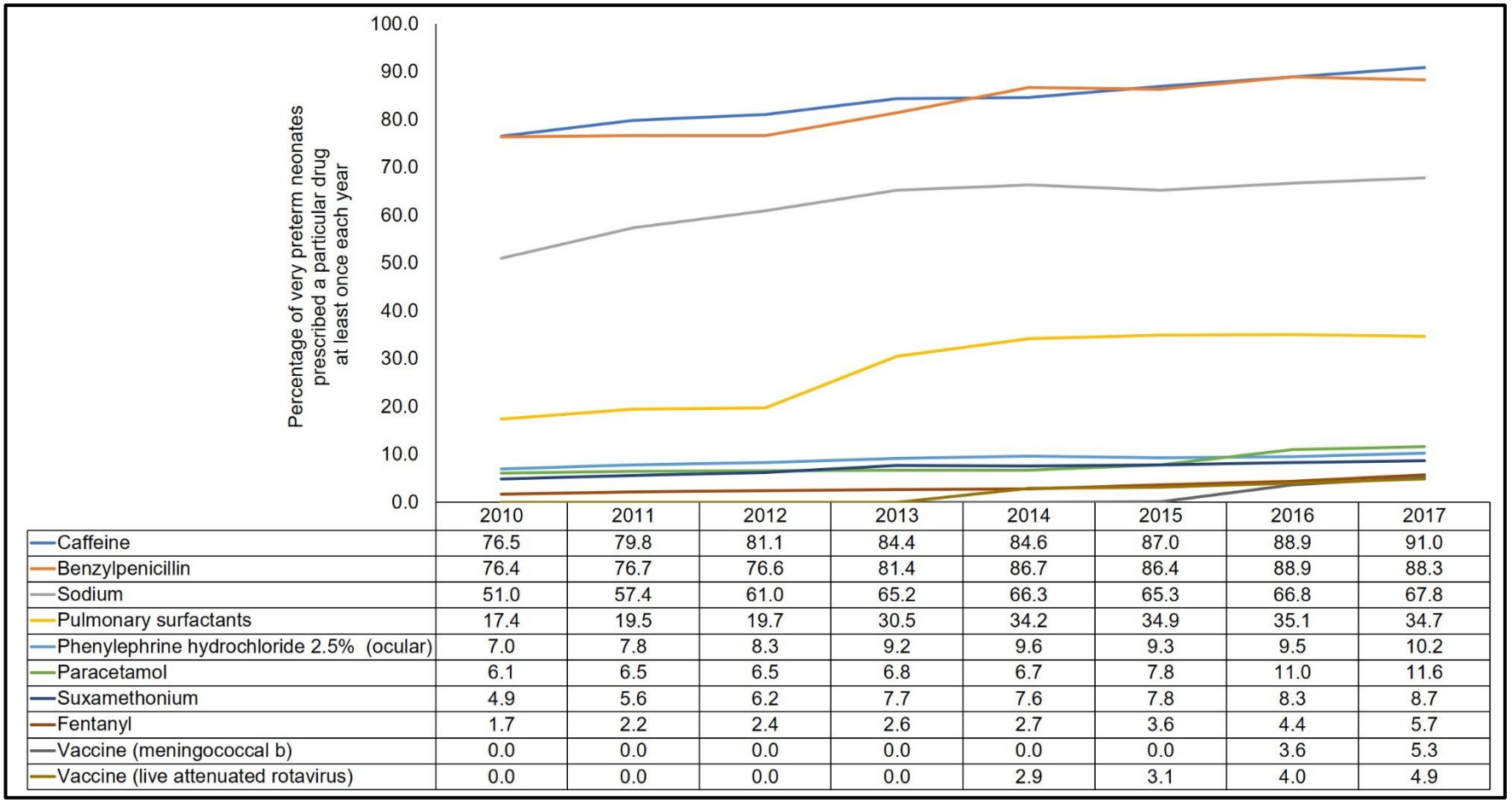


Figure 40. Overall decrease in the percentage of very preterm neonates receiving domperidone at least once from 2010 to 2017

Overall increase: 10 drugs were found to have an overall increase in the percentage of very preterm neonates receiving it at least once (Figure 41). The percentage of very preterm neonates who have been prescribed caffeine at least once had increased from 76.5% (3,868 neonates) in 2010 to 91% (4,945 neonates) in 2017, with 14.5% absolute increase from 2010 to 2017. This was followed by benzylpenicillin in which the percentage of neonates that have been prescribed this drug at least once was 76.4% (3,865 neonates) in 2010 to 88.3% (4,801 neonates) in 2017, and with 11.9% absolute increase from 2010 to 2017. The percentage of very preterm neonates who have been prescribed pulmonary surfactants at least once also noticeably increased from 17.4% (880 neonates) in 2010 to 34.7% (1,885 neonates) in 2017, with 17.3% absolute increase from 2010 to 2017.



	2010	2011	2012	2013	2014	2015	2016	2017
Caffeine	76.5	79.8	81.1	84.4	84.6	87.0	88.9	91.0
Benzylpenicillin	76.4	76.7	76.6	81.4	86.7	86.4	88.9	88.3
Sodium	51.0	57.4	61.0	65.2	66.3	65.3	66.8	67.8
Pulmonary surfactants	17.4	19.5	19.7	30.5	34.2	34.9	35.1	34.7
Phenylephrine hydrochloride 2.5% (ocular)	7.0	7.8	8.3	9.2	9.6	9.3	9.5	10.2
Paracetamol	6.1	6.5	6.5	6.8	6.7	7.8	11.0	11.6
Suxamethonium	4.9	5.6	6.2	7.7	7.6	7.8	8.3	8.7
Fentanyl	1.7	2.2	2.4	2.6	2.7	3.6	4.4	5.7
Vaccine (meningococcal b)	0.0	0.0	0.0	0.0	0.0	0.0	3.6	5.3
Vaccine (live attenuated rotavirus)	0.0	0.0	0.0	0.0	2.9	3.1	4.0	4.9

Figure 41. Drugs with an overall increase in the percentage of very preterm neonates receiving it at least once from 2010 to 2017

3.5.4.5 Change in drug use among extremely preterm neonates

There were 43 drugs that had a calculated range value greater than five percent (detailed in 9.17). Some of these drugs had an overall increase in the percentage of extremely preterm neonates receiving it at least once (n=11) or an overall decrease in the percentage of extremely preterm neonates receiving it at least once (n=1). Others displayed fluctuations in the percentage of extremely preterm neonates receiving it at least once (n=31). Those with fluctuations in their use are tabulated in 9.23.

Overall decrease: The percentage of extremely preterm neonates who have been prescribed domperidone at least once have decreased from 31.2% (699 neonates) in 2010 to 5.8% (139 neonates) in 2017, with 25.4% absolute decrease from 2010 to 2017 (Figure 42).

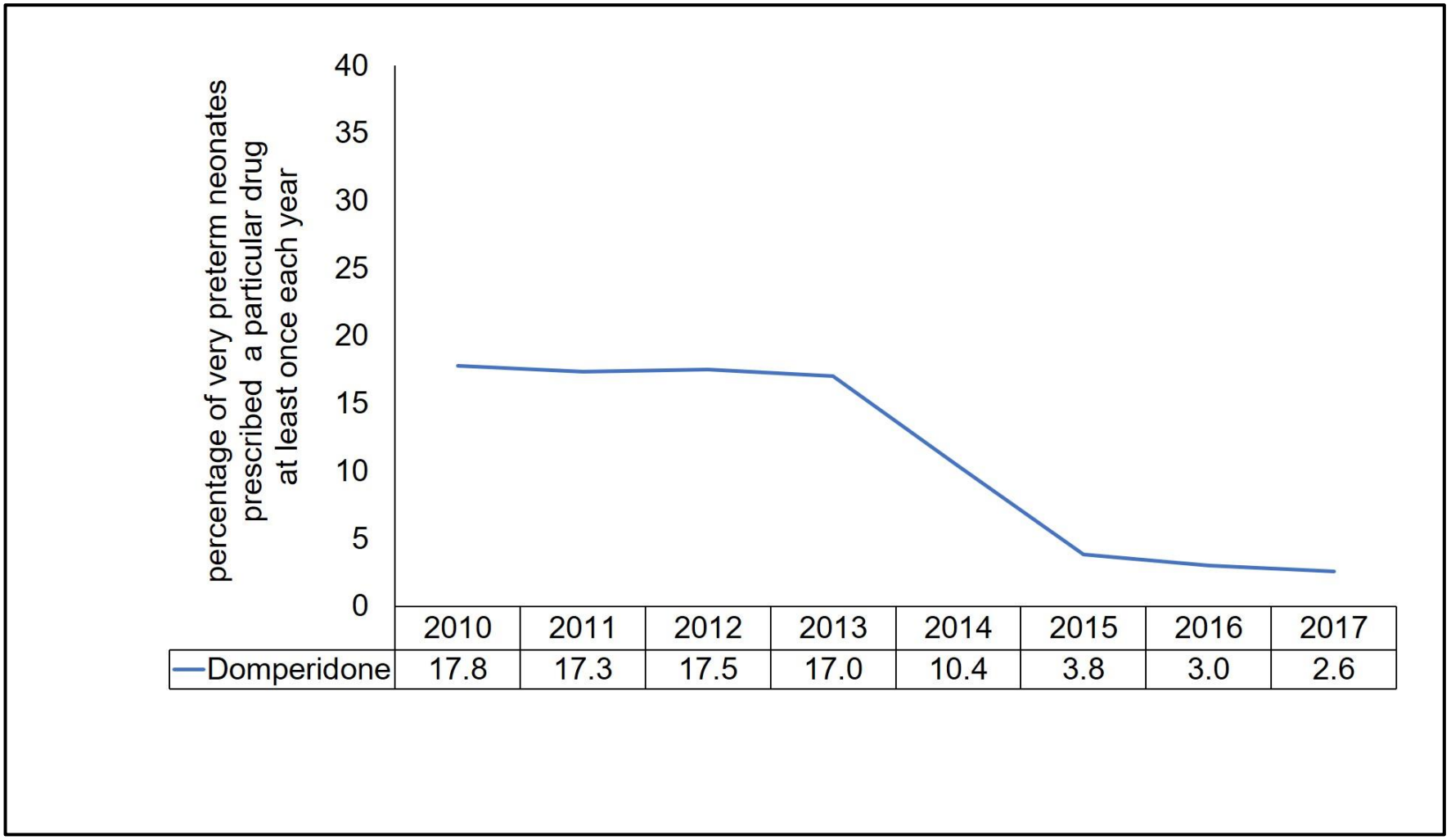
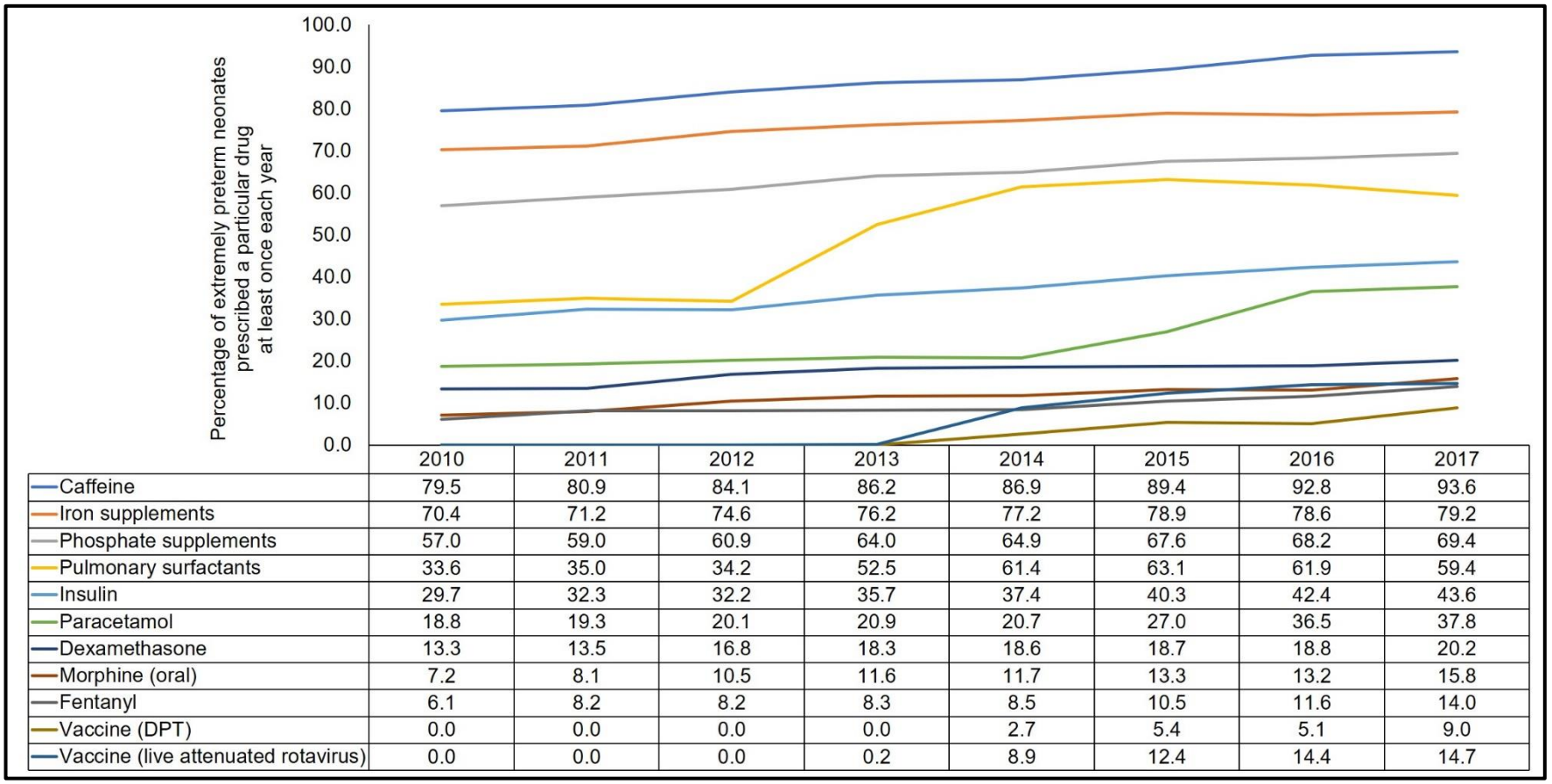


Figure 42. Overall decrease in the percentage of extremely preterm neonates receiving domperidone at least once from 2010 to 2017

Overall increase: One of the most obvious drugs that can be extracted from Figure 43 in terms of its increase in prescribing in this cohort is pulmonary surfactants. Despite the three minor decrease in the percentage of neonates being prescribed those agents in 2012, 2016 and 2017, the use of those agents has been found to be increased over time. The percentage of extremely preterm neonates who have been prescribed paracetamol at least once increased from 18.8% (420 neonates) in 2010 to 37.8% (907 neonates) in 2017, with 19% absolute increase from 2010 to 2017. Similarly, in the very preterm neonates, the percentage of extremely preterm neonates who have been prescribed caffeine at least once increased from 79.5% (1,781 neonates) in 2010 to 93.6% (2,248 neonates) in 2017, with 14.1% absolute increase from 2010 to 2017.



	2010	2011	2012	2013	2014	2015	2016	2017
Caffeine	79.5	80.9	84.1	86.2	86.9	89.4	92.8	93.6
Iron supplements	70.4	71.2	74.6	76.2	77.2	78.9	78.6	79.2
Phosphate supplements	57.0	59.0	60.9	64.0	64.9	67.6	68.2	69.4
Pulmonary surfactants	33.6	35.0	34.2	52.5	61.4	63.1	61.9	59.4
Insulin	29.7	32.3	32.2	35.7	37.4	40.3	42.4	43.6
Paracetamol	18.8	19.3	20.1	20.9	20.7	27.0	36.5	37.8
Dexamethasone	13.3	13.5	16.8	18.3	18.6	18.7	18.8	20.2
Morphine (oral)	7.2	8.1	10.5	11.6	11.7	13.3	13.2	15.8
Fentanyl	6.1	8.2	8.2	8.3	8.5	10.5	11.6	14.0
Vaccine (DPT)	0.0	0.0	0.0	0.0	2.7	5.4	5.1	9.0
Vaccine (live attenuated rotavirus)	0.0	0.0	0.0	0.2	8.9	12.4	14.4	14.7

Figure 43. Drugs with an overall increase in the percentage of extremely preterm neonates receiving it at least once from 2010 to 2017

3.5.5 Results for objective 3: Are there any variations in prescribing according to gestational age and birth weight of neonates and treatment location?

GA category: Benzylpenicillin and gentamicin were the most frequently prescribed drugs in term and moderate to late preterm neonates, whereas caffeine was the most frequently prescribed drug in very preterm and extremely preterm neonates (Figure 44). The average duration of drug exposure in days for the most frequently prescribed drugs was similar in each gestational age group (detailed in 9.24).

BW category: Benzylpenicillin and gentamicin were the most frequently prescribed drugs in normal, LBW and VLBW neonates. Caffeine was the most frequently prescribed drug in extremely LBW neonates (Figure 45).

The average duration of drug exposure in days for the most frequently prescribed drugs was similar in each BW group (detailed in 9.25).

Unit level: There was no difference in the most frequently prescribed drugs according to the unit level of care; benzylpenicillin and gentamicin were the most frequently prescribed drugs in all unit levels (Figure 46).

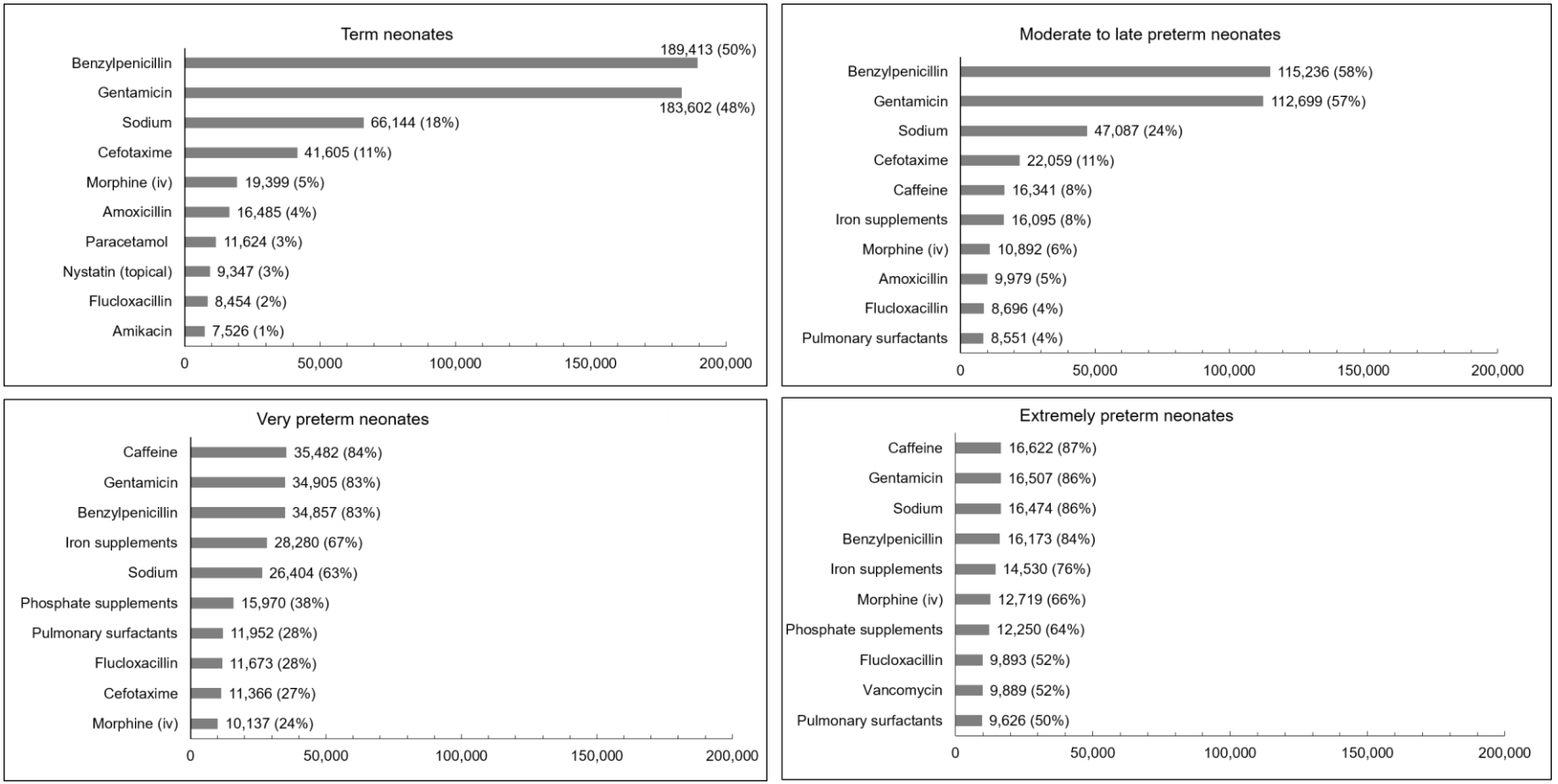


Figure 44. Most frequently prescribed drugs by gestational age group

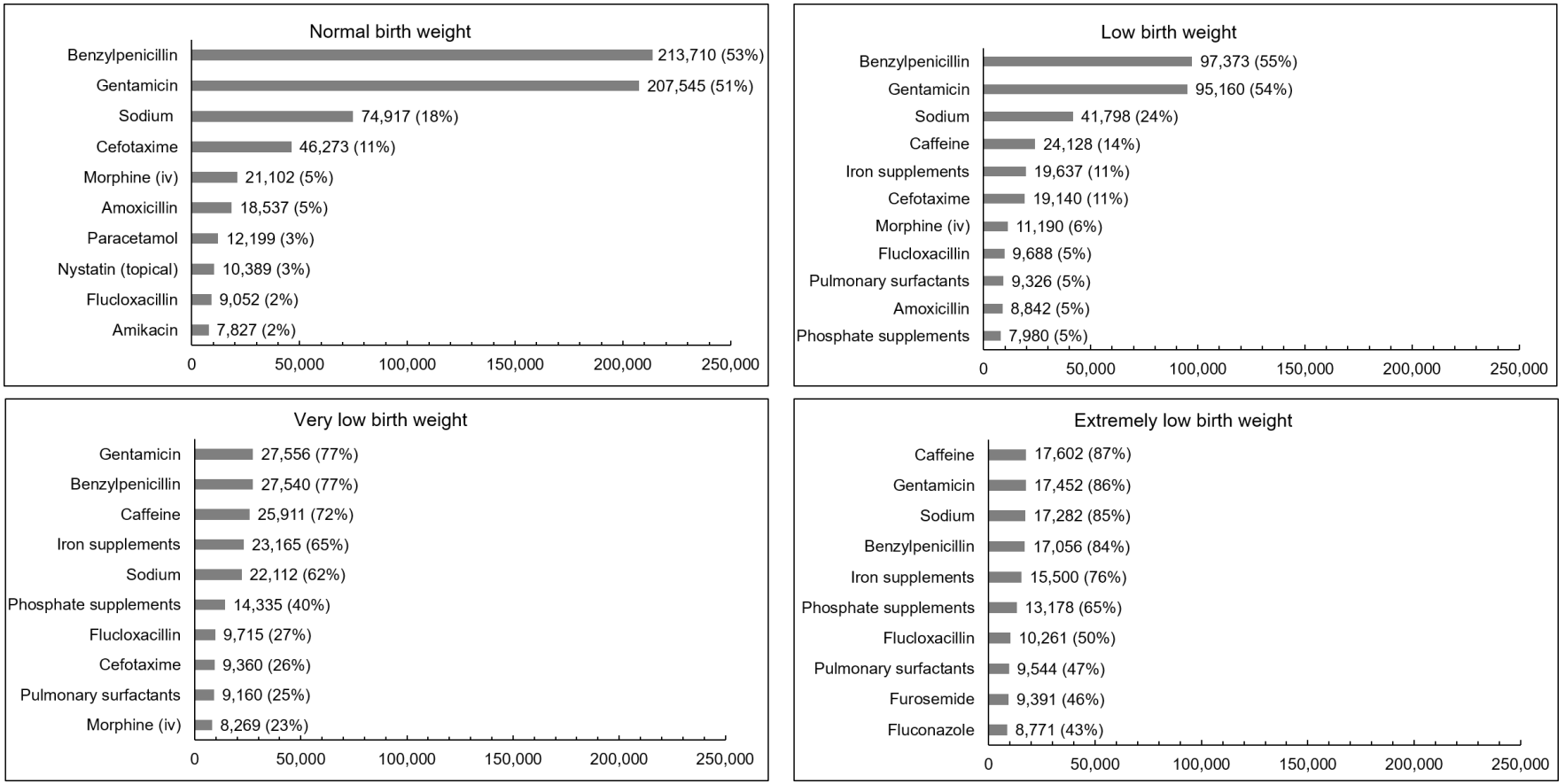


Figure 45. Most frequently prescribed drugs by birth weight group

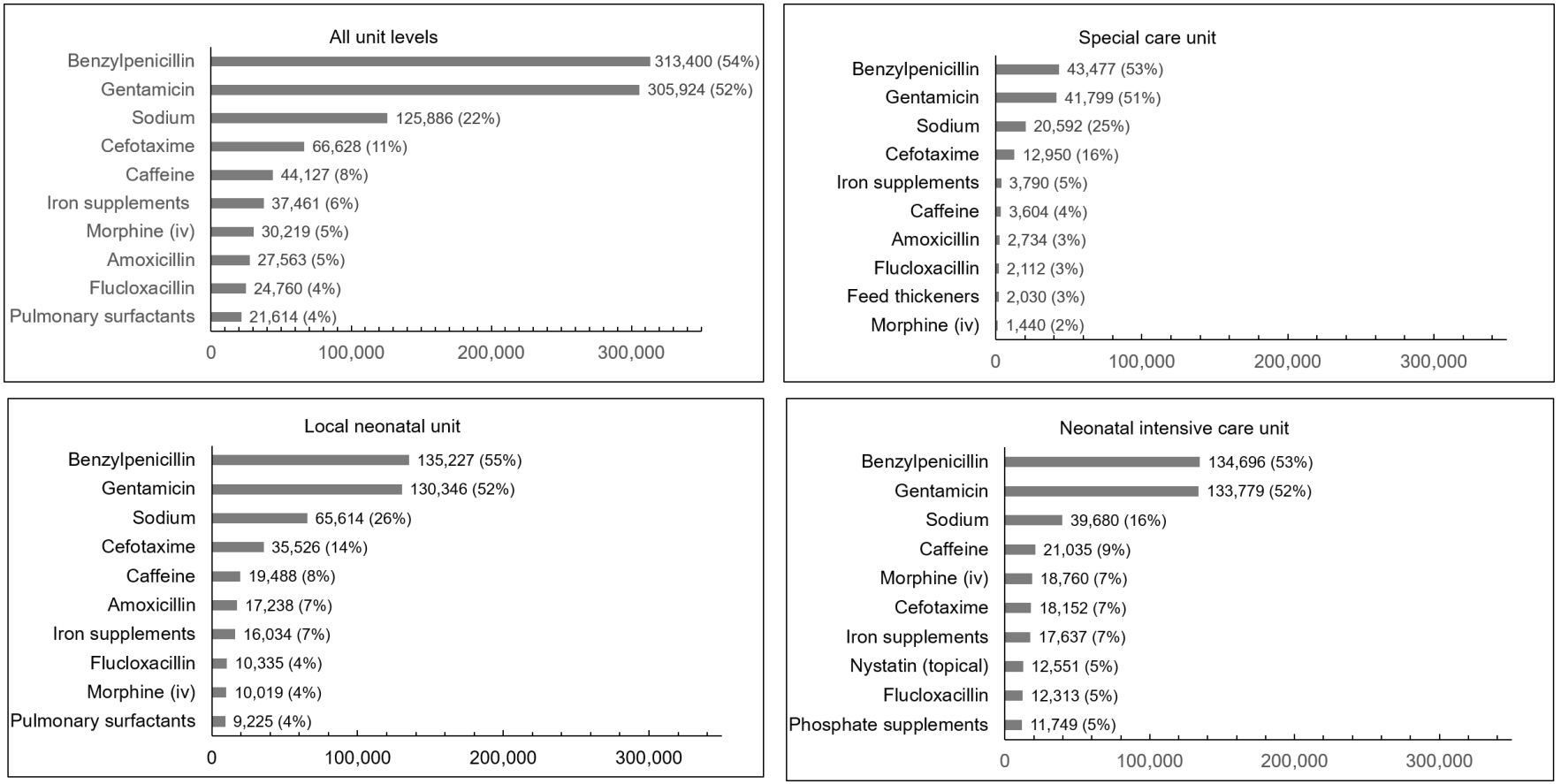


Figure 46. Most frequently prescribed drugs by unit level

3.5.6 Results for post-hoc objective: Are there any differences in antibiotic prescribing for each gestational age group?

The median number of antibiotics prescribed per neonate was two (IQR 2-2) (Table 18). The median number of different antibiotics prescribed to one neonate decreased with increasing GA, where extremely preterm neonates were prescribed a median of five different antibiotics (IQR 4-7).

The overall median (IQR) number of days of antibiotics across all GA was 3 (2-5) (Table 18). The number of days of antibiotics, as well as the length of hospital stay, increased with the level of prematurity. In extremely preterm neonates the median length of hospital stay and median number of days on antibiotics per neonate were 86 and 19, respectively. In term neonates, the median length of hospital stay and median number of days of antibiotics decreased to four and three, respectively.

Overall, neonates who were prescribed antibiotics for at least one day were prescribed antibiotics for an average of 60% of their hospital stay, and this percentage increased to 100% in term neonates.

The highest absolute number of courses of antibiotics lasting at least five days was amongst term neonates (65,487 neonates) (Table 18). Extremely preterm neonates had the highest number of antibiotic courses per neonate, with a median (IQR) of 2 (1-3).

Table 18. Antibiotic analysis for all and each gestational age groups

	All GA	Extremely preterm	Very preterm	Moderate to late preterm	Term
Number of neonates prescribed antibiotics at least once	423,918	18,245	40,113	136,753	228,807
Length of stay in days	7 (3-18)	86 (63-110)	44 (33-58)	13 (6-20)	4 (3-7)
Number of antibiotics per neonate	2 (2-2)	5 (4-7)	3 (2-4)	2 (2-2)	2 (2-2)
Number of days on antibiotics per neonate	3 (2-5)	19 (9-33)	6 (3-12)	3 (2-5)	3 (2-5)
Percentage of neonatal care days on at least one antibiotic	60 (26-100)	28 (17-47)	16 (10-26)	31 (18-60)	100 (60-100)
Number (%) of neonates who received at least one course* of antibiotics	136,859 (21%)	15,073 (79%)	22,167 (53%)	34,132 (17%)	65,487 (17%)
Number of courses* of antibiotics per neonate who received at least one course	0 (0-0)	2 (1-3)	1 (0-1)	0 (0-0)	0 (0-0)

All figures are Median (IQR)
* antibiotic course: antibiotics prescribed for at least 5 consecutive days. If there was a gap of ≥2 days between stopping and re-starting antibiotics, they were counted as two different courses

3.6 Discussion

This drug utilisation study is the first study to provide a benchmark for drug use across neonatal units in England and Wales. With the aim of exploring historic patterns of drug use across England and Wales neonatal units, several objectives were answered, and new questions have emerged which need to be answered in future research.

This discussion focuses on comparing the findings in the present study with the UK as well as international drug utilisation studies, that used a similar approach. It also includes a discussion on the quality of data and issues with the use of NNRD in DUR, strengths and limitations of this study. The suggestions for future work will be highlighted in the final discussion chapter of this thesis.

3.6.1 Comparison with other studies: Population characteristics

Two prospective studies have been conducted in the UK for the purpose of exploring drug use in neonates (28,29). One investigated the frequency of off-label and unlicensed drugs use in a single NICU (29) whereas the more recent study by Turner et al. aimed to investigate the most frequently prescribed drugs in several NICUs across the UK and highlighted therapeutic gaps in the field of neonatal pharmacotherapy (28). However, the latter study did not report any information regarding the sample size or the characteristics of the population, and only reported the number of NICUs that participated in the survey (37 units). Conroy et al. included a small number of neonates (70 neonates). It was prospective in design and conducted over a short period of

time in a single NICU. In addition to those two prospective studies, a recent multi-European study by Mesek et al. conducted to assess the drug prescribing patterns using a single-day point prevalence survey (65). In this study, 15 neonatal units from the UK contributed; however, the data of the UK could not be extracted. This is because the results in this study were reported by each European geographic region rather than single countries.

When turning to drug utilisation studies worldwide, two studies in the USA have used an approach similar to the present study in exploring drug use in neonatal units, by using large national datasets and setting out similar aims (66,185) which allows better comparison in terms of their findings to the present study. In the current study, 44% of included neonates were female; this matches the findings of Clark et al. (185) and Hsieh et al. (66) where both showed 44% of neonates were female. This is also similar to my findings in Chapter 2 where there were more males in 33 out of 56 drug utilisation studies included in the review. The median GA of the neonates included in the present study was 37 weeks (IQR 35-40) and this can be attributed to the high percentage of term neonates (59%) in the studied population. In the previous studies conducted in the USA, the median GA of the included neonates was 35 (IQR 33-38), which represents moderate to late preterm neonates (66,185). Neonates with ELBW accounted for 3.5% of the entire cohort in the present study. This percentage was lower than that the study by Hsieh et al. where 6.5% of the included neonates were ELBW. The length of neonatal hospital stay in this present study increased with the decrease in the GA of the neonatal population (longest for extremely preterm neonates). This is expected, as the medical complications related to

prematurity and the intensive care required for preterm neonates results in a longer hospital stay compared to term ones (105). This finding cannot be compared to the previous studies in the USA as the length of hospital stay was not reported for each GA group. However, in the present study, the median length of hospital stay for the entire cohort was lower (median 5 days, IQR 3-13) than the previous study by Hsieh et al. (median 10 days, IQR 5-21). This could be explained by the fact that the majority of neonates in the current study were term, who usually have the shortest length of hospital stay. In Hsieh's study the breakdown of admissions by GA group was not reported. However, it might be speculated that the longer neonatal hospital stay in Hsieh's study is due to a proportionally more babies admitted of a younger GA who would be expected to have longer lengths of stay.

3.6.2 Comparison with other studies: Drug use profile

Several methods have been reported in the literature quantifying drug use in neonates. Two studies in the USA, that used large datasets, represented drug use descriptively in three ways (courses, exposure, and frequencies), and interestingly, both reported no significant difference in the rank of the frequently prescribed drugs when comparing the three methods (66,185). In the current study, counts and proportions were used to rank the drugs and represent the frequencies of drug use across the population. Courses were defined differently by both studies that were conducted in the USA. In Clark et al. a course of a drug was defined as the number of times a unique medication was recorded for a single patient with a specific start date. Whereas in Hsieh et al. the course of a drug was defined as number of times

a unique drug name was reported in in the database. The limited information available in the NNRD database did not allow me to calculate the courses of each drug apart from antibiotics where an accepted definition of a course of antibiotics could be used. With regard to exposure, this term was defined exactly the same by both Clark et al. and Hsieh et al. as the number of unique drug names that were reported for each patient, which can be similarly applied to the counting method in the present study. I have used the term frequency to represent the raw count of each unique drug if it was prescribed at least once to a neonate. However, regardless of these inconsistencies in the terms used to define drug use, the results were similar when comparing the present study with Clark et al. and Hsieh et al. With regards to the drug use profile findings, the present study supports that as the prematurity of neonates increases, the total number of drugs a neonate is exposed to increases (115,119,186). The median number of drugs prescribed per neonate in England and Wales was lower (median 2, range 0-69) than Hsieh et al. (mean 4, range 1-14), which is a study with a similar setting, design, and approximately similar sample size to the current study (66). A lower median number of drugs per neonate may, again, be due to the larger percentage of the neonates in the present study being term-born, the group that was prescribed the smallest median number of drugs compared to the other GA groups. Gulati et al. assessed the changes in drug use patterns in preterm neonates and very low birth weight neonates and reported a lower number of prescribed drugs per neonate (median 9, IQR 5-15) (114). This might be due to the included criteria of preterm neonates in Gulati which was confined to very low birth weight neonates with completed data (5,529

neonates included), whereas in the presented study the cohort of preterm neonates was larger.

The top of the list of most frequently prescribed pharmacological groups was antibiotics, with 66% of neonates being prescribed at least one antibiotic during their neonatal stay; this is consistent with 23 studies from the previous literature review that found anti-infectives were the most frequently prescribed group of drugs in their NICUs (Chapter 2). With regards to the most frequently prescribed individual drugs, the present study supports evidence from two studies from the USA that utilised large databases in exploring drug utilisation in their NICUs (66,185). Penicillin and gentamicin were the most frequently prescribed drugs in the present study as well as the aforementioned studies. Also, this finding broadly supports the work of one of the two previous UK studies, in which gentamicin, followed by benzylpenicillin, were amongst the most frequently prescribed drugs (28). This was not an unexpected finding as most neonates are treated for presumed infections, especially early onset sepsis, with penicillin and aminoglycosides being the first line antibiotics used in Europe and North America (Chapter 2). Both are narrow spectrum antibiotics that are usually used to treat early onset sepsis. A review by Russell et al. reported that 70% of neonatal units in the UK use narrow spectrum antibiotics (penicillin/gentamicin) for treating early onset sepsis empirically, according to an audit across UK neonatal units (187). Clinicians often opt to use antibiotics empirically due to the fact that early onset sepsis is a life-threatening condition if not treated promptly.

Other antibiotics found among the top ten most frequently prescribed drugs in the present study were cefotaxime and flucloxacillin. Flucloxacillin is a narrow spectrum antibiotic used often in the empirical management of late onset sepsis in neonates, alongside cefotaxime. In addition, it is used in the management of skin and soft tissue infections, cellulitis, bone infections, and pneumonia. Cefotaxime, a broad spectrum third generation cephalosporin, is often used in treatment of neonatal sepsis. In Chapter 2, among the included studies, cefotaxime was reported amongst the ten most frequently prescribed antibiotics in Europe by three studies (74,101,122). However, none of those studies were conducted in the UK, and the two prospective studies that were conducted in the UK in 1999 (29) and 2009 (28) have not cited this drug among the ten most frequently prescribed drugs in the participating neonatal units. The concern with such an agent is the emergence of antibiotic resistance, and the appearance of this drug amongst the ten frequently prescribed drugs in the current study needs to be explored further to avoid the misuse of broad spectrum of antibiotics.

In the present study, comparing the number of antibiotics received by neonates in different GA groups showed that term neonates had the shortest length of hospital stay (median 4, IQR 3-7) with most of those days spent on antibiotics (median percentage of days on antibiotics 100, IQR 60-100). Term neonates are frequently admitted for suspected sepsis and/or treated empirically with antibiotics for this condition. They are then often, very quickly, discharged to the postnatal wards where they may or may not continue on antibiotics. Hence the majority of their time on neonatal units is spent on antibiotics.

Extremely preterm neonates were found to be prescribed the highest number of different antibiotics (median 5, IQR 4-7) and the highest number of days on antibiotics per neonate (median 19, IQR 9-33). Extremely preterm neonates are more prone to sepsis and require frequent sepsis screening, which leads to more antibiotics being prescribed.

Analgesics were amongst the ten most frequently prescribed pharmacological groups, with IV morphine ranked amongst the ten most frequently prescribed drugs. The popularity of this opioid analgesic has been observed in the literature as it was cited by eight studies (high income countries) amongst the ten most frequently prescribed drugs included in Chapter 2. Morphine is used as pain relief and for sedation during invasive mechanical ventilation in preterm neonates. However, it is known to be associated with respiratory depression, which can lead to prolonged mechanical ventilation and prolonged time to full enteral feeding (188). Two randomised controlled trials have been conducted to assess the use of morphine in preterm neonates in terms of its efficacy and safety (189,190). Both of those trials have not supported the routine use of morphine in ventilated preterm neonates in the short term. Simons et al. reported the lack of efficacy of morphine to improve pain relief (190). Use of morphine as a short-term analgesic for painful procedures was recently explored in the Poppi Study (191) when the study was prematurely stopped due to the profound respiratory adverse effects of morphine without any suggestion of efficacy. Despite this body of evidence showing lack of efficacy and high risk of adverse effects, in the current study, I found a widespread use of morphine especially among preterm neonates. The proportion of neonates being

prescribed intravenous morphine increased with a decrease in GA (5% in term vs. 66% in extremely preterm neonates). This suggests that further research and quality improvement work is needed to support evidence-based use of morphine and other opioid analgesics (such as fentanyl) in these cohorts.

Other drugs, not including antibiotics and analgesics, that are cited amongst the ten frequently prescribed drugs in this study were caffeine and surfactants, which are discussed in the next section (variation according to neonatal characteristics).

3.6.3 Variation in prescribed drugs according to neonatal characteristics

Caffeine was the most frequently prescribed drug in very and extremely preterm neonates in the current study. These results reflect those of Clark et al. who also cited caffeine citrate as the most frequently prescribed drug in preterm neonates born at GA < 32 weeks, followed by surfactants and vancomycin (185). Additionally, two prospective studies included in Chapter 2 (80,88) have cited caffeine amongst the most frequently prescribed drug in their neonatal units. One of those studies by Cuzzolin et al. was a multicentre study (36 NICUs) which included a majority of preterm neonates amongst the included population (191/220, 86.8%) with more than half of the neonates being ELBW and VLBW (140/220, 63.7%) (80). Caffeine is the mainstay pharmacological treatment of apnoea of prematurity in preterm neonates because of its longer half-life and wider therapeutic range, which leads to reduced drug monitoring and higher cost-effectiveness compared to other

methylxanthines (e.g. theophylline) (192,193). Apnoea of prematurity is a common condition in those born prematurely, especially at lower gestational ages (194). Also, apnoea of prematurity incidence is inversely correlated with BW, affecting nearly all neonates born weighing < 1000g (195).

When comparing the variation among units of levels of care, there were no differences in the most frequently prescribed drugs; gentamicin and benzylpenicillin were the most prescribed drugs overall in all units and each unit level. Another drug that was frequently cited across all unit levels is pulmonary surfactants. Surfactants were found to be amongst the ten most frequently prescribed drugs in level two units and ranked as number 11 in level three units. Level two and level three units care for neonates who require a higher level of ventilatory support, and the admitted gestational ages are usually between 28-32 weeks and GA< 28 weeks respectively. Exogenous pulmonary surfactants are usually indicated for the prevention and treatment of respiratory distress syndrome (RDS), a condition that is reported frequently with decreased GA; it is caused by structural immaturity of the lungs and insufficient production of surfactants (113,196). Hence, the use of those agents is expected in unit levels that care for neonates with lower GA and those presenting with medical complications.

3.6.4 Change in drug use over time

The change in drug use over time was observed across the entire cohort, and amongst very and extremely preterm cohorts, these observations will be discussed in this section for drugs highlighted in the results of this study.

3.6.4.1 Drugs used for GI conditions

There was an overall decrease in the percentage of neonates who were prescribed domperidone at least once across the entire cohort and among very and extremely preterm neonates. The decrease in the use of domperidone, usually given for gastro-oesophageal reflux disease (GORD), maybe a response to the restriction of its use in children following a report by the European Medicines Agency (EMA), released in 2014, with regard to its association with cardiac side effects (197). Also, a systematic review conducted in 2014 looked at the management of GORD in a paediatric population. It concluded that there is no robust evidence of using domperidone in neonates in terms of its efficacy and safety (198). This decrease in domperidone use was also observed by Cuzzolin et al. (80).

Ranitidine is another drug used for GORD. Its use has decreased across the entire cohort. This may be due to safety concerns about its use as well. Ranitidine use has been associated with NEC and increased risk of infections and death in VLBW neonates as published in a study by Terrin et al. (199). Furthermore, there are no studies to date that have advocated its efficacy and safety in neonates (200). A systematic review conducted in 2014 on the pharmacologic management of children with GORD concluded that weak evidence exists for using H2 antagonist (such as ranitidine) or proton pump inhibitors (such as omeprazole/ lansoprazole) in managing GORD in children (including neonates) (198). However, Clark et al. and Du et al. have reported an increase in ranitidine use over the period from 1997 to 2004 (185,186).

These studies assessed drug use prior to the publications that associated use of ranitidine with NEC and infections.

Feed thickeners, also used to manage GORD, are commonly used in neonates, in particular preterm neonates, as GORD is common in preterm neonates and can be exacerbated by the immaturity of the oesophagus and the lower oesophageal sphincter (201). The overall percentage of neonates prescribed feed thickeners decreased over time across the entire cohort, which might be attributed to the change in population composition (an increase in number of term babies in the database every year) rather than an actual shift in drug use (202).

3.6.4.2 Drugs used for respiratory conditions

Caffeine is a respiratory stimulant that is used for apnoea of prematurity. As the number of term neonates included in the cohort each year increased, across the entire cohort, the overall percentage of neonates who were prescribed caffeine at least once decreased from 2010 to 2017. However, the percentage of very and extremely preterm neonates who received caffeine increased over time. The vital role of caffeine in preterm neonates has become apparent following the Caffeine for Apnoea trial (CAP), the largest randomised controlled trial conducted to date on the efficacy and safety of caffeine in preterm neonates (203). The results of this trial supported the prophylactic use of caffeine for apnoea of prematurity as it reduces the frequency of Bronchopulmonary Dysplasia (BPD). This was followed by a Cochrane review in 2010 evaluating the effect of prophylactic effect of caffeine and included the CAP trial. However, the Cochrane review included

only three randomised trials and concluded against the use of prophylactic caffeine for preterm neonates at risk of apnoea due to insufficient available evidence on the effectiveness of this agent in decreasing episodes of apnoea or short term outcomes (e.g. use of mechanical ventilation, bradycardia, episodes of hypoxaemia) (204). This review was followed by series of retrospective studies and randomised trials supporting, overall, the initiation of caffeine especially within the first three days of life (192). A systematic review and meta-analysis by Park et al. assessed the early (0-2 days of life) vs. late use of caffeine (≥ 3 days of life). This meta-analysis has supported the early initiation of caffeine as it was associated with decreased incidence of death, and BPD without significantly affecting the duration of mechanical ventilation (205). Another more recent systematic review released in 2017 by Kua and Lee included 14 studies comparing early caffeine administration (< 3 days) with late caffeine, placebo or theophylline. The meta-analysis of cohort studies and randomised trials in this review showed a reduction in BPD rate and shorter duration of mechanical ventilation (206). The accumulating evidence in favour of using caffeine early had led to the increase in its use in extremely and very preterm infants.

Pulmonary surfactants have been used for the prevention and treatment of respiratory distress syndrome, which is common in preterm neonates who are deficient in surfactant production. The surfactant prescriptions included in this study do not include surfactants given in delivery rooms as those are reported separately in the NNRD. In the included data, overall, the percentage of neonates receiving pulmonary surfactants increased from 2010 to 2017. In the cohort of very preterm neonates only, the percentage of

neonates who have been prescribed pulmonary surfactants at least once increased over time as expected. However, the percentage of extremely preterm neonates who were given pulmonary surfactants fluctuated over time with a general increase from 2010 to 2017, apart from three minor decreases in 2012, 2016 and 2017. This overall increased recording of use may reflect the shift in clinical practice from routinely giving surfactants to preterm neonates in the delivery suite (which would not be recorded in this dataset) to provide early support with continuous positive airway pressure followed by surfactant administration in the neonatal unit if needed. This later administration would be recorded in the database and may have been captured as the increasing trend in use of surfactant on neonatal units. Some increase in recorded use may also be due to improvement in data entry practices over the years.

Evidence supporting the use of surfactants as prophylactic measures for preterm neonates suggests it reduces the risk of pneumothorax, pulmonary interstitial emphysema, and mortality according to a systematic review published in 2012 (207). However, this systematic review highlighted that some large trials included have supported the use of continuous positive airway pressure as early stabilisation with selective use of surfactants as a treatment strategy rather than prophylactic surfactant use. The use of antenatal steroids also has a role to reduce the risk of RDS and the use of surfactants, which has not been addressed in terms of analysis in the present study.

3.6.4.3 Antibiotics and drugs used in infections

Benzylpenicillin and gentamicin, are frequently prescribed to term neonates for the empirical treatment of neonatal sepsis, so the increase in the proportion of term neonates corresponds to the increase in percentage neonates being prescribed those drugs at least once over the years in the present study across the entire cohort. Interestingly, the percentage of very preterm neonates who have been prescribed benzylpenicillin also increased from 2010 to 2017, whereas the use of this agent fluctuated among extremely preterm neonates.

Percentage of neonates who have been prescribed amikacin increased from 2011 to 2017 across the entire cohort. This aminoglycoside antibiotic is active against gram-negative bacteria resistant to gentamicin and has a half-life of 7-14 hours in neonates (GA < 30 weeks) (208). Prescribers may often opt to use amikacin as an alternative agent in managing neonatal sepsis resistant to gentamicin (209). This raises the possibility of the emergence of bacterial resistance and warrants further studies exploring the use of amikacin in neonatal units in the UK.

There is a decrease in the percentage of neonates prescribed some antibiotics such as flucloxacillin, vancomycin, and metronidazole. These trends might be related to the increase in the number of term born infants included in the dataset as at least some of these are more frequently used in preterm neonates. Therefore, the use of the whole population as a denominator to calculate the proportion of neonates being prescribed these drugs to explore their change in use over time might lead to such results.

Vancomycin is used for the empirical management of late-onset sepsis due to its coverage of Coagulase-negative staphylococci, which are found in the majority of methicillin-resistant infections (210). Late-onset sepsis affects 10% of neonates, with more than 25% in those being VLBW (211). Flucloxacillin is also used in the management of late-onset sepsis, with an increase in its use as GA decreases (212). This was also shown in the results of this study as the percentage of neonates who received flucloxacillin increased with decreasing GA (2% term vs. 52% extremely preterm). Necrotising enterocolitis (NEC) also mostly affects preterm neonates and metronidazole is often used in its management. Cefotaxime is another antibiotic that the present study revealed the steady decrease in the percentage of neonates receiving it over time, apart from two minor increases in 2016 and 2017. This decrease might be associated with the emerging findings of the increased risk of fungal infections (candidiasis) in neonates with the use of third generation cephalosporins (213,214). Two retrospective studies by Hsieh et al. and Gulati et al. investigating the patterns in drug use have also reported a decrease in the use of third generation cephalosporins in the included neonatal care units and attributed the decrease to the emerging information of the increase risk of candida infections with third generation cephalosporins (66,114).

The percentage of neonates who were prescribed ocular chloramphenicol decreased over time across the entire cohort from 2010 to 2017.This may be due to safety issues. The use of systemic chloramphenicol has been associated with toxicity in neonates, with symptoms such as grey baby syndrome, haemopoietic disturbances, and bone marrow aplasia (215).

However, debates and insufficient evidence exist with regard to the use of the topical formulation (i.e. ocular) for treating neonatal conjunctivitis. The topical form can be absorbed directly through the nasal mucosa or swallowed and absorbed into the intestine. This small amount might also be of concern as aplastic anaemia (also known as bone marrow aplasia) may be dose-independent (216). This uncertainty and insufficient evidence for the safety in using the topical form of chloramphenicol might be the drive behind the decrease of its use in neonatal units in England and Wales.

Lack of evidence may be attributed to the decrease in the percentage of neonates who have been prescribed topical nystatin which was captured in the database 2014 onwards. Topical nystatin is usually used as a prophylactic agent against invasive fungal infections, especially in preterm neonates and those born with VLBW. Invasive fungal infections are more common in such cohorts due to several risk factors, such as the use of multiple courses of antibiotics, severe illness at birth, and the use of a central catheter (14). A Cochrane systematic review in 2015 (14) assessed the effectiveness of prophylactic oral/topical non-absorbed antifungals (nystatin or miconazole) on the incidence of invasive fungal infection, mortality, and morbidity in very preterm or VLBW neonates. It concluded that there is insufficient data to provide conclusive evidence that supports the efficacy of those agents and recommended larger high-quality trials to resolve the uncertainty of the findings.

The use of some antibiotics such as amoxicillin fluctuated over time. In addition, the percentage of neonates who have been prescribed probiotics

also fluctuated over time. Probiotic use increased between 2013 to 2014 and then fell in 2015 and 2016. This demonstrates the continuing debate about the routine use of probiotics in neonates. The Cochrane review published in 2014 compared the efficacy and safety of prophylactic use of probiotics in the prevention of severe NEC or sepsis, or both, in preterm neonates (217). This review strongly supported the use of probiotics to prevent severe NEC and all cause of mortality in preterm neonates. However, several reports of probiotic sepsis published in 2015 and 2016 and one neonatal death due to fungal infection from a contaminated probiotic raised concern regarding their use (218,219). Furthermore, the use of probiotics in the UK may have been discouraged following the results of a large multicentre trial in the UK in 2016 (PIPs trial), (220,221). This trial has concluded the ineffectiveness of using probiotics in preventing NEC and late-onset sepsis in very preterm neonates. Another randomised trial conducted in the UK, ELFIN trial, to enhance the validity of the available evidence on the use of lactoferrin supplements in neonates, especially preterm ones (222). Enteral lactoferrin is a supplement that promotes the growth of probiotic bacteria and is involved in several mechanisms of the immune system. It has been proposed as an alternative to compensate for the little/no intake of the mammalian lactoferrin that presents in human breast milk during the early neonatal period. As a result of this trial, the use of enteral lactoferrin was discouraged in very preterm neonates as those supplements did not show any reduction in the risk of late-onset infections and associated morbidity (NEC, ROP, BPD) or mortality in this cohort.

3.6.4.4 Other drugs

The percentage of neonates being prescribed chlorhexidine fluctuated during the study period across the entire cohort. Chlorhexidine is a topical antiseptic that is widely used in NICUs to prevent nosocomial infections. Although some fluctuations in recorded use may be due to inconsistency in data entry into electronic patients records, the dilemma in the effective and safe use of antiseptics, including chlorhexidine, in neonates, may have contributed to some variation in use. An evidence-based review by Sathiyamurthy et al. concluded that chlorhexidine is associated with local reactions compared to other antiseptics (iodine) which is associated with an increased risk of systematic absorption and toxicity (223). In June 2014, the UK Medicines and Healthcare products Regulatory Agency (MHRA) urged physicians to use chlorhexidine with maximum care in preterm neonates due to several reports of erythema and local burns in extremely preterm neonates (224,225).

The percentage of extremely preterm neonates who were prescribed insulin at least once increased from 2010 to 2017. Insulin is used in extremely preterm neonates as they are more prone to hyperglycaemia (226). The increase might be related to the increase in the records of insulin in the database. Other reasons that may drive increased use of insulin may be related to more intensive nutritional strategies with higher concentrations of parenteral nutrition given to extremely preterm neonates leading to the increased chance of glucose intolerance and need for insulin. Increase in the percentage of extremely preterm neonates who have been prescribed dexamethasone (from 13.3% in 2010 to 20.2% in 2017) may also drive

higher insulin use. Dexamethasone, which can cause hyperglycaemia as one of its adevrse effects, is often prescribed in the prevention and treatment of BPD in preterm neonates. Several Cochrane reviews conducted in 2009, 2010, 2014 and the most recent in 2017 (227–230) investigated the effectiveness and safety of administring postnatal corticosteriods in pereterm neonates at risk of developing BPD. The authors of these reviews concluded that dexamethasone is effective in facilitating extubation and reducing BPD in preterm neonates, but the risk of the adverse effects of such agents may not outweigh the benefit.

It is worth highlighting the fact that not all the drugs that are actually prescribed are meticulously entered into NNRD. But as data entry has improved in general over the years, the entry of routinely used drugs, such as sodium supplements, might have increased which then shows as an increase in the percentage of neonates who have been prescribed this supplement. In very preterm neonates, the increase in the percentage of neonates being prescribed drugs such as immunisations and topical agents such as phenylephrine have increased over time, which may also be due to improvement in data entries and recording over the years. Supplements such as iron and phosphate are known for their prevalent use in preterm neonates as this cohort are usually born with low stores of phosphate and iron. Therefore, the percentage of extremely preterm neonates who have been prescribed those supplements increased in the study period.

3.6.5 NNRD data quality

Secondary data sources in drug utilisation studies have been used to estimate incidence, prevalence, duration of drug use, and investigate drug use patterns over periods of time (231). The NNRD was used to answer several questions that were proposed in this drug utilisation study, as so far this is the only database that captures information about drug prescriptions to neonates from almost all neonatal units in the UK. This database is a repository of pre-defined clinical data that is extracted by NDAU quarterly on all neonatal admissions to the NHS from any point of care in England, Wales, and Scotland. It is worth highlighting that by 2012, all neonatal units in those three countries contributed their data into the NNRD to cover the whole population admitted to neonatal units. A recent validation study in England set out to assess the validity of the NNRD in terms of the population coverage from 2008 to 2014 by assessing the accuracy and the completeness of the data held in this database (202). The completeness was assessed by calculating the percentage of 7 data items of patients' characteristics that includes GA, sex, and BW, and reported over 90% completeness. This study also linked the NNRD with independently collected data from the Office for National Statistics and the Probiotics in Preterm babies Study (PiPS) to assess the accuracy of the data and compared the agreement between 44 prespecified items in both databases. The specificity of the NNRD was found to be > 85% for all outcomes and the sensitivity ranged between 50-100%. So, it can be concluded that the completeness and the quality of data held in the NNRD is high, which assures its applicability for research purpose use (202).

Despite these assurances on data quality and completeness, this study revealed several drawbacks of the NNRD when used for drug utilisation studies. First, not all neonates who received drugs are admitted to neonatal units and thus, their data are not included in the NNRD. This is because many neonates are treated in postnatal wards, discharged from postnatal wards, or discharged from neonatal units and returned to the hospital to be treated by a paediatric unit and as such, their data is not included in the NNRD.

The second observation made while analysing this data is the limitation of the drug data available in this database, which can impede a firm conclusion with regards to the rational use of the drugs in this population; this is the ultimate goal of any drug utilisation study and as such, is deemed pertinent. Although the name of drugs is recorded daily, limited information was available on the route of administration, such as some drugs were coded as ‘morphine-iv’ and ‘beclomethasone-inhaler’, while most others were missing such information. There was no information recorded on the dose given, actual duration, adverse effects, and most importantly the indication of drug use.

Thirdly, poor coding of the drugs is another drawback of the NNRD, as all drugs were coded in free text with several incorrect spellings as illustrated in the coding section of this study. Also, there were many unrecognised drug entries encountered while extracting the drugs, and all were excluded from the analysis. For example, 41 neonates were prescribed ‘supplements’ and four neonates were prescribed an ‘unlisted drug’. So, there was no standardisation of coding such as those by WHO-ATC classification system

that was observed in other drug utilisation studies that appeared in the previous review chapter. Diagnosis coding had some drawbacks that was observed while analysing the characteristics of neonates with no drugs. First, 22% (n=137,578) of the included neonates across the entire cohort and 39% (n=74,698) of those who were not prescribed any drugs had no entries of diagnosis at admission. The reason for missing such necessary entry is worth to be explored. Also, the term 'other' in diagnosis at admission was used in at least 7% (n=46,373) of the entire cohort and in at least 10 % (n=18,540) of neonates who have not been prescribed any drugs. Using a general broad entry, such as other, requires further exploration to understand what this term exactly includes.

The fourth observation related to the data quality that may constitute a limitation of this work is the fact that admission criteria appear to have changed over the study period. This is demonstrated by the increase in the number of neonates admitted every year, especially those born at term gestations. Consequently, the interpretation of some drugs used, especially those that are used mostly in preterm neonates is not representative of actual change in use when the whole cohort is considered together.

Lastly, data entered at the point of care (i.e. Bager.net platform) by a variety of staff, who might not necessarily be those who prescribed the drug or be appropriately trained in data entry (175). How drugs are entered into the dataset may between units and from one year to another and some changes in drug use over time might be due to these variations rather than actual change is use.

While some data are known to be accurate and complete such as those related to the population characteristics as per the validation study mentioned earlier (202), the accuracy and completeness of other important data points for a drug utilisation study such as those related to the drugs have not been evaluated or validated.

Despite these limitations, NNRD provides a unique opportunity to conduct large scale data analysis and this study has utilised this to produce an overall picture of drug utilisation in neonatal units in England and Wales.

3.6.6 What does this study add?

This is the largest study to date reporting on drug utilisation in neonates in England and Wales. It is the first study that has used a national database to explore drug use in neonates and to lay the groundwork for future researchers interested in this field. Furthermore, this study has explored the usefulness, as well as the drawbacks, of the NNRD when used in drug utilisation research. The variety of designs and methods used in drug utilisation studies in neonates have been pointed out in a systematic review by Rosli et al. (2017), which highlighted the need for future research to identify the best measure in quantifying drug utilisation in this age group (10). For the UK, there were no studies that investigated drug use patterns in neonates on a national level. And since there is still no gold standard to quantify drug consumption in neonates as pointed by Rosli et al., the use of secondary data sources can provide an initial step towards exploring drug use in neonatal units in the UK. The results of this study are generalisable as it is a multicentre study and includes data from more than half a million

neonates and captured medication use over an eight year period. Previous studies conducted in the UK, both prospective, included either a small sample size (one NICU) (29) or had a low response rate from participating units (28). Thus, both had insufficient data to describe drug use in neonatal units in the UK to be generalisable. Another strength is that the present study has sub-analysed drug use across the neonatal population according to different GA, BW, and level of care. This was not observed in the UK studies or drug utilisation studies in the USA that have used a national dataset. Drug utilisation in neonates is dynamic and is prone to changes with different neonatal GA or BW as it was seen from the findings of the current study. This is because each age or BW group of neonates is admitted with different conditions and requires tailored neonatal care.

In summary, this study lays the groundwork for future research on the use of drugs in neonates. It has identified the most frequently prescribed drugs across neonatal units in England and Wales and whether these drugs have changed in frequency of use over an eight-year period.

In the UK, one of the main therapeutic gaps that requires research, as identified by previous drug utilisation studies and highlighted by clinicians, is PDA (28). PDA pharmacological management is one of the most challenging areas in neonatal therapeutics. Several studies exist in the literature aiming towards finding the optimal management of this condition that affects preterm neonates. Indomethacin, ibuprofen and more recently paracetamol are the most studied drugs that are used in management of PDA, with several controversies that exist around them in terms of their efficacy and safety.

Therefore, I chose to further explore drug use in PDA across the same time period, to look at the prescribing pattern of those three drugs and whether it has changed over time. This will be further detailed in the next chapter (Chapter 4).

CHAPTER 4 DRUG UTILISATION IN PATENT DUCTUS ARTERIOSUS (PDA) ACROSS NEONATAL UNITS IN ENGLAND AND WALES

4.1 Introduction

Management of PDA remains one of the most debated and challenging areas in neonatal therapeutics. As discussed in Chapter 1, PDA can be managed pharmacologically with indomethacin, ibuprofen, and most recently paracetamol. Surgery may, sometimes, be used in case of failure or contraindication of those agents.

In Chapter 3, I found that among extremely preterm neonates, 21% were prescribed ibuprofen at least once; this drug was ranked as number 25 in the top 50 drugs (detailed in 9.19). PDA, although present at birth at all gestational age, is a condition that mostly adversely affects very and extremely preterm neonates. Delayed closure of PDA in very preterm neonates is associated with several complications including intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), BPD, and higher mortality (232). In addition, small to moderate PDA tends to close spontaneously especially in those born over 28 weeks and often left without any treatment (33).

In addition to ibuprofen, as shown in Chapter 3, 8% and 25% of very and extremely preterm neonates respectively were prescribed paracetamol at least once. Paracetamol may have been prescribed either as an analgesic or

for PDA treatment although its use as an analgesic is limited as is thought to have a poor effect in postoperative pain and procedures in neonates (233).

In this chapter, I aimed to do an analysis of different treatment modalities used in PDA management in extremely and very preterm neonates across neonatal units in England and Wales and to investigate if their use has changed over time.

4.2 Study design

This was a retrospective pharmacoepidemiologic study to explore drug utilisation in PDA management from 2010 to 2017 across neonatal units in England and Wales. The same dataset National Neonatal Research Database (NNRD) that was used as in Chapter 3.

4.3 Aim and objectives

The aim of this study was an analysis of different treatment modalities used in PDA management in extremely and very preterm neonates across neonatal units in England and Wales and to investigate if their use has changed over time.

Five main objectives were set out to approach this aim.

- Objective 1: What is the prevalence of PDA in <32 weeks neonates across neonatal units in England and Wales, and has it changed over time?
- Objective 2: What is the prevalence of no treatment in neonates who have a record of PDA, and has it changed over time?
- Objective 3: What is the prevalence of use of each PDA treatment strategy across neonatal units in England and Wales from 2010 to 2017 and has it changed over time?
- Objective 4: What is the prevalence of use of paracetamol in neonates with PDA across neonatal units in England and Wales?
- Objective 5: What is the duration of treatment for the drugs used for treating PDA?

4.4 Methods

A detailed overview of the study dataset is described in the previous chapter of drug utilisation patterns in neonatal units in England and Wales (Chapter 3).

4.4.1 Study dataset and population characteristics

All neonates admitted to a neonatal unit in England or Wales from 01 January 2010 to 31 December 2017 with a GA < 32 weeks (very and extremely preterm neonates only) were eligible for inclusion. This restriction in GA was selected as PDA mostly affects very and extremely preterm neonates. Neonates who met exclusion criteria as in Chapter 3 were excluded from this analysis too. The population demographics were summarised for the entire cohort, neonates with PDA, neonates without PDA.

4.4.2 Specific methods for each objective

4.4.2.1 Objective 1: What is the prevalence of PDA in <32 weeks neonates across neonatal units in England and Wales, and has it changed over time?

For this objective, the following steps were undertaken:

1. The Daily dataset was inspected for variables that indicate a record of PDA. This could either involve an actual record of the PDA in one of the diagnosis variables or one of the treatments (record of drugs/ surgery) in one of the variables that indicate a treatment of PDA. Three variables were identified in the daily dataset, and those include the ‘diagnosis day’ variable, ‘treatment for PDA’ variable, and the ‘drugs day’ variable.
2. The Episode dataset was inspected for variables that also could indicate a record of PDA whether from diagnosis or treatment aspects (‘diagnosis at admission’ variable and the ‘principal diagnosis at discharge’ variables).
3. Created different binary variables for each source of information which were coded as zero and one. ‘Zero’ was generated to indicate that a neonate does not have a PDA diagnosis record or has not been treated with ibuprofen/indomethacin/surgery at any point of their neonatal stay. ‘One’ was generated to indicate a diagnosis or a treatment of PDA (drugs/surgery) of a neonate at any point during their neonatal stay.

4. Converted the daily dataset into one row per neonate dataset, and only neonates who had a GA of less than 32 were kept. The Episode dataset is a one row per neonate dataset; therefore, this conversion was not required but neonates who had a GA ≥ 32 weeks were dropped from it.
5. Merged the information of the PDA from episode and daily datasets to create a final PDA dataset to identify records of PDA that could assist in calculating the prevalence of it.
6. Created variable to merge all the sources of information that indicate a neonate has a record of PDA in one variable based on either diagnosis or treatment variables.

Appendix 9.26 details the variables used to calculate the number of neonates who have PDA records based on diagnosis and/or treatment indicating the presence of a PDA. Following these steps, prevalence of PDA was calculated. These steps were also repeated to demonstrate the PDA prevalence for each GA.

4.4.2.2 Objective 2: What is the prevalence of no treatment in neonates who had PDA, and has it changed over time?

Neonates included in this analysis were only those with a record of PDA. For this analysis paracetamol was included as a treatment strategy as it can be used for PDA. Prevalence of any treatment was calculated based on either including or excluding paracetamol as a treatment strategy in addition to other treatment strategies (indomethacin, ibuprofen and surgery). Then for each cohort the corresponding prevalence of no treatment was calculated. Similar variables created for each treatment strategy in the previous objectives (2 and 3) were used.

4.4.2.3 Objective 3: What is the prevalence of use of each PDA treatment strategy across neonatal units in England and Wales from 2010 to 2017, and has it changed over time?

For this objective, neonates who have been identified to have a PDA record from the first objective were analysed only. Then the following steps were followed:

1. Created variables to identify neonates who had records of ibuprofen or indomethacin at least once during their neonatal stay. And this was either identified from ‘drugs day’ variable or ‘treatment for PDA’ variable.
2. Created a variable to identify neonates who had records of surgery from ‘treatment for PDA’ variable.
3. Counted the variables used to calculate the number of neonates who had any treatment strategy for PDA (detailed in 9.27).
4. The number of neonates receiving any treatment strategy either alone or in combination was counted across the entire cohort and across each GA.
5. The prevalence of each treatment received was calculated by dividing the number of neonates having a record of each treatment strategy by the total number of neonates admitted each month with a record of PDA.

4.4.2.4 Objective 4: What is the prevalence of use of paracetamol in neonates with PDA across neonatal units in England and Wales?

This was done by first comparing paracetamol prevalence in neonates who had PDA records and those who don't and making the assumption that neonates with any record of paracetamol only (i.e. neonates have no records of indomethacin/surgery/ibuprofen or text diagnosis) does not indicate that a neonate have PDA. This was assumed as only one percent of neonates (n=478) across the entire cohort had a record of ibuprofen or indomethacin or surgery as treatment for PDA without having recorded text diagnosis. Appendix 9.28 details the variables used to extract records of paracetamol across the entire cohort. Then the prevalence in (%) of paracetamol use in neonates with and without PDA was calculated.

4.4.2.5 Objective 5: What is the duration of treatment for the drugs used for treating PDA?

The analysis was done across the entire cohort (all neonates < 32 weeks) for indomethacin, ibuprofen, and paracetamol. The same codes that were used in objective three to extract the free text of the drugs were used. Then the following steps were followed:

1. Sorted the data by two variables: anonymised ID of the neonate and the 'daydateanon' variables. The daydateanon, is a variable that shows the time difference between time of birth and each particular date in the database. From this variable the first day of life of each neonate can be estimated, which can be considered as the 'chronological age' of the neonate.
2. Created a variable to identify first day of prescribing of each drug amongst those who were prescribed that drug.
3. The total number of days of prescribing variable was created for each drug.
4. Variables in steps (two and three) were kept and all duplicates were dropped.
5. All the steps from one to four were repeated for all daily data files.
6. The created demographic data file was merged into the daily data file to summarise demographics of the neonates for this question.

4.5 Results

4.5.1 Study dataset and population characteristics

Study dataset: The total number of neonates for whom records were initially received was 643,233. The final number of very and extremely preterm neonates included in this study was 61,265, as detailed in Figure 47.

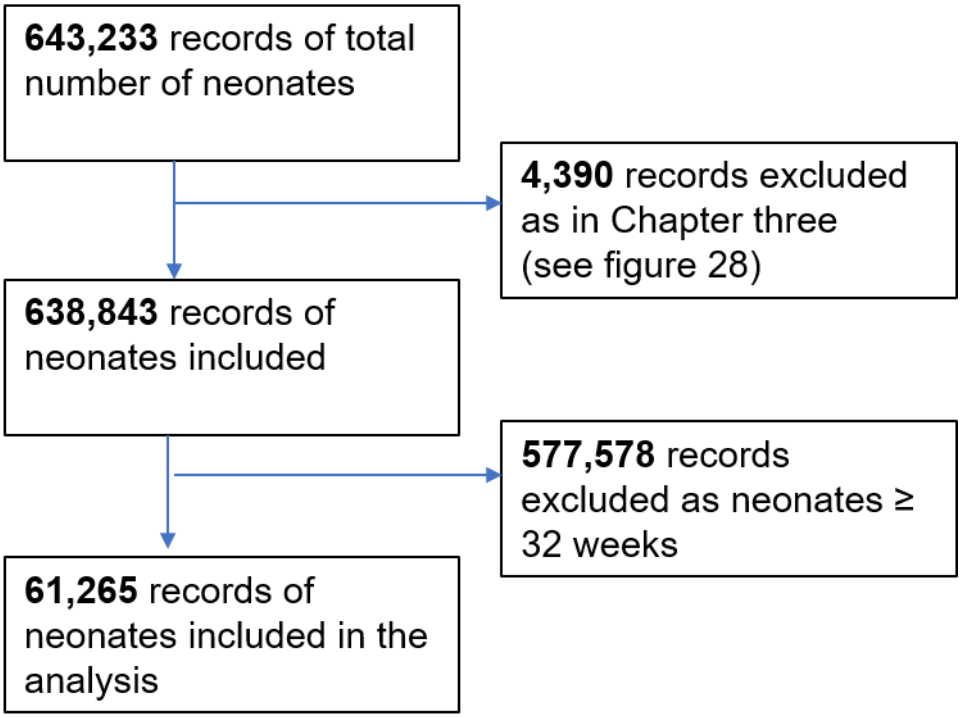


Figure 47. Derivation of the study dataset for patent ductus arteriosus analysis

Population characteristics: Total number of very and extremely preterm neonates included in this study was 61,265. Of these, 18,181 (30%) had a diagnosis of PDA identified within the database (Table 19). Neonates with PDA records had smaller GA and lower BW when compared to those with no records of PDA. Also, a higher percentage of neonates with PDA records died (11%) before discharge compared to those without any PDA records (8%).

Table 19. Population characteristics of neonates (<32 weeks gestation) with and without record of PDA

Demographic comparison		All	PDA	No PDA	P value (PDA vs. No PDA)
Number, n (%)		61,265	18,181 (30)	43,084 (70)	
GA (weeks) Median (IQR)		29 (27-30)	27 (25-28)	30 (28-31)	<0.001*
BW (grams) Median (IQR)		1200 (900-1490)	905 (725-1140)	1320 (1050-1565)	<0.001**
Female, n (%)		27,887 (46)	8,398 (46)	19,489 (45)	0.03***
Discharge destination n (%)	**Home**	52,690 (86)	14,620 (81)	38,070 (88)	<0.001***
	Died	5,581 (9)	2,109 (11)	3,562 (8)	
	Ward	912 (1)	410 (2)	502 (1)	
	Transfer	1,911 (3)	1,054 (6)	857 (2)	
	Missing	171 (0)	78 (0)	93 (0)	

BW, birth weight; GA, gestational age; PDA, patent ductus arteriosus
*Mann-Whitney test; **Two sample t-test; ***Pearson Chi-square test

4.5.2 Results for objective 1: What is the prevalence of PDA in <32 weeks neonates across neonatal units in England and Wales, and has it changed over time?

The overall prevalence of PDA in this study period was 30% (Table 19). Despite month to month variations, overall, the prevalence of PDA has not changed from 2010 to 2017 (Figure 48). A detailed table of neonates who have PDA based on the diagnosis and/or treatment indicating a PDA on each month of admission is attached in appendix 9.29.

Figure 49 shows the prevalence of PDA by GA weeks and shows that prevalence increased with decreasing GA except in 22- and 23-weeks neonates who had a lower prevalence.

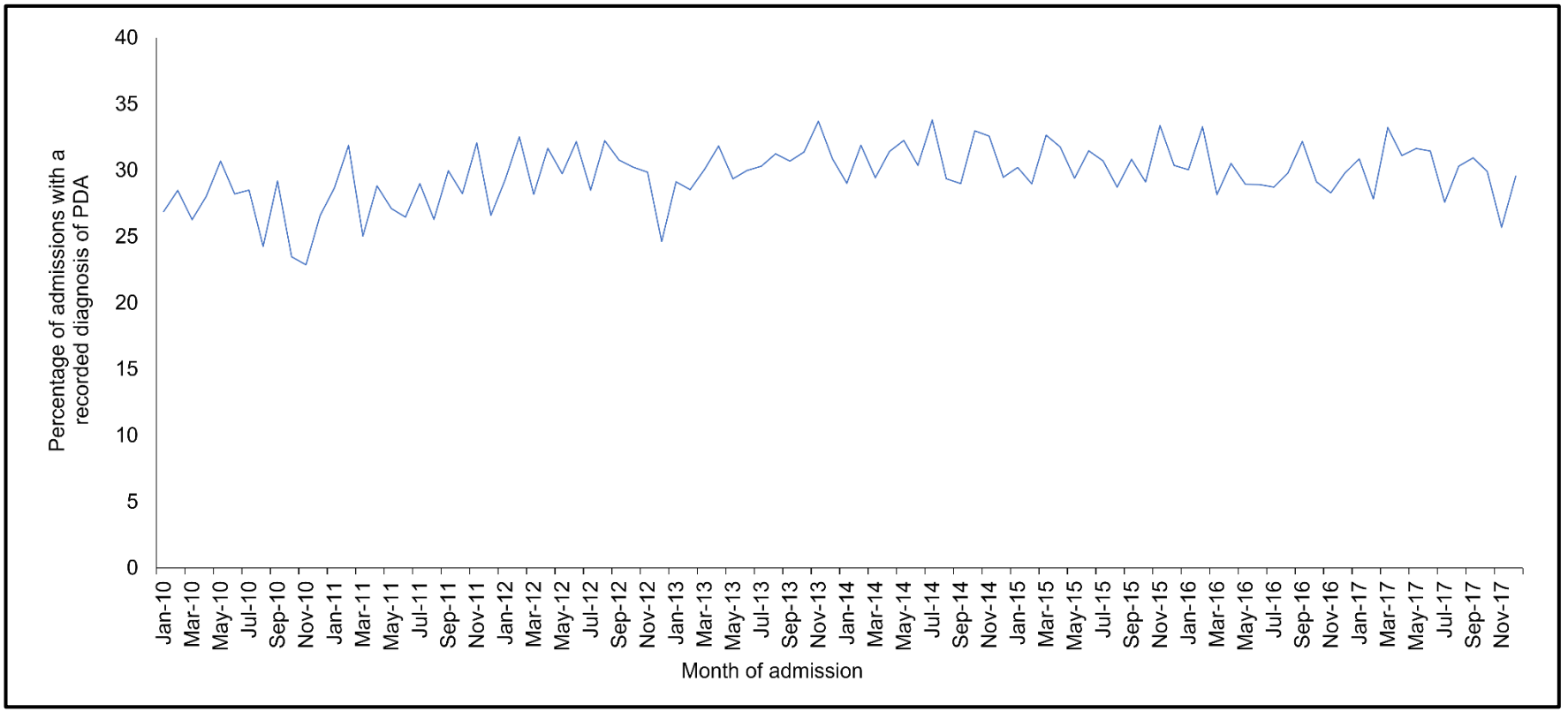


Figure 48. PDA prevalence (by month of admission) in <32 weeks neonates from 2010 to 2017 in England and Wales

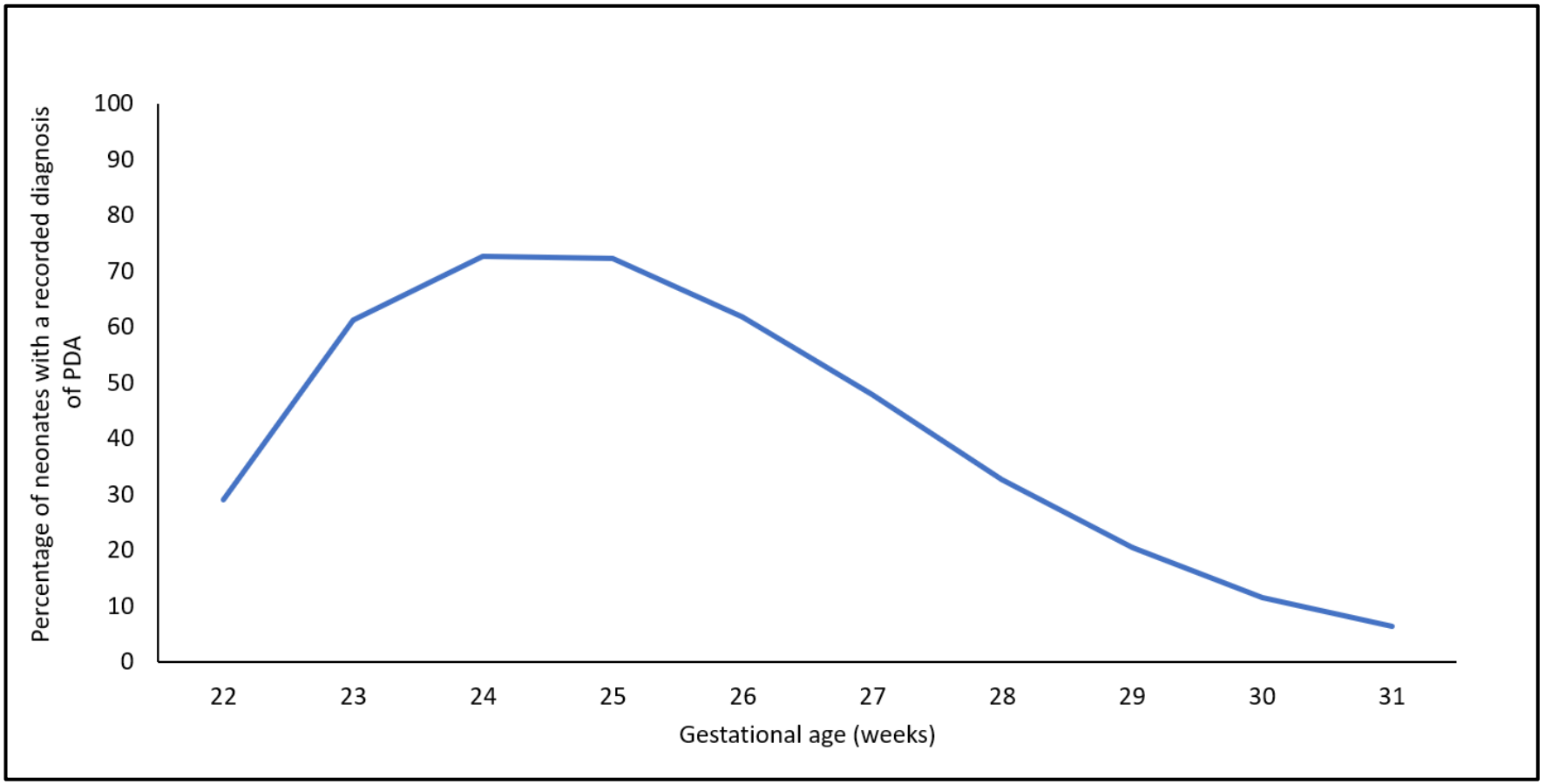


Figure 49. Prevalence of PDA across different GA

4.5.3 Results for objective 2: What is the prevalence of no treatment in neonates who have a record of PDA, and has it changed over time?

Table 20 shows how many neonates did or did not have any treatment for PDA. When including paracetamol as a treatment strategy, 49% of neonates with a diagnosis of PDA received some treatment.

Table 20. The prevalence of treatment for PDA among neonates < 32 weeks gestation who had a diagnosis of PDA (n=18,181)

	Prevalence of any treatment, n (%)	Prevalence of no treatment, n (%)
Indomethacin and/or ibuprofen and/or surgery	6,384 (35%)	11,797 (65%)
Indomethacin and/or ibuprofen and/or paracetamol and/or surgery	8,981 (49%)	9,200 (51%)

In Figure 50 any treatment which included ibuprofen and/or indomethacin and/or surgery showed little variation over time. Whereas when paracetamol was not counted as one of the treatment strategies, the prevalence of neonates who have not received any treatment increased over time.

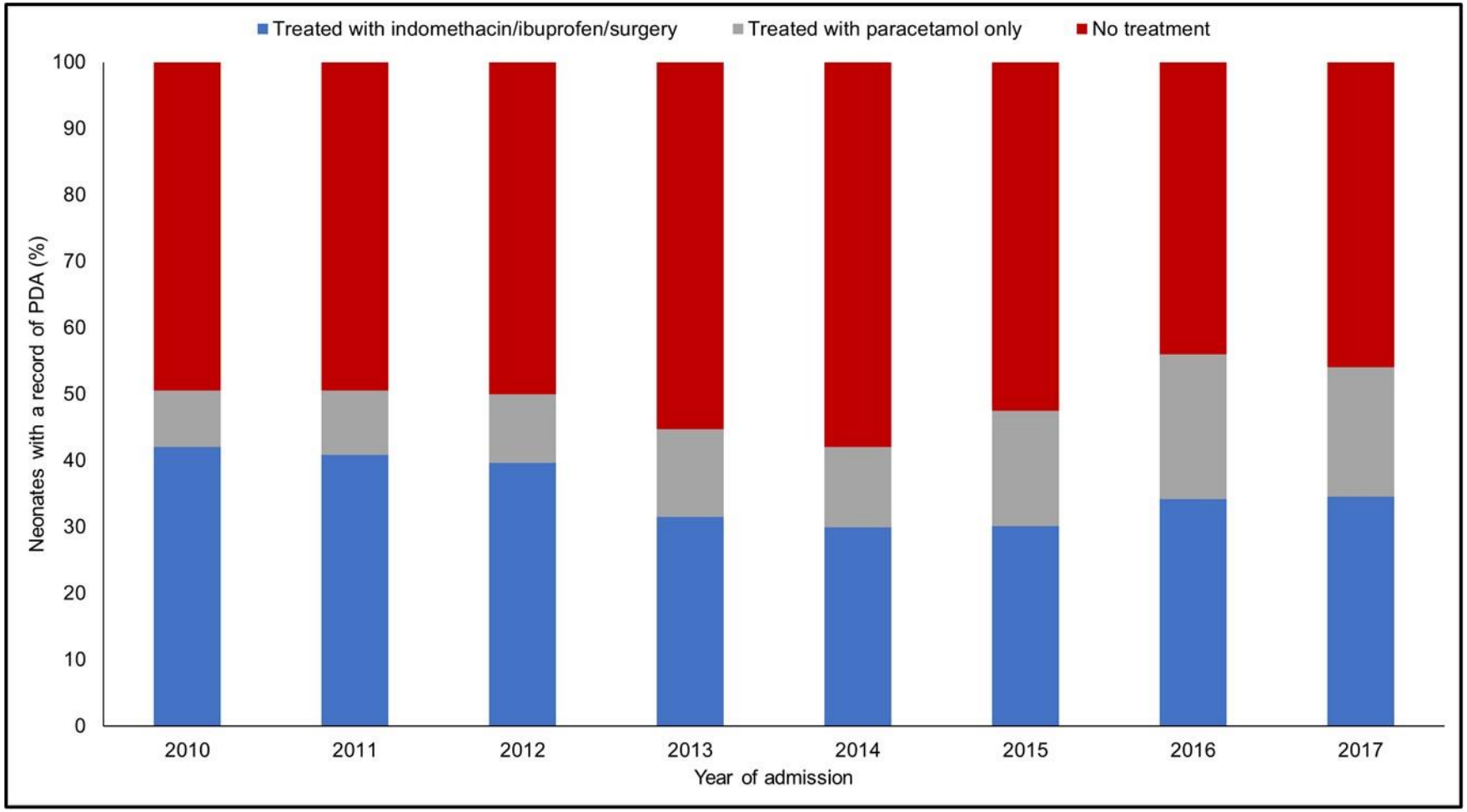


Figure 50. Prevalence of no treatment in neonates with a record of PDA

4.5.4 Results for objective 3: What is the prevalence of use of each PDA treatment strategy across neonatal units in England and Wales, and has it changed over time?

In this section, use of indomethacin, ibuprofen, and PDA surgery are presented. Paracetamol use is described in section 4.5.5.

Overall, as shown in Table 21, amongst neonates who have records of PDA, 35% (6,384 neonates) had at least one treatment strategy. More were treated with ibuprofen (4,926 (27%)) as compared to indomethacin (1,417 (8%)) or surgery (1,037 (6%)). Figure 51 shows the prevalence of use of each treatment strategy across each GA. The use of treatment increased with decreasing GA. Use of treatment strategies in combinations (including paracetamol) in neonates with PDA by GA is given in appendix 9.30.

Table 21. Treatment of neonates with PDA born at <32 weeks in England and Waled (2010-2017)

Gestation age (weeks)	Total number of neonates	Received any treatment (indomethacin/ibuprofen/ surgery) n (%)		Received indomethacin n (%)		Received ibuprofen n (%)		Had PDA surgery n (%)	
22	27	12	(44%)	1	(4%)	11	(41%)	2	(7%)
23	997	557	(56%)	126	(13%)	420	(42%)	144	(14%)
24	2,339	1,327	(57%)	286	(12%)	1,038	(44%)	295	(13%)
25	2,636	1,310	(50%)	316	(12%)	1,002	(38%)	215	(8%)
26	2,900	1,160	(40%)	261	(9%)	892	(31%)	157	(5%)
27	2,807	910	(32%)	208	(7%)	702	(25%)	104	(4%)
28	2,479	597	(24%)	122	(5%)	466	(19%)	66	(3%)
29	1,772	320	(18%)	61	(3%)	249	(14%)	37	(2%)
30	1,276	130	(10%)	20	(2%)	104	(8%)	10	(1%)
31	948	61	(6%)	16	(2%)	42	(4%)	7	(1%)
22-27 weeks	11,706	5,276	(45%)	1,198	(10%)	4,065	(35%)	917	(8%)
28-31 weeks	6,475	1,108	(17%)	219	(3%)	861	(13%)	120	(2%)
22-31 weeks	18,181	6,384	(35%)	1,417	(8%)	4,926	(27%)	1,037	(6%)

PDA, patent ductus arteriosus

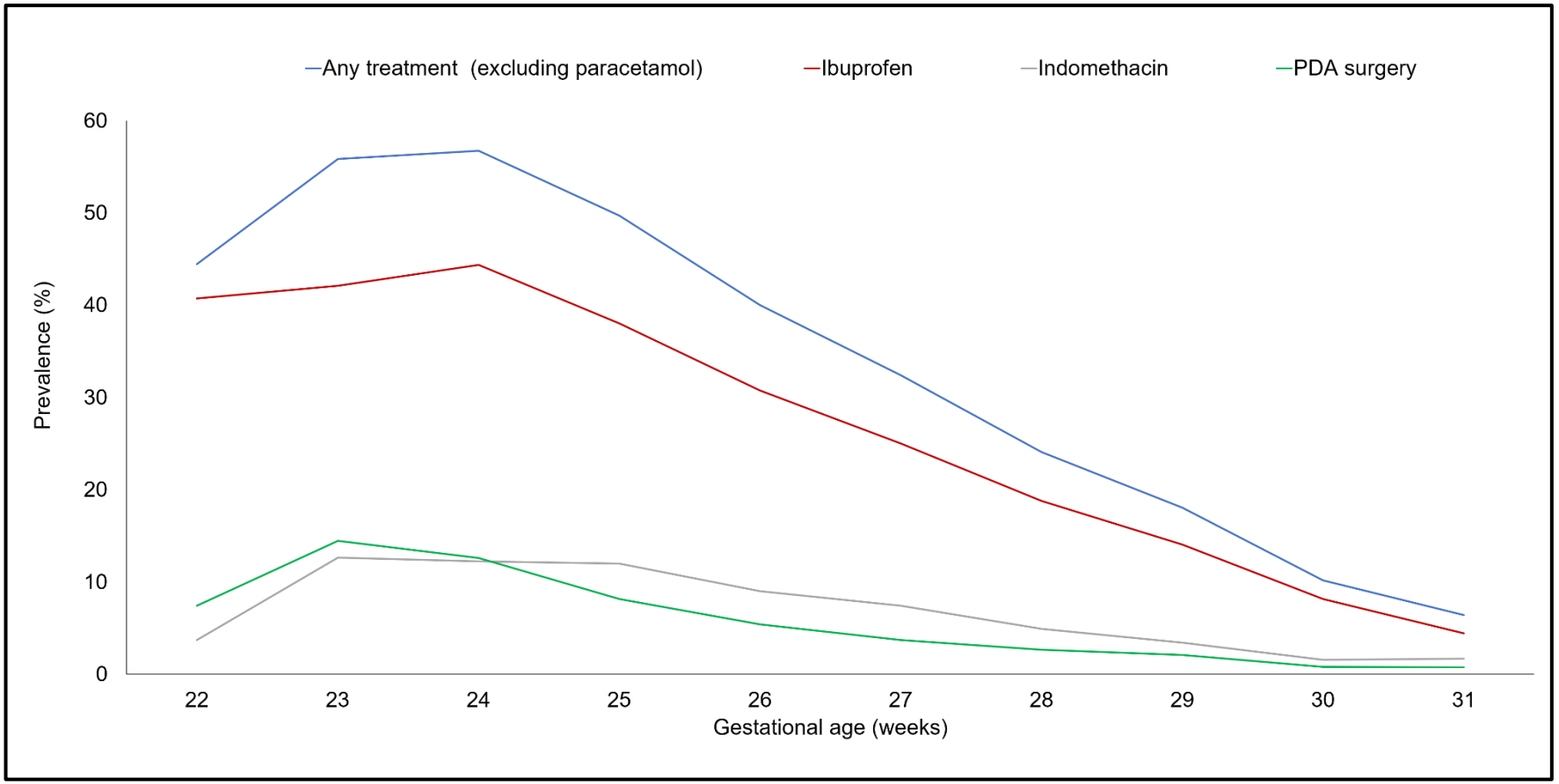


Figure 51. Prevalence of each treatment strategy according to each GA

Overall, there were several fluctuations in use of PDA treatment strategies in the study period (Figure 52). From January 2010 to April 2011 as there was an increase in the percentage of neonates with records of ibuprofen use with a decline in the percentage of neonates with records of indomethacin use. Following April 2011, several fluctuations in the prevalence of use of each modality. Figure 52 shows an overall decline in the use of surgery as treatment strategy over time.

Table with prevalence of recorded use of indomethacin and ibuprofen at each month of admission is given in 9.31 .

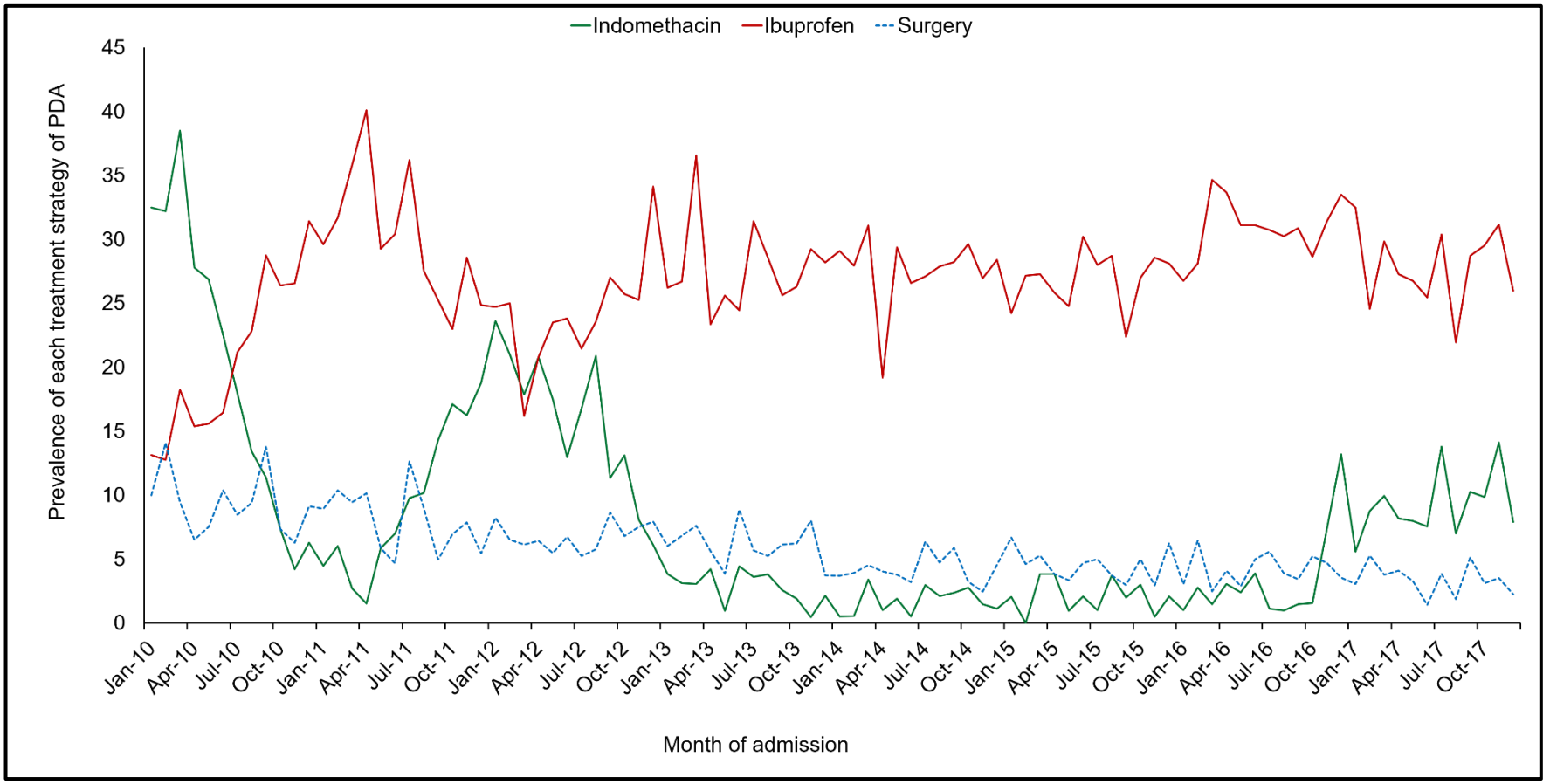


Figure 52. Prevalence in the percentage of different treatment strategies of PDA over time in England and Wales neonatal units from January 2010 to December 2017

4.5.5 Results for objective 4: What is the prevalence of use of paracetamol in neonates with PDA across neonatal units in England and Wales?

As shown in Table 22, 27% (4,889 neonates) of neonates with PDA had paracetamol use recorded at some point during their neonatal stay. However, only 8% (3,280 neonates) of neonates without PDA had paracetamol use recorded.

Table 22. Prevalence of use of paracetamol in neonates with and without PDA

	Number of neonates	Treatment with paracetamol n (%)
With PDA	18,181	4,889 (27)
Without PDA	43,084	3,280 (8)
Total	61, 265	8,169 (13)

PDA, patent ductus arteriosus

Figure 53 shows that there was a noticeable increase in the number of neonates with a record of PDA who were treated with paracetamol from March 2015 onwards. The prevalence of paracetamol used in neonates without PDA diagnosis recorded was lower but also appears to be increasing.

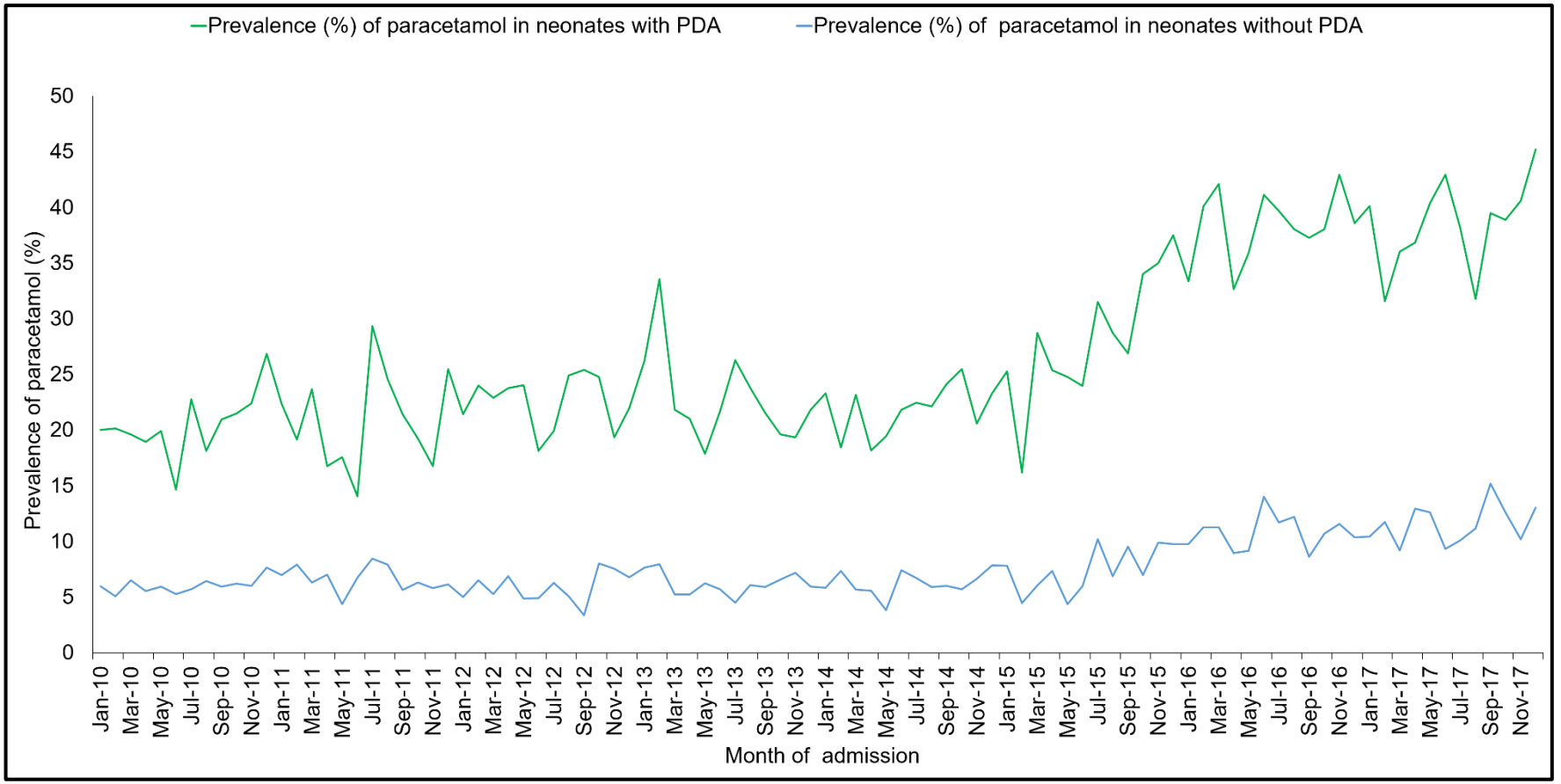


Figure 53. Prevalence of paracetamol used in neonates with PDA and those without PDA across neonatal units in England and Wales

4.5.6 Results for objective 5: What is the duration of treatment for the drugs used for treating PDA?

Table 23 details the total number of days of use of, day of life and corrected GA when indomethacin, ibuprofen, or paracetamol were first given.

Table 23. Duration of the drugs used for PDA

	Indomethacin	Ibuprofen	Paracetamol**
Number of neonates prescribed the drug	1,417	4,926	8,169
Number of days of use*	3 (1-22, 2-5)	3 (1-55,2-4)	3 (1-101,1-7)
Day of life when drug was first prescribed*	8 (1-173,4-15)	10 (1-257,6-15)	56 (1-308,20-68)
Corrected GA when the drug was first prescribed (weeks)*	27 (23-52,25-29)	27 (23-63,26-29)	34 (23-68,31-37)

*Median (range, IQR)

**includes all records of paracetamol irrespective of whether the neonate did or did not have a record of patent ductus arteriosus (PDA)

4.6 Discussion and conclusion

PDA is a key clinical example for exploring evidence-based pharmacotherapy in neonatal practice. It has been the subject of numerous clinical trials and its optimal management is an unresolved debate.

4.6.1 The prevalence of PDA

In the present study, 30% of neonates born at <32 weeks gestation had a record of PDA and/or a treatment indicating the presence of a PDA. Previously published reports estimate that on day three of life neonates with GA< 32 weeks the prevalence of PDA is 20 to 50% (234–236). Similar to other reports (237), I also found that the prevalence of PDA increased with decreasing GA (15% at 28-31 weeks compared to 61% at 22-27 weeks). Prevalence of PDA was lower at 22 and 23 gestational age which may be due to lower survival at these gestations or incomplete records. A previous analysis of NNRD data showed that record completeness is much lower for 23 week neonates as compared to those who are more mature (202).

4.6.2 Change in the prevalence of no treatment over time

I found that, in the study period, there was an increase in the percentage of neonates who did not received any treatment for PDA. The ductus closes without any treatment in most babies especially those who are less immature, have BW > 1000 g, and who do not have respiratory distress syndrome (RDS) (237,238). However, late ductal closure in preterm neonates or those with RDS does not always happen spontaneously and

interventions are needed. However, a growing body of evidence suggests that inducing ductal closure in preterm neonates, particularly in the first two weeks after birth, does not improve the long term outcomes (237,239).

4.6.3 Change in use of ibuprofen and indomethacin over time

I found that more neonates with a diagnosis of PDA were treated with ibuprofen as compared to indomethacin and surgery. The popularity of ibuprofen reflects the evidence, published as several Cochrane reviews (59) (45,47,60,240) that show that ibuprofen is as effective as indomethacin and is associated with a lower risk of necrotising enterocolitis (NEC) and transient renal insufficiency when used for PDA closure.

I found variations in the use of the three treatment strategies. Use of ibuprofen increased in 2010-2011 possibly following the publication of the first Cochrane review (59). In April 2011, amongst neonates who had a record of PDA, 40% (79 neonates) had ibuprofen and only 2% (three neonates) had indomethacin. This pattern is however not consistent. My results show several fluctuations in the use of each treatment modality reflecting the continuous debates and the dilemma in the PDA management. Interestingly, use of indomethacin increased again from April 2011 until the mid of 2012 and with a parallel decrease in use of ibuprofen. By this time, other evidence was emerging describing higher risks of BPD with use of ibuprofen as compared to indomethacin. Jones et al. (241), in a systematic review, reported that IV ibuprofen was associated with approximately 30% increase in the risk of BPD compared to intravenous indomethacin [RR:1.28 (95% CI 1.03 to 1.60)] or placebo [RR 1.29 (95% CI 0.99 to 1.70)]. Further

fluctuations with decrease in use of indomethacin and increase in use of ibuprofen from November 2012 continue to reflect the ongoing debate. The revised Cochrane review (59) reiterated that ibuprofen is the drug of choice for treatment of PDA and that there was no statistically significant increase in the risk of chronic lung disease, a finding that contradicted Jones et al. Thereafter, we see periods of fluctuations but an overall increase in the use of ibuprofen as compared to indomethacin.

4.6.4 Change is use of surgery over time

Surgical intervention is generally reserved for those whose ductus fails to close despite pharmacological treatment, those who have contraindications to pharmacological treatment, or those who have a large duct which may pose a greater risk such as poor neurodevelopmental outcome, BPD and severe retinopathy of prematurity (ROP) (235). I found that only 6% of neonates (n=1,037) with PDA had surgery either alone or in combination with pharmacologic treatment(s). There was a decline in the percentage of neonates with a diagnosis of PDA who had surgery between 2010 (183 neonates, 9% of those with PDA) and 2017 (79 neonates, 3% of those with PDA).

4.6.5 Use of paracetamol

Paracetamol can be used as an analgesic as well as for PDA closure. In this study, 13% (n=8,169) neonates out of the entire cohort had paracetamol. Among those who had a record of a PDA, 27% (n=4,889) had paracetamol whereas 8% (n=3,280) of neonates without PDA diagnosis had paracetamol. As it was not possible to link the drug with the indication of use, I am unable to be certain that paracetamol was used for PDA closure or for analgesia.

Although limited, evidence suggests that paracetamol has a poor analgesic effect in preterm neonates (242). Allegaert et al. evaluated the efficacy of paracetamol for postoperative pain in neonates and found three prospective studies. This review concluded that paracetamol has a very poor analgesic effect when used for postprocedural pain such as heel prick and retinopathy of prematurity screening (233). My findings support the limited use of paracetamol in preterm neonates as I found very few neonates who did not have a PDA but had use of paracetamol recorded.

In addition, some neonates may have received the paracetamol for PDA closure, but a diagnosis of PDA was not recorded. On the other hand, some neonates with a record of PDA may have had the paracetamol as an analgesic.

Assuming that in neonates with a record of PDA, paracetamol was used for PDA closure, from March 2015, there is an increase in the number of neonates treated with paracetamol. In March 2015, the first Cochrane review that investigated the efficacy and safety of paracetamol in preterm neonates with PDA was published (243). It concluded that oral paracetamol is as

effective as oral ibuprofen in PDA closure. However, this review also highlighted the importance of assessing the long-term outcomes of paracetamol when used in preterm neonates. Further updates in in 2018 (244) and 2020 (46) had similar conclusions.

4.6.6 Duration of pharmacological treatment

The median number of days of indomethacin use was 3 (range 1-22, IQR 2-5). Different dosage regimens of indomethacin have been used in studies across the literature. A review by Pacifici et al. reported several studies that used indomethacin for three days while others used it for six days (245). Most studies used three days regimen rather than six days and attained a higher rate of PDA closure of ≥91% (246,247). Interestingly, in my study, there was a neonate who had indomethacin use recorded for 22 days. This was a very preterm neonate with PDA, respiratory distress, and BPD and is likely to be a data entry error.

The median number of days of ibuprofen use was 3 (range 1-55, IQR 2-4). This supports the approved regimen for PDA treatment with ibuprofen which consists of three doses given 24 hours apart (248). An extremely preterm neonate had 55 days of ibuprofen, and following data inspection, this neonate was also diagnosed with BPD at 36 weeks, in addition to PDA, RDS and septicaemia. This is also likely to be a data entry error.

The median number of days of paracetamol use was also 3 (range 1-101, IQR 1-7). Singh and Gooding (2016) summarised the available literature on the role of paracetamol in PDA closure including two RCTs and 14 observational studies (249). The range of paracetamol duration (in days)

reported in those studies was 1 to 11 days, with half of the studies (eight studies) reporting three or 3-6 days as duration of the treatment.

The median first day on which indomethacin was given was day eight (range 1-173, IQR 4-15) at the median corrected GA 27 (range 23-52, IQR 25-29) weeks. Ibuprofen, similarly, was given first on day 10 (range 1-257, IQR 6-15) and at the median corrected GA of 27 (range 23-63, IQR 26-29) weeks. These results suggest that most clinicians deferring the pharmacological treatment of PDA to the second week of life, possibly waiting for spontaneous ductal closure. Ductal closure is delayed in preterm neonates. By day 7, 36% and 32% of 27- 28 weeks and 25-26 weeks neonates, respectively will have spontaneous ductal closure (250). Another study reported that 75% of ≤ 27 weeks neonates (or weighing < 1000 g) with persistent PDA will attain spontaneous ductal closure by hospital discharge (31,32). The median first day on which paracetamol was given was day 56 (6-8 weeks of life). This maybe related to neonates receiving paracetamol following immunisation.

With high rates of spontaneous ductal closure that discourage the early treatment and the fear of co-morbidities associated with persistent PDA, the optimal time to treat PDA remains a dilemma. A recent retrospective study in Sweden investigated whether the timing of indomethacin or ibuprofen is associated with a higher risk of BPD or secondary PDA surgery or death before three months of age in extremely preterm neonates (252). This study concluded that the timing of pharmacological treatment with indomethacin or ibuprofen is not associated with death or secondary PDA surgery and also

the late start of PDA treatment (beyond seven days of postnatal age) was associated with a lower risk of BPD.

4.6.7 Limitations and strengths

This is the first study to provide an overall picture of PDA prevalence across neonatal units in England and Wales. Also, it has compared the different approaches (no treatment vs. treatment) used to manage this condition in terms of their prevalence and whether they have changed over time. I further extended the analyses to provide an overview of the prevalence of pharmacological agents used for PDA and the change in their pattern of use over time.

However, limitations of the NNRD and limited data access hinder full analysis to describe current practice. It was not possible to link the use of drugs with their specific indications. This was not an issue for indomethacin and ibuprofen, drugs that are exclusively use for PDA closure. For paracetamol, however, I was unable to discern if the neonates who had this drug received it for PDA closure or for analgesia. Also, the increase in the use of paracetamol might be related to neonates being received immunisation during their hospital stay, which often lasts longer due to their prematurity. This is another area that required to be further explored from the data set.

The quality of data entered into the NNRD also raised some issues. The human factor of data entry error cannot be neglected (e.g. indomethacin used for 22 days or ibuprofen for 55 days).

Another limitation is that I was unable to gather any information of the dose, regimen, or route of administration of the drugs. Also, as I did not have access to results of any echocardiography or other clinical assessment, I have no information on how PDA was diagnosed, basis for decisions to treat or not, and whether the treatment was successful.

4.6.8 Conclusion

In summary, this study is a useful overview of how PDA is managed across neonatal units in England and Wales, but further research is needed to define details. Some additional areas for future work which are highlighted in Chapter 7.

Although these results show that pharmacological treatment is often used in PDA management, the debate about whether to treat at all continues. In this context, understanding the limitations and dangers of using drugs is an important aspect. Ibuprofen is associated with less risk of NEC and transient renal impairment compared to indomethacin (60,240) but it does have significant side effects. Cochrane and other systematic reviews include RCTs or quasi-experimental randomised trials and mostly focus on the efficacy of the intervention. They report the most known and anticipated adverse effects. These do not give the complete profile of adverse effects of any treatment modality. Several observational studies published in 2012 have reported cases of pulmonary hypertension (51) and GI bleeding (53) associated with ibuprofen use which might lead clinicians to prefer alternative treatment or no treatment. In the next chapter I present an in-depth systematic review of the adverse effects of ibuprofen when used in preterm neonates with PDA.

CHAPTER 5 SYSTEMATIC REVIEW AND META-ANALYSES OF ADVERSE EFFECTS OF IBUPROFEN IN PRETERM NEONATES WITH PDA

5.1 Introduction

5.1.1 Pharmacological management of PDA and their adverse effects: Is it worth a review?

Indomethacin and ibuprofen are pharmacological agents used in PDA management (253–258). Indomethacin has been used since it received' Food and Drug Administration (FDA) approval in 1985. Ibuprofen lysine was approved by the FDA in 2006. Both are non-selective cyclooxygenase inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs). They block the biosynthesis of prostaglandin from arachidonic acid (253). It is believed that their mechanism of action manifests through the reduction of plasma concentration of Prostaglandin E2 (PGE2) (259). PGE2 is known to be the most potent circulatory prostaglandin responsible for the patency of the ductus especially in premature neonates (33). The immature ductus in preterm neonates (particularly those < 28 gestational weeks) is more sensitive to the vasodilating effects of PGE2 (256). Hence, NSAIDs including ibuprofen may be used for the closure of PDA.

The rising frequency of adverse effects such as renal (e.g. oliguria, rise in serum creatinine), gastro-intestinal (GI) (e.g. NEC, haemorrhage), and cerebrovascular events (e.g. intraventricular haemorrhage (IVH)) (15) associated with indomethacin use in neonates triggered the researchers to

use an alternative i.e. ibuprofen. These adverse effects are attributed to the reduction in renal and mesenteric blood flow caused by indomethacin (261). Also, indomethacin reduces cerebral blood flow velocity and cerebral oxygenation (260). Unlike indomethacin, ibuprofen is not associated with a reduction in mesenteric and cerebral blood flow and has a smaller effect on renal perfusion when compared to indomethacin (262). Other adverse effects such as hyperbilirubinemia are also cause of a concern. Both ibuprofen and indomethacin are highly protein bound (253). However, the small dose of indomethacin used in neonates is unlikely to reach drug concentration that displaces bilirubin from albumin binding sites (263). With ibuprofen, an increase risk of hyperbilirubinemia occurs due to its high percent (99%) of protein binding which can displace bilirubin from albumin (255,264).

5.1.2 Defining medication harm in neonates: Adapted definitions in this review

The definition of medication harm is a challenge (265). Falconer et al. collated key studies that define or classify terminology used for medication harm. This review concluded diversity in terminology which may hinder appropriate extrapolation and comparison of data (266). In my study, the terms “Adverse drug reactions (ADRs)”, “toxicity”, and “adverse effects” are used to describe medication harm. ADR is defined by the WHO as “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiologic function”(267). It can be taken from this definition, that there is a causal relationship between the medication and the

reactions. However, in neonates, this may be difficult to apply or assume. This is because ADR definition-related assumptions (known doses and pharmacology, quantification of interactions, the anticipation of side effects or secondary effects, etc.) cannot be speculated (268). Hence, further broader definition of ADRs may be better adopted in this population as suggested by Allegaert and Anker. They describe ADR as “an unintended and harmful effect resulting from the use of medications intended for diagnostic or therapeutic reasons (irrespective of the dose)” (268).

The rationale of using the term “adverse effects” in this review is to follow the overall framework methodology suggested by Adverse Effects Subgroup of the Cochrane Collaboration (269). This term was introduced in 1966 to describe harms related to drugs, chemicals or biological agents when used in accepted dosage (270). Toxicity is a type of ADRs that occur when there is an over ingestion of the drug, elevated blood levels or enhanced drug effects (e.g. impaired metabolism, drug-drug or drug-disease interactions) (271).

The term adverse event is used in clinical trials and covers both drug-related and non-drug related events. According to the WHO, an adverse drug event is defined as ‘ any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relation to the treatment’ (267). Adverse drug event extends beyond ADRs to include harm that is related from medication errors (e.g. under doses, overdoses, etc.) (272). All ADRs are adverse events but not vice versa (266).

5.1.3 Aim of the systematic review

The aim of this systematic review is to identify all the reported adverse effects associated with ibuprofen use for PDA closure in preterm neonates, and to quantify, where possible, their risk per 100 patients.

This review aims to be comprehensive, with minimal restriction of language, study design, settings, and include all existing published and grey literature. This review is guided by the following PICO model (Population, Intervention, Comparator and Outcomes) summarised in Table 24.

Table 24. Summary of the PICO used in this systematic review

Population	Intervention	Comparator	Outcomes
Preterm neonates (born at < 37 weeks gestational age)	Ibuprofen administered by any route, in any dose regimen as treatment or prophylaxis of patent ductus arteriosus	Any conservative, pharmacological or surgical intervention(s)	All reported adverse effects

Patients and indications for use of ibuprofen

There have been several studies that investigated the efficacy of ibuprofen in PDA management. They have compared the use of ibuprofen as a treatment or prophylaxis for PDA closure. In this review, I have considered use of ibuprofen as “prophylactic” where it was administered to all neonates with or without PDA diagnosis who were included based on certain criteria (e.g.

gestational age (GA) at birth or birth weight (BW)). Studies where ibuprofen is given only after a confirmation of echocardiographic or clinical diagnosis of PDA is classified as study using ibuprofen “as a treatment”.

Comparators

Studies have compared the use of ibuprofen with various alternatives: ibuprofen vs. indomethacin; ibuprofen vs. placebo/no treatment; ibuprofen vs. paracetamol. In addition, some have compared different dose regimens or different modes of administration of ibuprofen (such as intravenous vs. oral).

Adverse effects outcomes

The specific product characteristics (SPC) of ibuprofen when used in preterm neonates, lists several adverse effects (273). The most common are related to renal and blood systems (e.g. increase in serum creatinine and thrombocytopenia). Some other adverse effects such as BPD is also classified as possible adverse effect. However, the causality of such adverse effects is hard to determine in preterm neonates as they may be due to prematurity itself. Such effects cannot be differentiated from those that may have been caused by the direct effect of ibuprofen administration.

5.2 Methods

I followed the methodology detailed in Cochrane Collaboration Handbook and systematic reviews of adverse effects frame work (269,274,275) . The adverse effects systematic review framework was developed to provide a detailed approach on conducting systematic reviews of adverse effects. It was structured through a consensus of expert reviewers and members of

adverse effects Subgroup of the Cochrane Collaboration. For this study, a protocol was established and registered in Prospero (ID: 67600; registration number: CRD 42018067600).

5.2.1 Search strategy

5.2.1.1 Information sources

A systematic literature search was carried out to identify all relevant papers describing the adverse effects or ADRs of ibuprofen in premature neonates. The search strategy was developed and tested with the help of the specialised paediatric clinical librarian, Cathryn James, of the University Hospitals of Derby and Burton NHS Trust.

Eight databases [EMBASE, MEDLINE, PubMed, International Pharmaceutical Abstracts (IPA), Cochrane Library, CINAHL, British Nursing Index (BNI), and clinicaltrials.gov] were searched from 1964 to 31 January 2019 without any other limits. This start date was selected because ibuprofen was developed in 1964 (276). A combination of both ‘free text’ and Medical subject headings ‘MeSH terms’ was applied for each database separately to attain a comprehensive literature search. The results of the search were then combined via the End-note software (Thomson Reuters, version X7.7.1) to remove duplications. Duplicates that were not removed by electronic de-duplication were subsequently removed manually. Information on studies in progress, or research reported in the grey literature was sought by searching clinical trials.gov and greylit.org, respectively. In addition, further attempts to identify studies were made by contacting the authors of published conference abstracts and examining the reference lists of all retrieved articles.

5.2.1.2 Search terms

Various ‘free text’ keywords, as well as MeSH terms were used as search terms across the selected databases to provide a comprehensive search. For the population search terms, premature or preterm infants are defined as infants who were born prior to GA of 37 weeks (WHO 2016) (5). Therefore ‘prematurity, preterm, premature*, premmie*, preemie*’ were used to represent population free text key words search terms.

For the intervention free text key words search terms, a combination of both generic and most commonly used brand names of ibuprofen was applied in the search strategy. Most commonly used brand names of ibuprofen were ‘ibumetin, motrin, nuprin, advil, nurofen, brufen’. These were used in addition to the generic name ‘ibuprofen’.

For the adevrse effects outcomes free text keywords search terms, were as recommended by the Cochrane Adverse Effects Methods Group (CAEM) for systematic reviews of adverse effects (269). For example, ‘toxicity* or adverse drug reaction* or side effect* or adverse effect*’.

All of the previously mentioned free text key words were used in addition to the MeSH terms identified in each database separately. The full search strategy is detailed in 9.32.

5.2.1.3 Study selection

Both title and abstracts of the search results were screened independently by two reviewers for initial inclusion, and any disagreements were resolved by consensus or a third reviewer. Ms. Janine Abramson (Research Nurse,

School of Medicine, University of Nottingham) was the second reviewer and disagreeements were resolved by my supervisor, Dr Ojha. The two reviewers (Ms. Abramson and I) then assessed the full texts for inclusion.

5.2.1.4 Inclusion and exclusion criteria

All studies in which ibuprofen is used for treatment or prophylaxis of PDA closure and reported adverse effects/ADRs without any restriction in the study design and publication type were included. This includes randomised controlled trials (RCTs), case reports, case series, and prospective and retrospective cohort studies. Systematic reviews, laboratory studies such as pharmacokinetic or pharmacodynamics (PKPD) evaluations, studies in adults (more than 18 years old of age), studies in the paediatric population but where ibuprofen was used for indications other than PDA closure, studies where information about adverse effects in premature neonates could not be extracted separately were excluded. In addition, reviews, editorials, preliminary reports and letters which did not include any primary data on ibuprofen adverse effects when used for PDA closure were also excluded. Conference poster abstracts were assessed for primary data of ibuprofen adverse effects when used in premature neonates, and the authors were contacted by email for more information if those data were relevant to the review question.

5.2.2 Data synthesis and statistical analysis of the studies

All included studies were tabulated (using Microsoft Excel, Version ‘15’ Microsoft Corporation) to summarise the number of neonates who had received ibuprofen and the number of adverse effects reported.

The risk of adverse effects per 100 patients was calculated from the RCTs and prospective cohort studies only. The risk was calculated by dividing the number of patients with a particular adverse effect by the total number of patients who received ibuprofen and then multiplying it by 100. This was done following the methodology of previous systematic reviews of drug toxicity (277).

Due to the sufficient number of the included RCTs, meta-analyses were performed, using RevMan (version 5.3), to obtain an overall measure of the risk of adverse effects. To ensure homogeneity, RCTs were grouped together according to the types of comparators. The risk ratio was calculated with 95% confidence interval (CI). Statistical heterogeneity was measured using I^2. This statistical test measures the variation across the studies in a percentage figure. Fixed effect model was used in the forest plots where I^2 was less than 50 %, and random effect model was used where I^2 is more than 50% (25).

5.2.3 Quality assessment

Two reviewers (Ms. Abramson or Dr Ojha and I) assessed all of the RCTs included in the review independently for risk of bias (ROB) using the Cochrane 'Risk of bias' tool (278). The domains for assessment included the following:

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)

- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Any other bias (defined as any bias related to the funding/sponsorship and other issues related to the methodology)

Non-randomised trials (observational studies) were assessed by two reviewers (Ms. Abramson or Dr Ojha and I) using Joanna Briggs Institute (JBI) appraisal tools to assess the quality of the observational studies (e.g. case reports, cohort studies, case series, etc.) (279). Any discrepancies were resolved through discussion and adjudication by a third reviewer. However, it is of note that the decisions made by using this tool are subjective and it is recommended that all studies are included after assessing their quality (279).

5.2.4 Data extraction

I extracted all data using a structured proforma. To ensure completeness, all data extraction was performed in duplicate and a selection (20%) were checked by Dr Ojha.

The data extracted includes:

- All types and number of adverse effects related to ibuprofen administration
- Route of ibuprofen administration (IV or oral)
- Dose and frequency of ibuprofen
- Number of courses of ibuprofen administered
- Indication of ibuprofen given for PDA (treatment/prophylaxis)

- Comparator of ibuprofen used in the study (e.g. placebo, indomethacin, paracetamol, other ibuprofen formulations)
- Adverse effects that led to discontinuation of ibuprofen, and adverse effects of ibuprofen that resulted in prolonged hospital stay or hospital admission or death. Adverse effects were classified according to the organ system and tabulated with the corresponding numbers.

5.3 Results

5.3.1 Description of chracteristics of included studies

Initial search returned 2458 titles and abstracts and after exclusions 93 studies were included in the review. Reason of excluded studies and trials are given in appendix 9.33 and 9.34.

Figure 54 represents the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart of the total number of references identified in the searched databases.

This included 42 RCTs. Three publications, Pistulli et al., Eras et al. and Oncel et al. (280–282) were follow up publicaiton of the same RCT reported in Hoxha et al., Gokmen et al. and Oncel et al. (283–285) respectively. These three publications have been included with the first publication of resutls of their original RCTs.

This review also includes non-randomised studies: 33 cohort studies, four case series, two case-control studies and nine case reports.

In addition, ten ongoing trials awaiting results were reviewed (detailed in appendix 9.35).

No study was excluded after quality assessment.

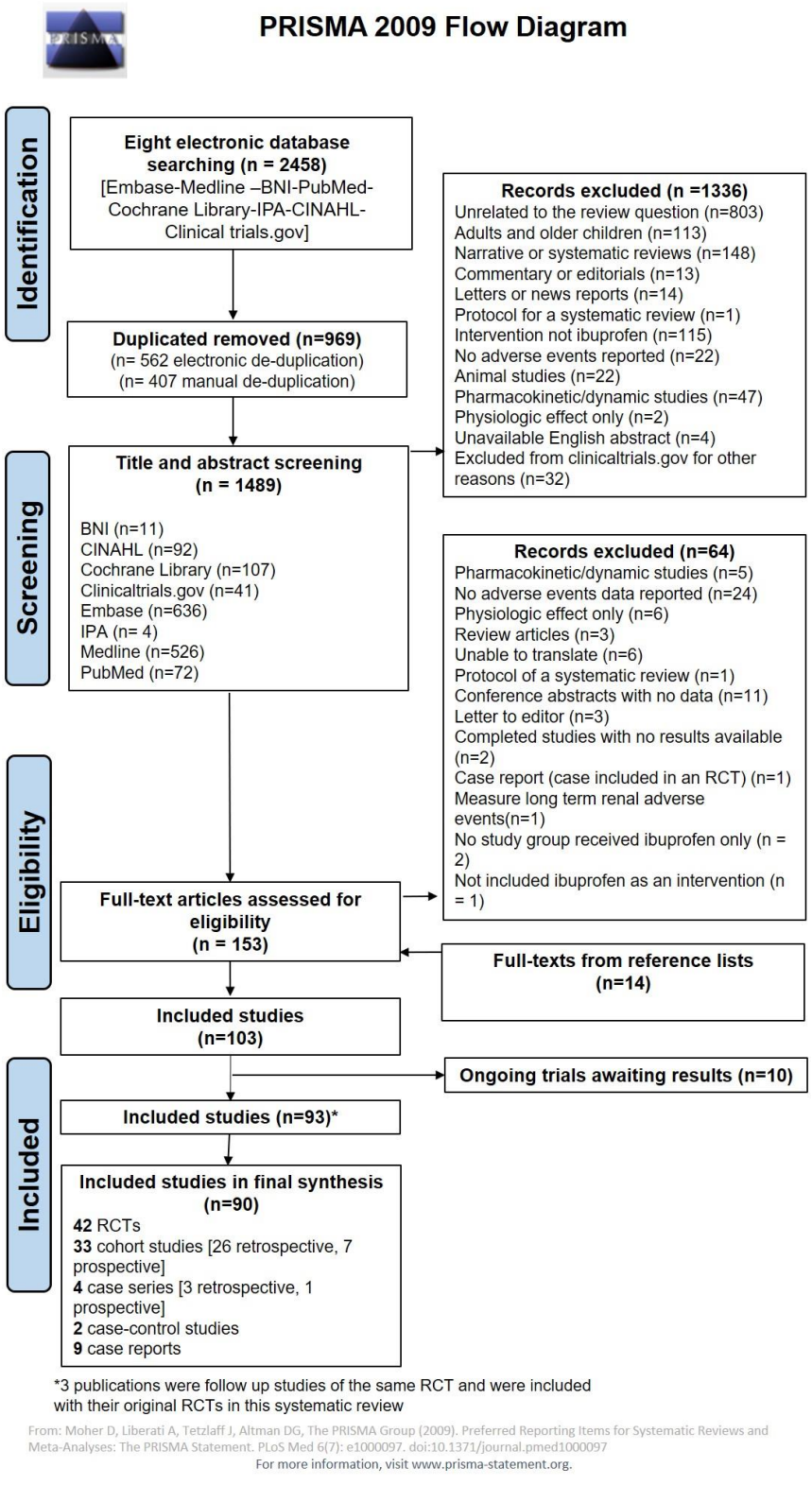


Figure 54. PRISMA flow chart of the total number of references identified in the searched databases

5.3.2 Sub-classification of included studies

Ibuprofen was administered for PDA treatment in 35 RCTs (179,262,280,281,283–315) and in 44 observational studies (50,52–54,316–353) (Figure 55). Ibuprofen was administered for PDA as prophylaxis in six RCTs (262,354–359) and in five observational studies (41,346,360–362) (Figure 56).There was one retrospective case series study with unclear reporting of the indication for use (43) and one RCT that compared ibuprofen when used as treatment vs. use as prophylaxis (44).

The comparators are classified as:

- Comparator 1:Ibuprofen vs. placebo/no treatment
- Comparator 2:Ibuprofen vs. indomethacin
- Compatrator 3:Ibuprofen vs. paracetamol
- Comparator 4:Other studies (detailed in section 5.3.3.2.4)

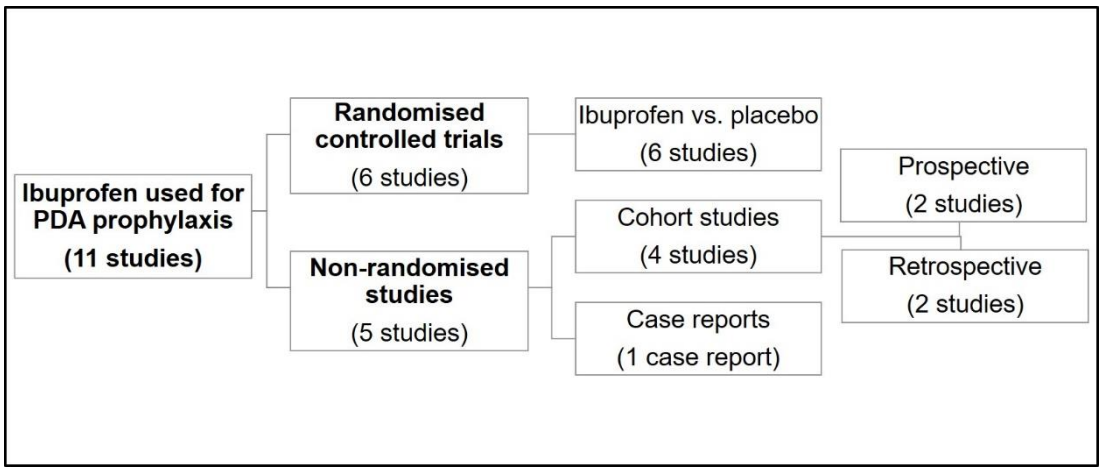


Figure 55. Included studies: Ibuprofen for prophylaxis of patent ductus arteriosus (PDA)

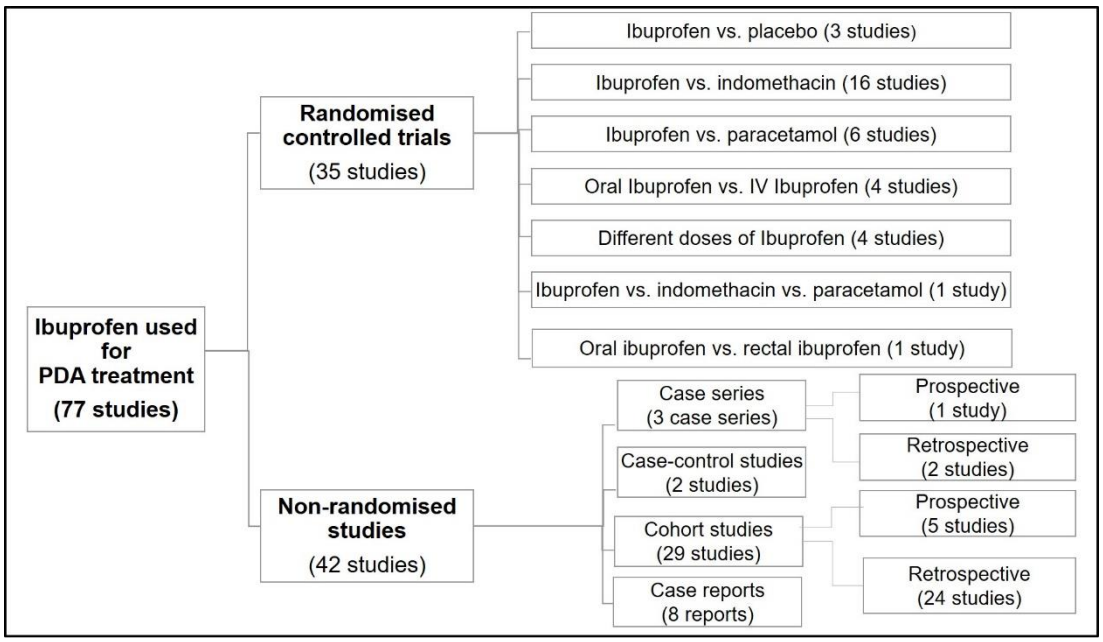


Figure 56. Included studies: Ibuprofen for treatment of patent ductus arteriosus (PDA)

5.3.3 Quality assessment of included studies (RCTs)

5.3.3.1 Studies of ibuprofen use for PDA prophylaxis

Six RCTs (354–358) included in this review compared ibuprofen to placebo when used in PDA prophylaxis.

Summary of ROB assessment, as per the Cochrane risk of bias tool (278) for RCTs is given in Figure 57 and Figure 58.

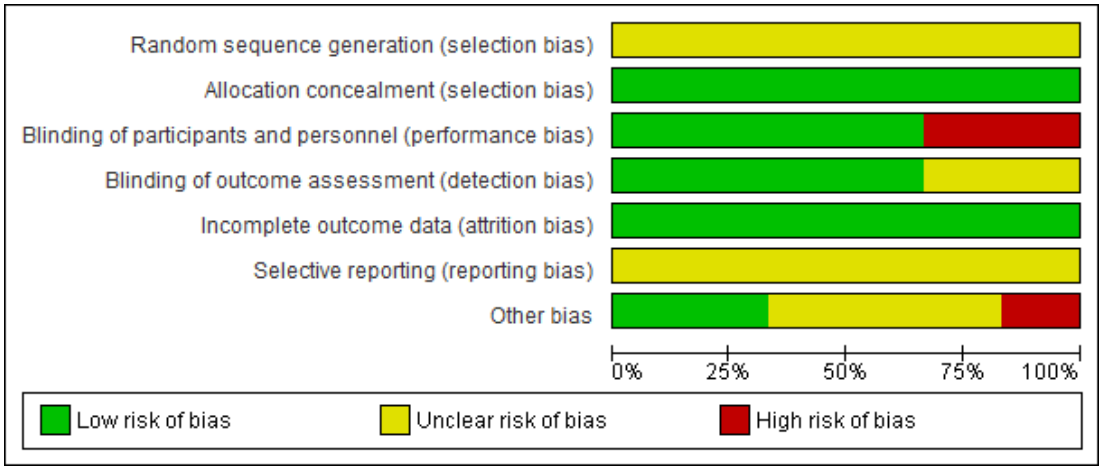


Figure 57. Risk of bias graph of studies comparing ibuprofen vs. placebo (PDA prophylaxis)

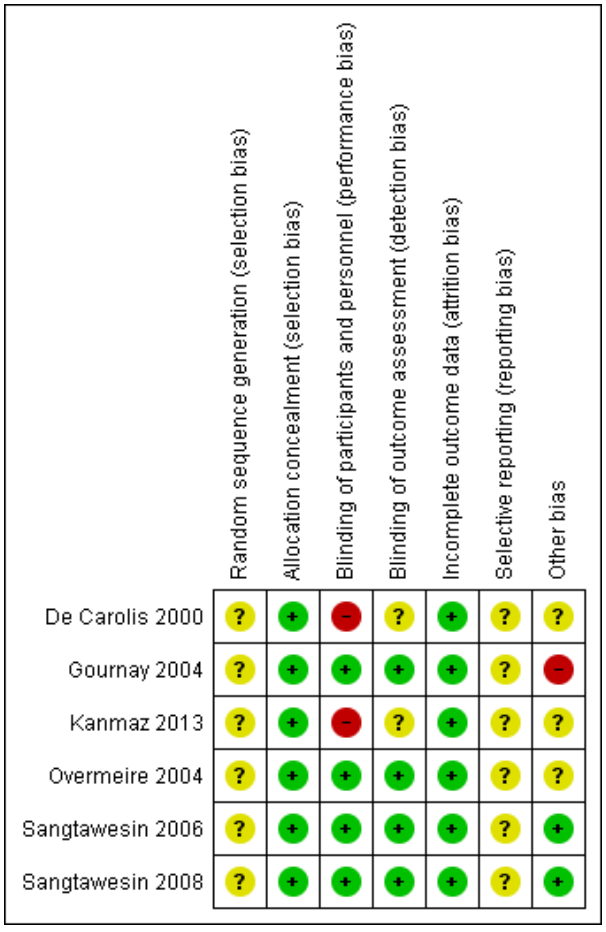


Figure 58. Risk of bias summary of studies comparing ibuprofen vs. placebo (PDA prophylaxis)

5.3.3.2 Studies of ibuprofen use for treatment of PDA

5.3.3.2.1 Comparator 1: Studies comparing ibuprofen to placebo/no treatment

There were three studies (286–288) included in this comparison. ROB is given in Figure 59 and Figure 60.

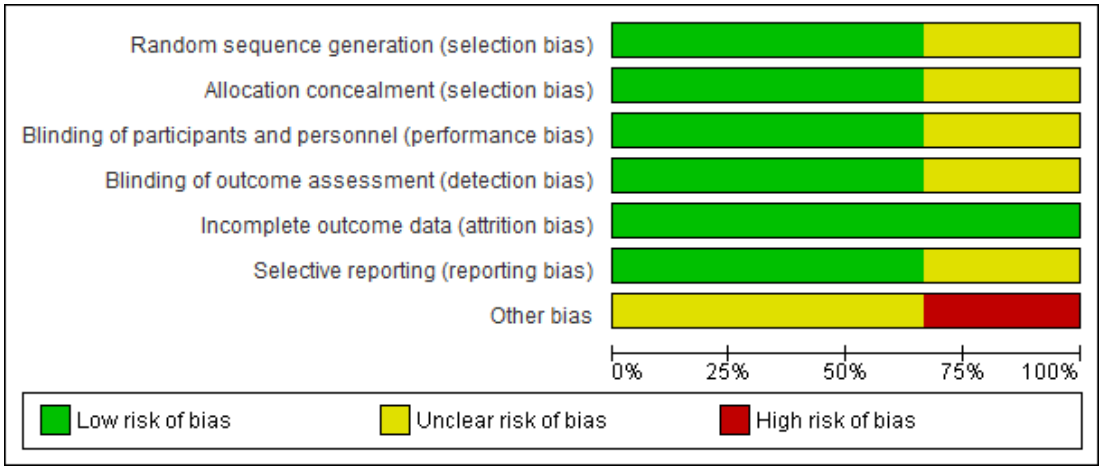


Figure 59. Risk of bias graph of studies comparing ibuprofen vs. placebo or no treatment (PDA treatment)

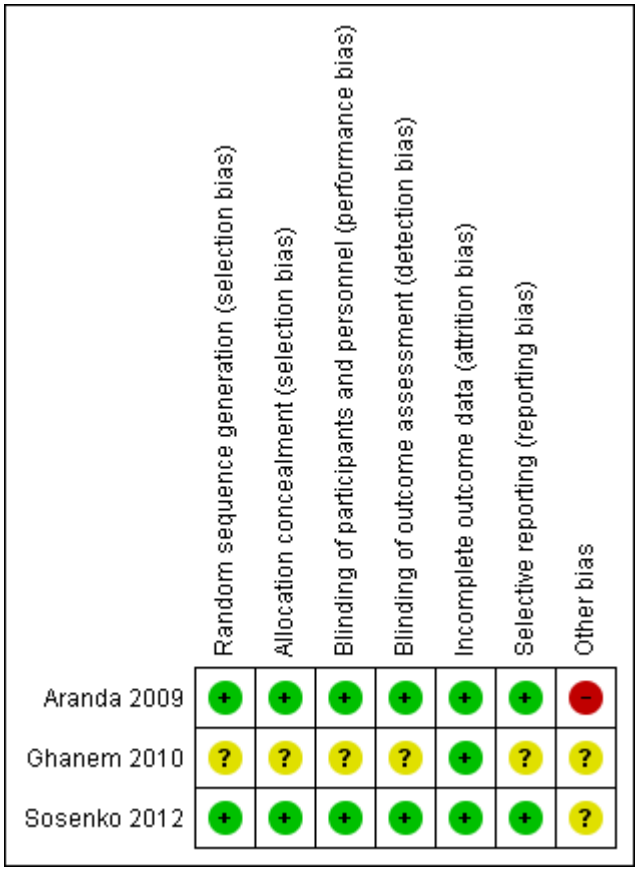


Figure 60. Risk of bias summary of studies comparing ibuprofen vs. placebo or no treatment (PDA treatment)

5.3.3.2.2 Comparator 2: Studies compaing ibuprofen to indomethacin

There were 16 studies (56–69, 82) included in this comparison. ROB is given in Figure 61 and Figure 62.

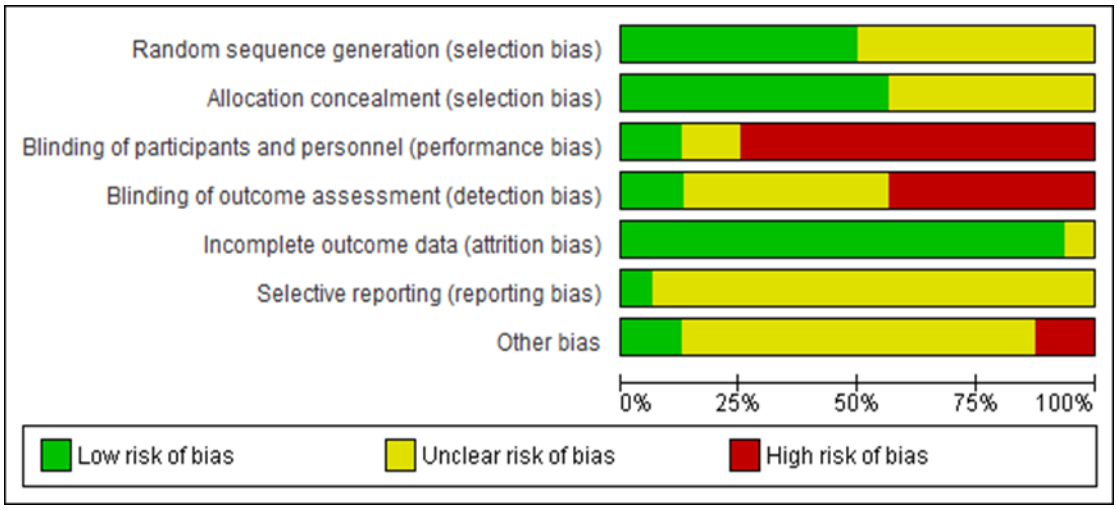


Figure 61. Risk of bias graph of studies comparing ibuprofen vs. indomethacin (PDA treatment)

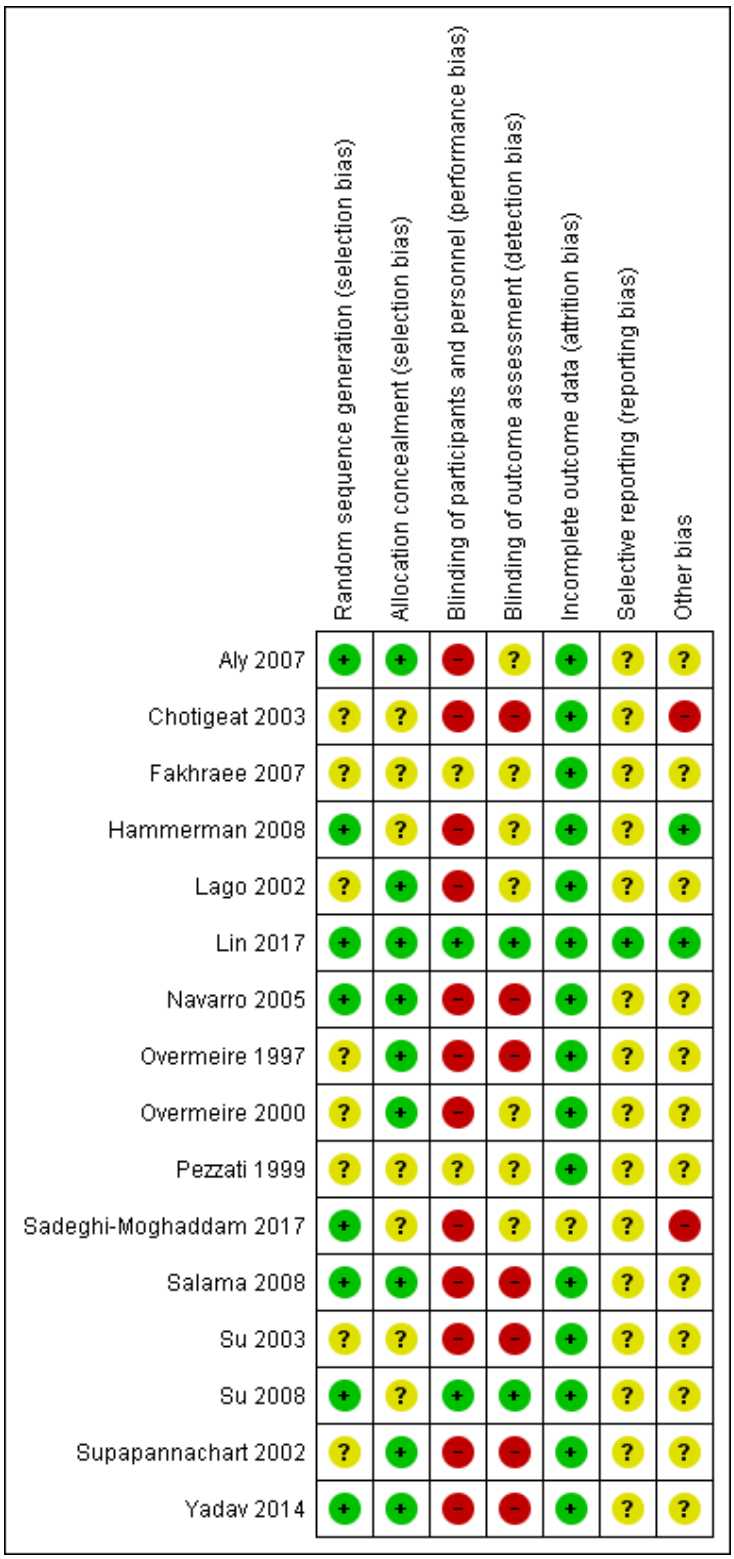


Figure 62. Risk of bias summary of studies comparing ibuprofen vs. indomethacin (PDA treatment)

5.3.3.2.3 Comparator 3: Studies comparing ibuprofen to paracetamol

There were six studies (179,282,285,303,304,311,312) included in this comparison. ROB is given in Figure 63 and Figure 64.

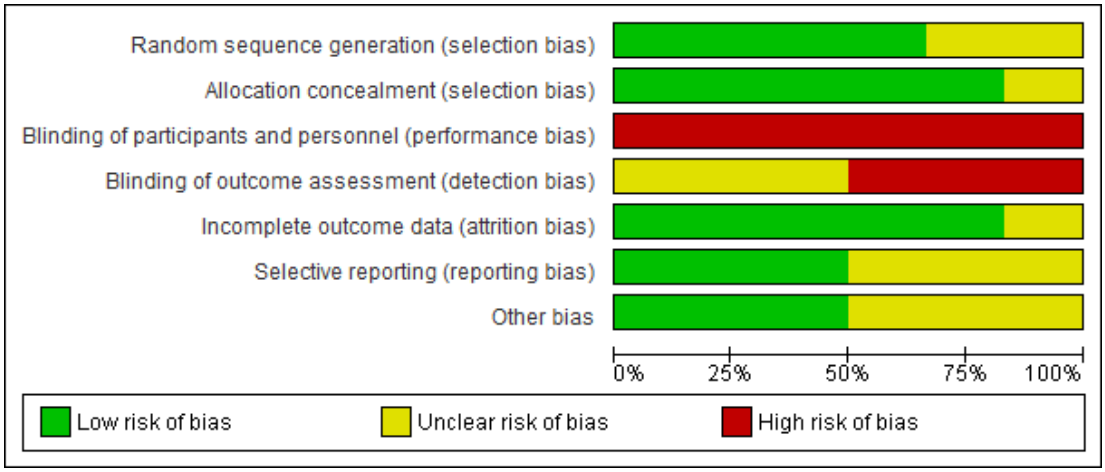


Figure 63. Risk of bias graph of studies comparing ibuprofen vs. paracetamol (PDA treatment)

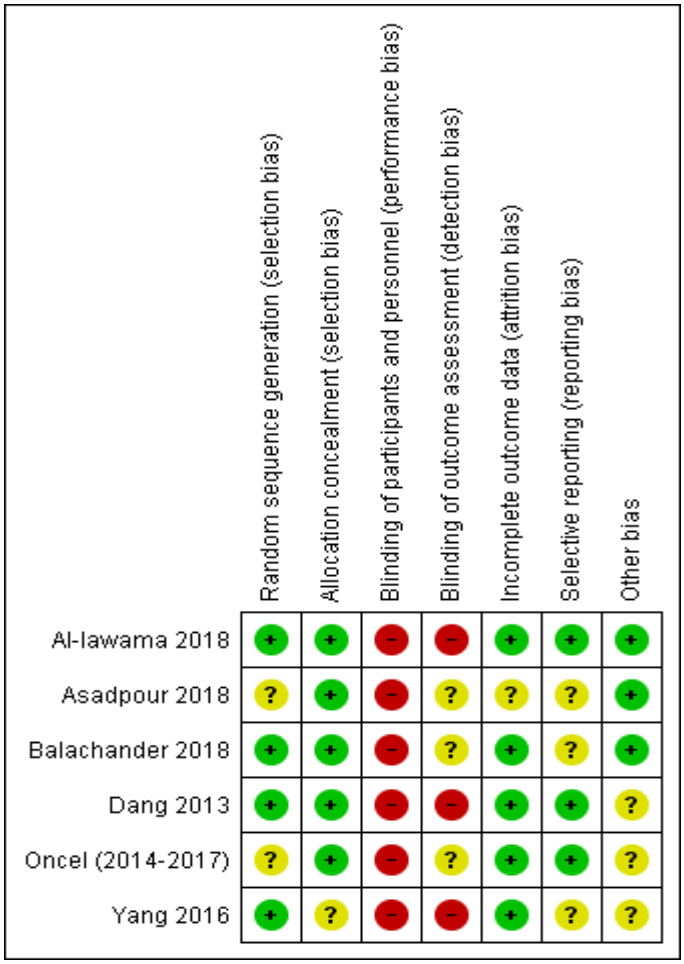


Figure 64. Risk of bias summary of studies comparing ibuprofen vs. paracetamol (PDA treatment)

5.3.3.2.4 Comparator 4: Other studies

This category includes studies where ibuprofen is used in different regimen, routes of administration and indications, including:

- Oral ibuprofen vs. IV ibuprofen (four studies) (280,281,283,284,305,306)
- Standard dose ibuprofen vs. high dose ibuprofen (two studies) (309,363)
- Ibuprofen IV bolus vs. ibuprofen IV continuous infusion (one study) (310)
- Oral ibuprofen vs. rectal ibuprofen (one study) (313)

In addition, El-Mashed et al. (2017) was a three arm study which compared ibuprofen, indomethacin and paracetamol (307). Dani et al. (2000) compared ibuprofen used as prophylaxis vs. treatment (44) while Bravo et al. (2014) compared ibuprofen used in standard doses vs. ibuprofen doses given only if the PDA persisted (on ECHO examination) after each dose (315). The ROB for these is given in Figure 65 and Figure 66.

The detailed risk of bias assessment of all included RCTs is given in appendix 9.36 .

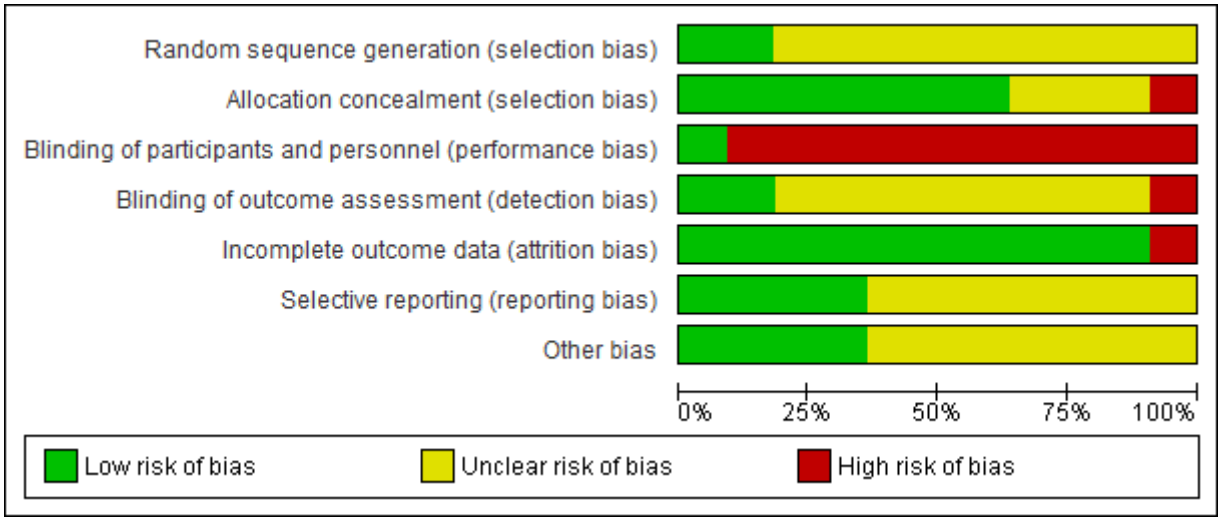


Figure 65. Risk of bias graph of studies comparing ibuprofen in different regimen, routes, and indications

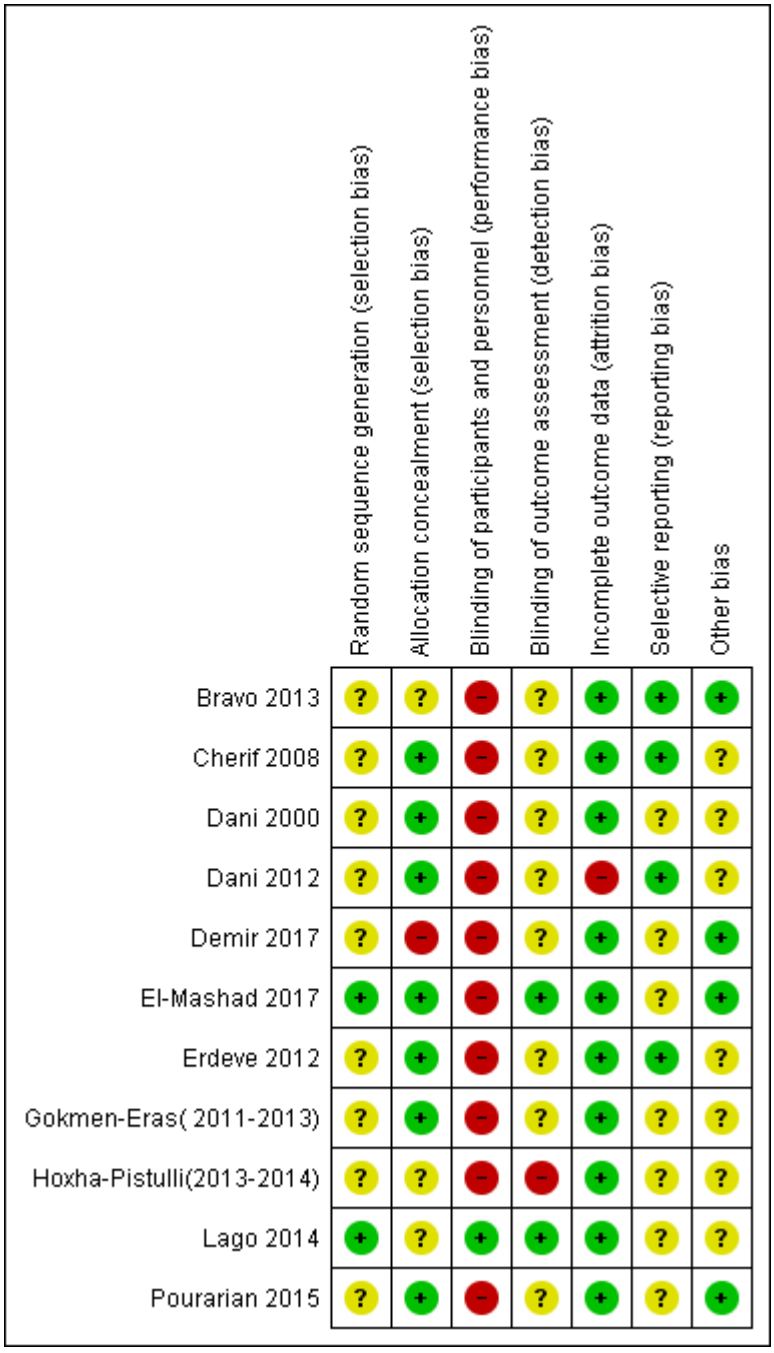


Figure 66. Risk of bias summary of studies comparing ibuprofen in different regimen, routes, and indications

5.3.4 Quality assessment of non-RCTs

5.3.4.1 Cohort studies of ibuprofen use for PDA prophylaxis

Three cohort studies (41,360,361) compared ibuprofen when used in PDA prophylaxis to placebo. Only one cohort study (346) compared ibuprofen when used in PDA prophylaxis to indomethacin.

Summary of risk of bias assessment, using the JBI tool (279) is given in Figure 67 .

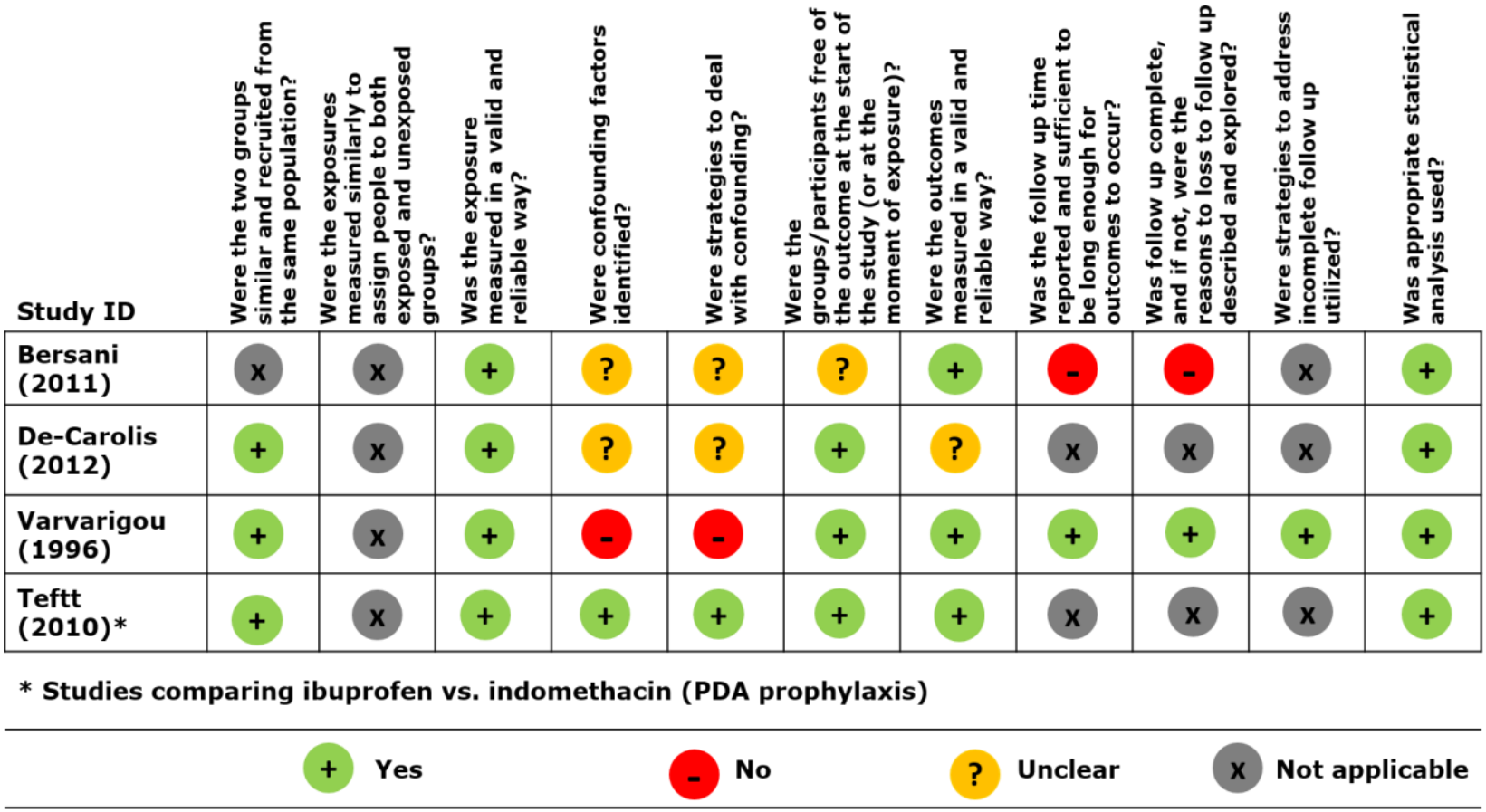


Figure 67. Risk of bias assessment for cohort studies comparing ibuprofen to placebo/no treatment and ibuprofen to indomethacin (PDA prophylaxis)

5.3.4.2 Cohort studies of ibuprofen use for treatment of PDA

Twenty nine cohort studies were included in which ibuprofen was used for PDA treatment.

5.3.4.2.1 Cohort studies comparing ibuprofen to placebo/no treatment and ibuprofen to indomethacin

Thirteen cohort out of the 29 cohort studies compared ibuprofen to indomethacin (324,326,327,329–331,333–335,343–345,349). Only two compared ibuprofen to placebo (321,336).

Summary of risk of bias assessment, using the JBI tool is given in Figure 68.

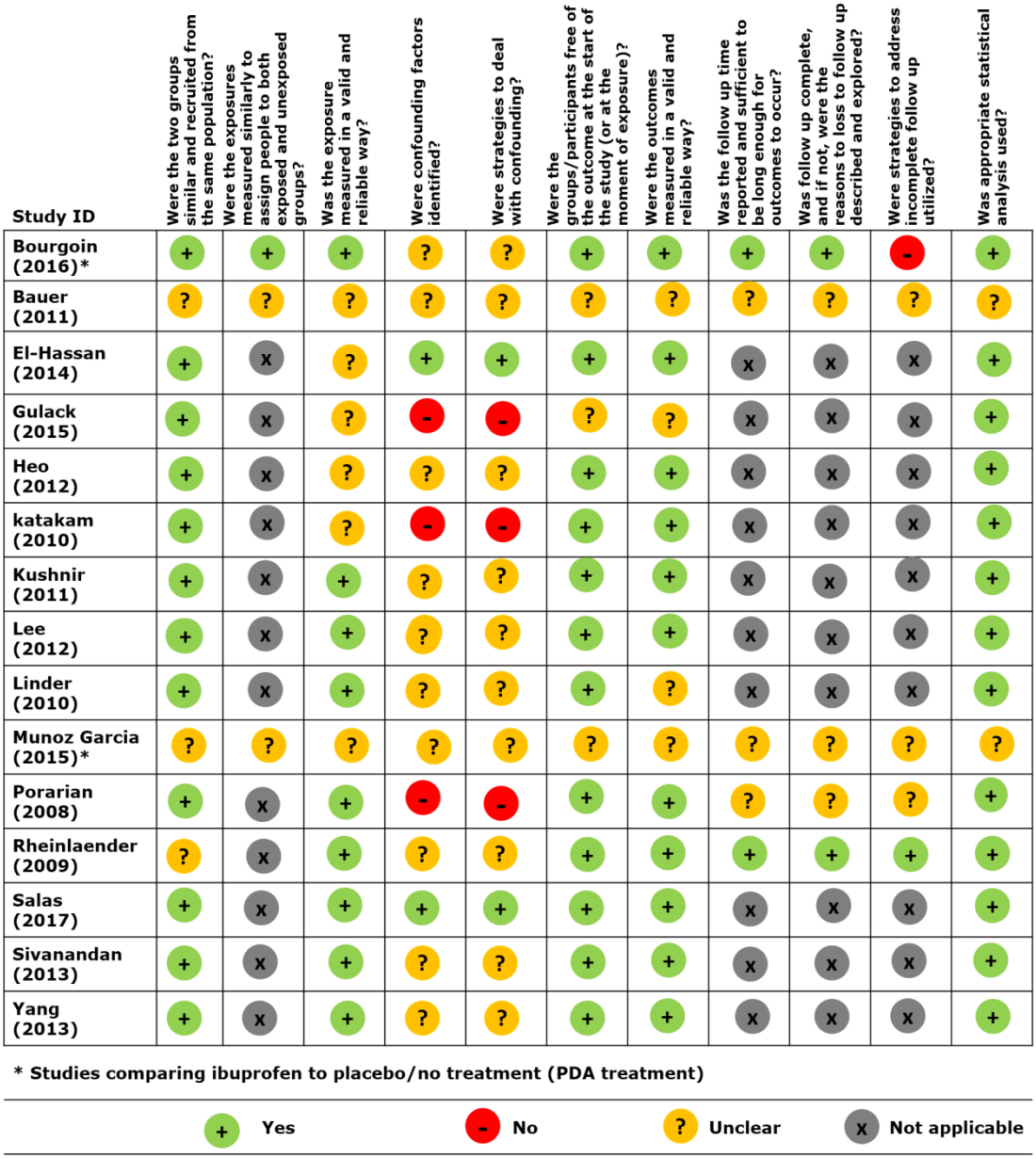


Figure 68. Risk of bias assessment for cohort studies comparing ibuprofen to placebo/no treatment and ibuprofen to indomethacin (PDA treatment)

5.3.4.2.2 Cohort studies comparing ibuprofen to paracetamol

There were no cohort studies comparing ibuprofen (used for PDA treatment) to paracetamol that met the inclusion criteria.

5.3.4.2.3 Other cohort studies included in this review

There was 11 cohort studies (322,323,325,332,337,338,340,341,347,348,364) that compared ibuprofen in different dose regimens. Two cohort studies (339,342) did not report a comparison group while one (328) compared several arms (ibuprofen vs. indomethacin vs. control vs. no treatment).

Summary of risk of bias assessment, using the JBI tool is given in Figure 69 and Figure 70.

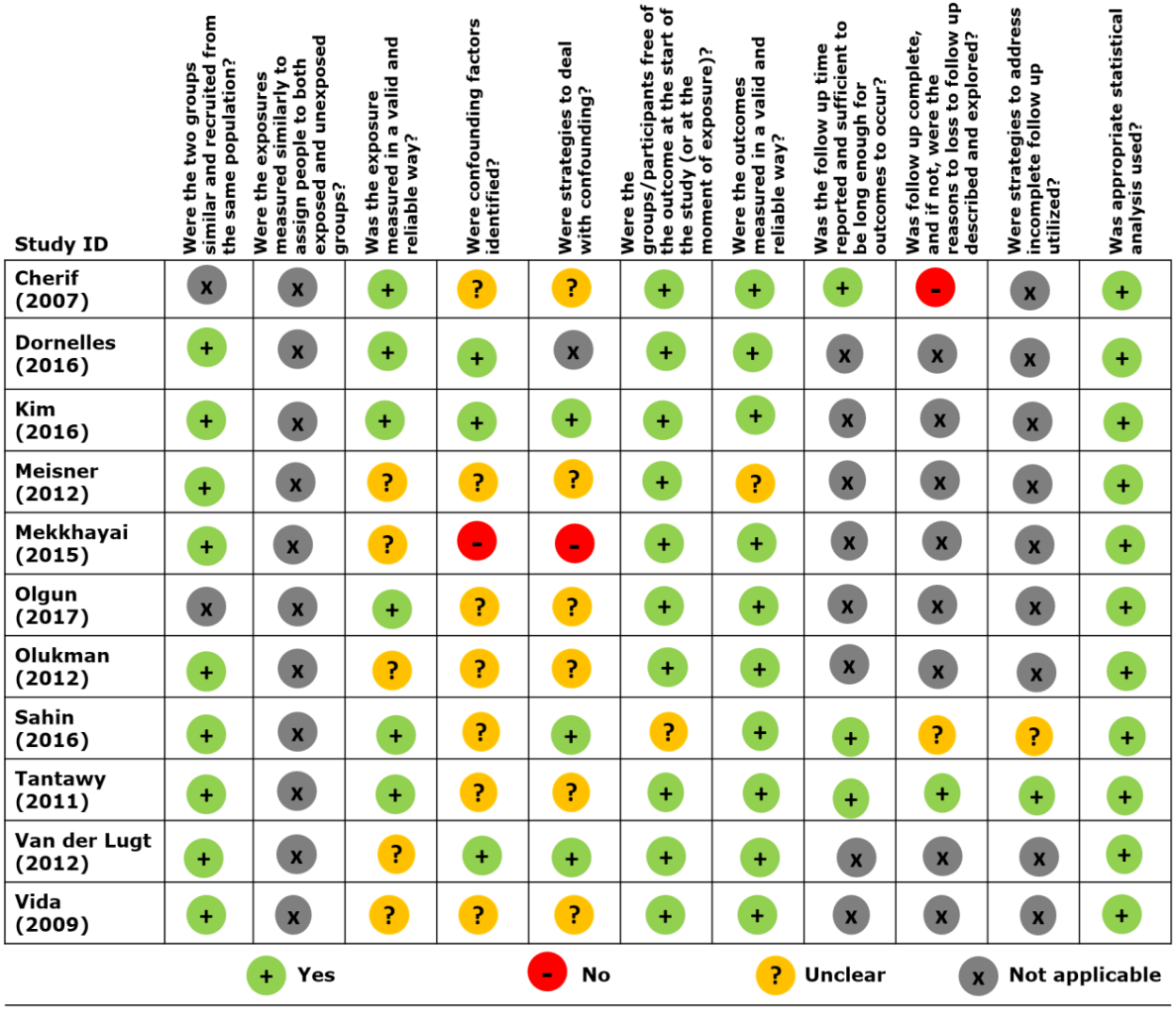


Figure 69. Cohort studies comparing ibuprofen in different dose regimen (PDA treatment)

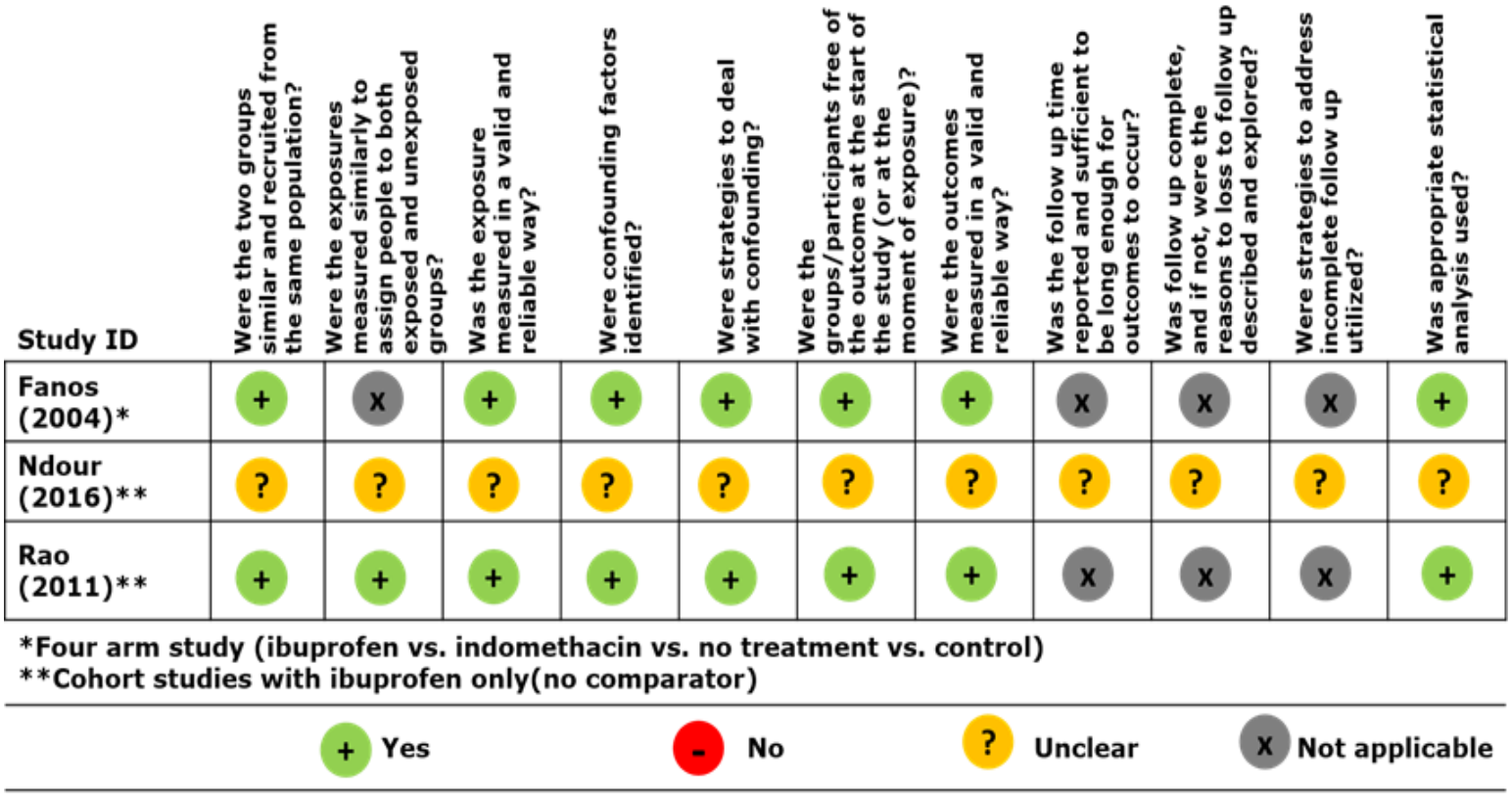


Figure 70. Other cohort studies where ibuprofen used for PDA treatment

5.3.5 Overview of adverse effects across all studies

A total of 6,937 neonates received ibuprofen for PDA management and a total of 4,700 adverse effects were reported (Table 25). The largest number of neonates (3,831) receiving ibuprofen were recruited within the 26 retrospective cohort studies. This group also reported the highest number of adverse effects (2,264 adverse effects). The 42 RCTs reported the second largest number of adverse effects (1,911 adverse effects).

Table 25. Summary of the reported adverse effects in the included studies

Study type	Number of studies	Number of patients who received ibuprofen N (%)*	Number of adverse effects reported N (%)[#]
Randomised controlled trials	42	2,200 (32%)	1,911 (40.7%)
Prospective cohort studies	7	681 (9.8%)	309 (6.6%)
Prospective case series	1	22 (0.3%)	7 (0.1%)
Retrospective cohort studies	26	3,831 (55%)	2,264 (48.2%)
Retrospective case series	3	96 (1.4%)	99 (2.1%)
Case-control studies	2	96 (1.4%)	99 (2.1%)
Case reports	9	11 (0.1%)	11 (0.2%)
Total	90	6,937	4,700

*as a percentage of total number of neonates who received ibuprofen across all types of studies

[#]as a percentage of total number of adverse effects among neonates who received ibuprofen across all types of studies

5.3.6 Risk of adverse effects from RCTs and prospective cohort studies

The calculated risk of each adverse effect per 100 patients in the RCTs and prospective cohort studies included in this review is shown in Table 26. The most common adverse effects in GI and renal systems were NEC and oliguria, respectively. BPD was the most frequently reported respiratory adverse effect. There was hertrogenity in the defintion of BPD used in the studies.

Table 26. Calculated risk of adverse effects from RCTs and prospective cohort studies

Adverse effects	Number of patients with adverse effects (numerator)	Number of studies reported advere effects	Number of patients received ibuprofen (denominator)	Risk per 100 patient
Gastro-intestinal system				
NEC	190	46	2548	7.5
Intestinal/bowel perforation	23	17	1036	2.2
GI bleeding	87	19	1047	8.3
Feeding intolerance	34	4	120	28.3
Renal system				
Oliguria*	146	21	1917	7.6
Renal failure**	29	7	333	8.7
Increase in serum creatinine	33	6	548	6.0
Respiratory system				
BPD at 28 days	277	6	638	43.4
BPD at 36 weeks	260	14	1039	25.0
BPD (not defined)	170	18	749	22.7
Pulmonary hypertension	17	9	616	2.8
Pulmonary haemorrhage	20	9	455	4.4
Hypoxaemia	15	1	65	23.1
Nervous system				

IVH (any grade)	313	26	1561	20.1
IVH (grade III-IV)	44	8	595	7.4
PVL	66	17	1103	6.0
Neurodevelopmental impairment	88	2	288	30.6
Blood system				
Thrombocytopenia	18	3	88	20.5
Prolonged coagulogram	4	1	22	18.2
Others				
Hyperbilirubinaemia	28	1	80	35
Hypoglycaemia	35	1	60	58.3
Jaundice	25	1	55	45.5
Cholestasis	2	1	55	3.6
All cause mortality	233	37	1919	12.1

*study by Asadpour et al. (2018) reported abnormal urine output (unclear definition) and was not included

**some studies reported acute kindney injury and were included in the calculation of this adverse event

BPD, Bronchopulmonary dysplasia; GI, gastrointestinal; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, Periventricular leukomalacia

5.3.7 Meta-analyses of adverse effects of ibuprofen reported in RCTs

Forty two RCTs were included in this review. In six RCTs, ibuprofen was used as a prophylaxis (354–357,359,365) and in 35 for treatment (179,262,280–307,309–315,363). Characteristics of the included RCTs and the reported adverse effects is given in appendix 9.37.

The next sections summarise the results of the meta-analyses of the adverse effects reported in the included RCTs.

5.3.7.1 GI adverse effects

NEC was the most frequently reported GI adverse effect among the included RCTs (40 RCTs), followed by GI bleeding (17 RCTs), intestinal/bowel perforation (15 RCTs), and feeding difficulties (four RCTs) (Table 27).

The meta-analyses for NEC did not show any difference between ibuprofen when compared to placebo/no treatment or when compared to paracetamol. Ibuprofen had a lower risk of NEC when compared to indomethacin [16 studies; 1125 patients; RR: 0.66, 95% CI: 0.47 to 0.93, p=0.02] (Figure 71). Other studies (ten RCTs) are discussed in section 5.3.7.7.

Higher risk of GI bleeding was found with ibuprofen when compared to placebo/no treatment [three studies; 140 patients; RR: 2.09, 95% CI: 1.20 to 3.66, p=0.010], and with paracetamol [two studies; 240 patients; RR: 7.00, 95% CI: 1.91 to 25.61, p=0.003]. There was no difference in the risk of GI bleeding when ibuprofen was compared to indomethacin (Figure 72). Other studies (seven RCTs) are discussed in section 5.3.7.7.

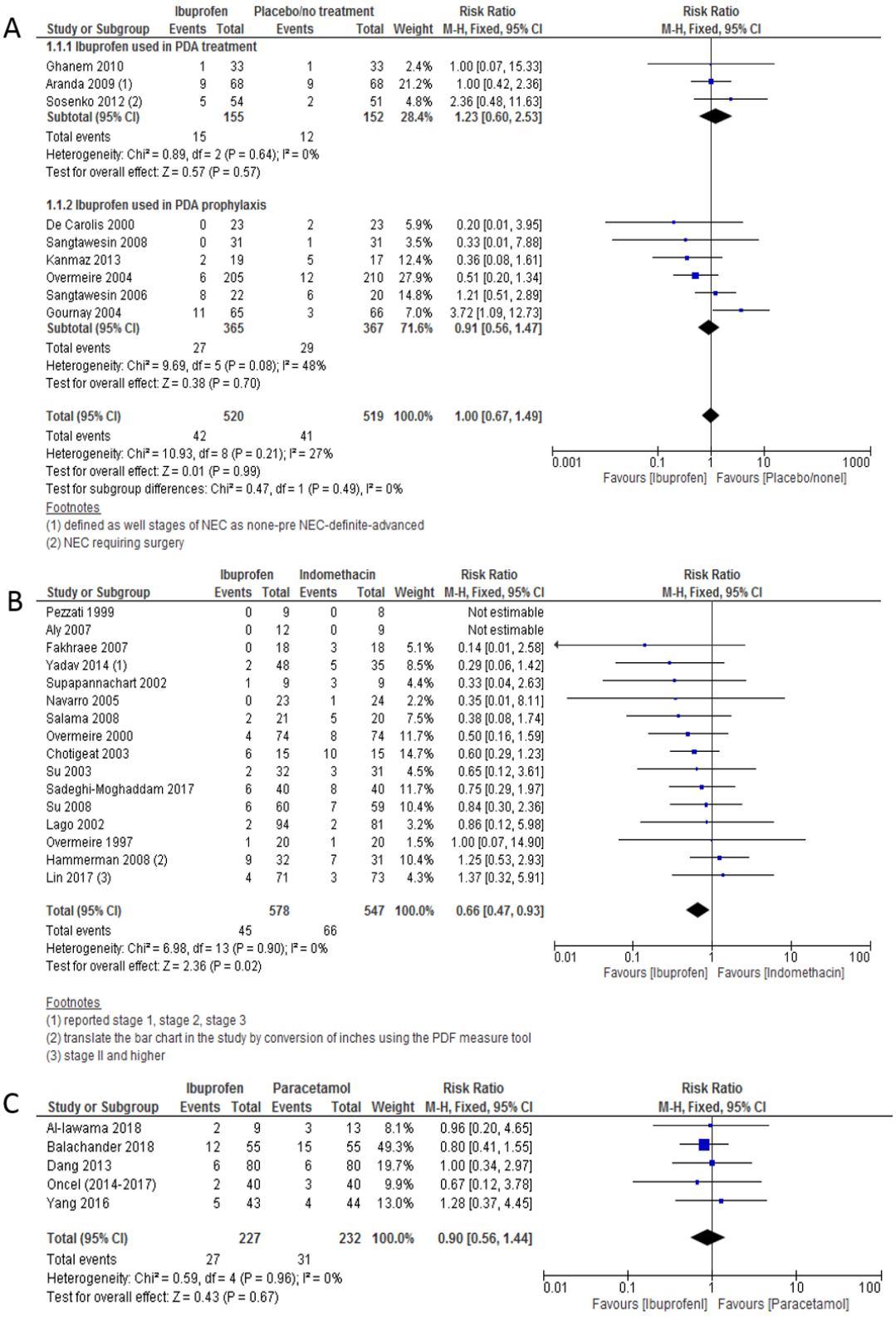


Figure 71. Meta-analyses for the risk of NEC comparing ibuprofen to A. placebo/no treatment B. indomethacin C. paracetamol

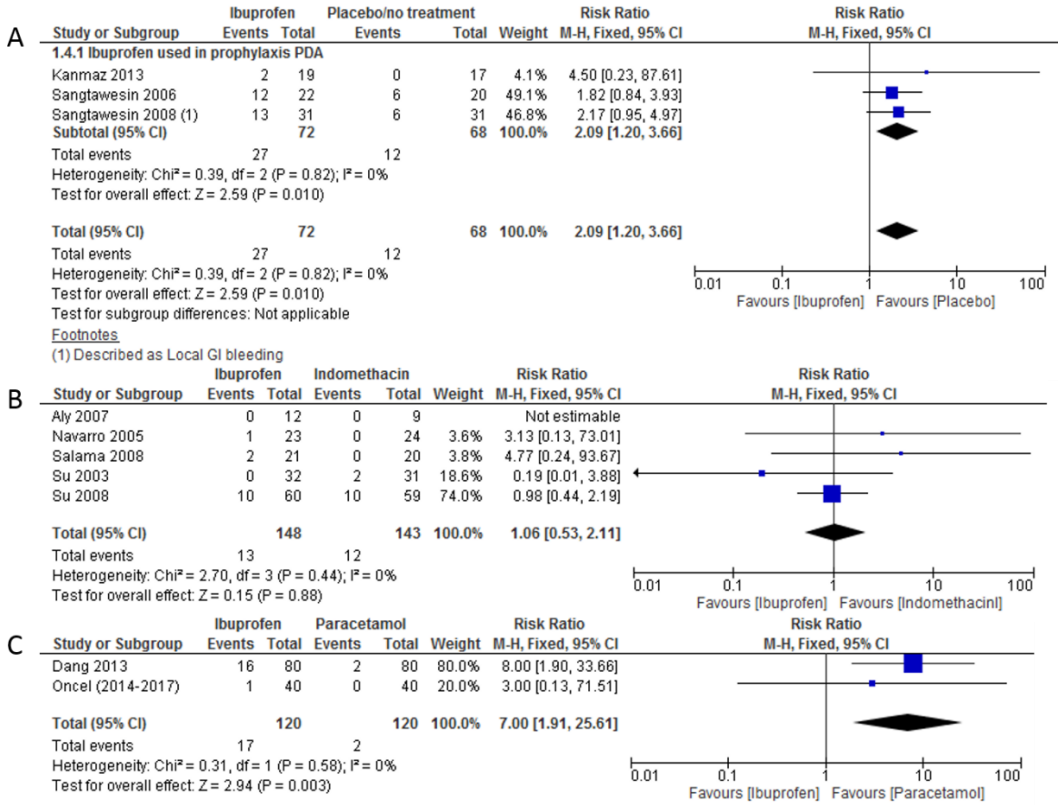


Figure 72. Meta-analyses for the risk of GI bleeding comparing ibuprofen to A. placebo/no treatment B. indomethacin C. paracetamol

Table 27. Summary of meta-analyses of GI adverse effects following ibuprofen use in preterm neonates with PDA

Outcome	Intervention	Comparator	Studies	Number of patients	RR (95% CI)	P value	I^2 (%)
NEC	Ibuprofen	Placebo/no treatment	9	1039	1.00 [0.67, 1.49] ¶	0.99	27
	Ibuprofen	Indomethacin	16	1125	0.66 (0.47,0.93)	0.02	0
	Ibuprofen	Paracetamol	5	459	0.9 (0.56, 1.44)	0.96	0
Intestinal/ bowel perforation	Ibuprofen	Placebo/no treatment	4	338	1.78 (0.32, 9.85) ¶	0.51	46
	Ibuprofen	Indomethacin	7	591	0.60 (0.28, 1.30)	0.20	0
	Ibuprofen	Paracetamol			No eligible studies		
GI bleeding	Ibuprofen	Placebo/no treatment	3	140	2.09 (1.20, 3.66) ¶	0.010	0
	Ibuprofen	Indomethacin	5	291	1.06 (0.53, 2.11) ¶	0.88	0
	Ibuprofen	Paracetamol	2	240	7.00 (1.91,25.61) ¶	0.003	0
Feeding difficulties	Ibuprofen	Placebo/no treatment	2	88	1.77 (1.08, 2.91) ¶	0.02	10
	Ibuprofen	Indomethacin	1	40	Not estimable as zero events in both groups		
	Ibuprofen	Paracetamol	1	110	0.89 (0.37,2.13)	0.79	n/a

¶ RR value >1 denotes higher rates of adverse effects with ibuprofen compared with the comparator
GI; gastrointestinal bleeding, NEC; necrotising enterocolitis, n/a; not applicable

5.3.7.2 Renal adverse effects

Oliguria was the most frequently reported renal adverse effect in the included RCTs (18 RCTs) followed by renal failure (six RCTs) (Table 28).

There was no difference in the risk of oliguria when ibuprofen was compared to placebo/no treatment (two RCTs) and when compared to paracetamol (three RCTs). However, lower risk of oliguria with ibuprofen was found in comparison to indomethacin [five studies; 626 patients; RR: 0.38, 95% CI: 0.25 to 0.56, p<0.00001] (Figure 73). Other studies (eight RCTs) are discussed in section 5.3.7.7.

The pre-defined cut off for definition of oliguria in this review was < 1 ml/kg/hour. In studies with unclear definition of oliguria or that defined oliguria as urine output < 0.5 ml/kg/hr are also included. Therefore, a sensitivity analysis including only those studies that defined oliguria as < 1 ml/kg/h was performed for the comparison between ibuprofen and indomethacin [four studies; 482 patients; RR: 0.27, 95% CI: 0.14 to 0.52, p<0.0001] and this did not change the outcome.

Higher risk of renal failure was found with ibuprofen when compared to paracetamol [two studies; 270 patients; RR: 3.91, 95% CI: 1.63 to 9.37, p=0.002], and no difference in the risk of renal failure when ibuprofen was compared to placebo (one RCT) or indomethacin (two RCTs). One RCT is described in section 5.3.7.7.

Twenty two RCTs reported the absolute levels of serum creatinine following ibuprofen administration (18 RCTs detailed in Table 28, four RCTs detailed in section 5.3.7.7). In four RCTs, only the increase in serum creatinine following ibuprofen administration was reported (one RCT detailed in Table 28, three RCTs detailed in section 5.3.7.7).

Table 28. Summary of meta-analyses of renal adverse effects following ibuprofen use in preterm neonates with PDA

Outcome	Intervention	Comparator	Studies	Number of patients	RR (95% CI)	P value	I^2 (%)
Oliguria (<1ml/kg/hour)	Ibuprofen	Placebo/no treatment	2	545	1.35 (0.96, 1.90) ¶	0.09	24
	Ibuprofen	Indomethacin	5	626	0.38 (0.25, 0.56)	<0.00001	38
	Ibuprofen	Paracetamol	3	327	2.16 (0.91, 5.11) ¶	0.08	33
Renal failure	Ibuprofen	Placebo/no treatment	1	36	4.50 (0.23, 87.61) ¶	0.32	n/a
	Ibuprofen	Indomethacin	2	110	0.26 (0.06, 1.10)	0.07	n/a
	Ibuprofen	Paracetamol	2	270	3.91 (1.63, 9.37) ¶	0.002	0
Increase in serum creatinine after treatment	Ibuprofen	Placebo/no treatment	1	131	8.12 (1.05, 63.13)	0.05	n/a
	Ibuprofen	Indomethacin	No eligible studies				
	Ibuprofen	Paracetamol	No eligible studies				
Serum creatinine levels after treatment*	Ibuprofen	Placebo/no treatment	5	631	5.53 (-0.96, 12.02)	0.10	55**
	Ibuprofen	Indomethacin	9	689	-1.65 (-9.13, 5.83)	0.67	71**
	Ibuprofen	Paracetamol	4	377	1.43 (-2.32, 5.19)	0.45	21

* Mean difference (95% CI) for serum levels (mmol/l) measured at 72 hours following the intervention

** Used random effect model. All others are with fixed effects model.

¶RR value greater than 1 denotes higher rates of adverse effects with ibuprofen compared with the comparator drug

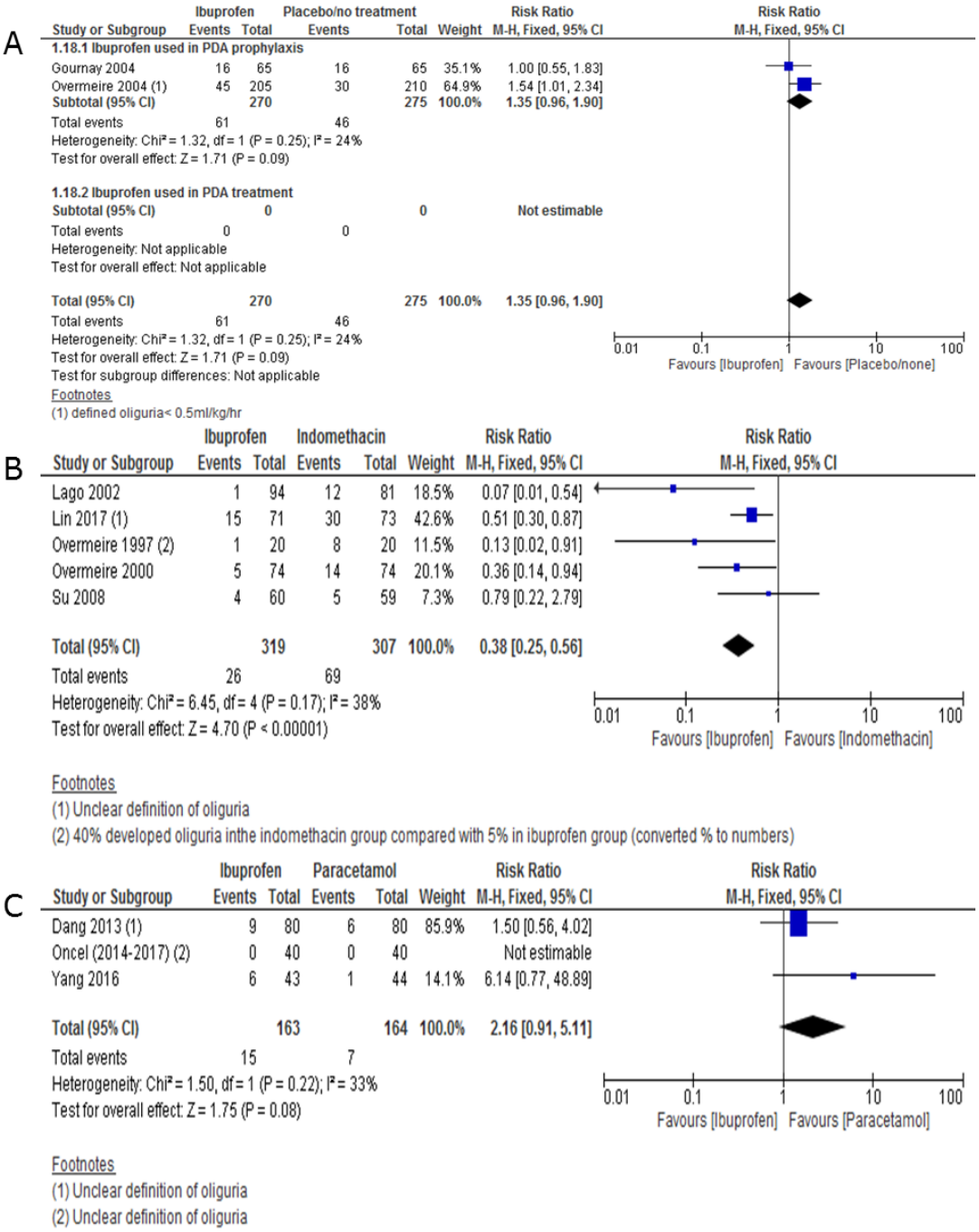


Figure 73. Meta-analyses for the risk of oliguria comparing ibuprofen to A. placebo/no treatment B. indomethacin C. paracetamol

5.3.7.3 Respiratory adverse effects

BPD (undefined) was the most frequently reported respiratory adverse effect in the included RCTs (15 RCTs), followed by BPD (at 36 weeks) (13 RCTs), pulmonary haemorrhage (eight RCTs), pulmonary hypertension (seven RCTs), BPD (at 28 days) (five RCTs), and hypoxaemia (one RCT) (Table 29).

From this table, the only statistically significant difference in those adverse effects was found to be for BPD (at 28 days) favouring indomethacin when compared to ibuprofen. All the other respiratory adverse effects were statistically insignificant regardless of the comparator to ibuprofen. Other studies are discussed in section 5.3.7.7.

Table 29. Summary of meta-analyses of respiratory adverse effects following ibuprofen use in preterm neonates with PDA

Outcome	Intervention	Comparator	Studies	Number of participants	RR (95% CI)	P value	I^2 (%)
BPD (oxygen requirement undefined)	Ibuprofen	Placebo/no treatment	3	170	1.01 (0.28, 3.60) ¶	0.99	54*
	Ibuprofen	Indomethacin	5	302	0.95 (0.80, 1.11)	0.97	0
	Ibuprofen	Paracetamol	4	379	1.42 (0.67, 3.01) ¶	0.36	0
BPD (oxygen requirement at 36 weeks)	Ibuprofen	Placebo/no treatment	4	408	1.01 (0.81, 1.25)	0.95	0
	Ibuprofen	Indomethacin	3	357	1.12 (0.77, 1.61) ¶	0.56	0
	Ibuprofen	Paracetamol	1	80	1.00 (0.21, 4.66)	1	n/a
BPD (oxygen requirement at 28 days)	Ibuprofen	Placebo/no treatment	3	597	1.08 (0.94, 1.24) ¶	0.28	0
	Ibuprofen	Indomethacin	2	188	1.37 (1.01, 1.86) ¶	0.04	0
	Ibuprofen	Paracetamol	No eligible studies				
Pulmonary hypertension	Ibuprofen	Placebo/no treatment	4	293	4.28 (0.76, 24.14) ¶	0.10	0
	Ibuprofen	Indomethacin	1	83	Not estimable as zero events in both groups		
	Ibuprofen	Paracetamol	No eligible studies				
Pulmonary haemorrhage	Ibuprofen	Placebo/no treatment	2	267	0.90 (0.09, 8.67)	0.92	65*

	Ibuprofen	Indomethacin	2	68	0.38 (0.06, 2.30)	0.29	0
	Ibuprofen	Paracetamol	2	102	1.75 (0.30, 10.15) ¶	0.53	0
Hypoxaemia	Ibuprofen	Placebo/no treatment	1	131	1.69 (0.80, 3.59) ¶	0.17	n/a
	Ibuprofen	Indomethacin	No eligible studies				
	Ibuprofen	Paracetamol	No eligible studies				

* Used random effect in those forest plots instead of fixed effect model

¶ RR value greater than 1 denotes higher rates of adverse effects with ibuprofen compared with the comparator drug

BPD; Bronchopulmonary dysplasia

5.3.7.4 Central nervous system adverse effects

IVH-any grade was the most frequently reported CNS adverse effect in the included RCTs (22 RCTs), followed by PVL (16 RCTs), severe IVH (grades 3-4) (seven RCTs), and neurodevelopmental adverse effects outcomes (measured at 18-24 months) (two RCTs) (Table 30). Other studies (seven RCTs) are discussed in section 5.3.7.7.

The meta-analyses for IVH (any grade) did not show any difference between ibuprofen when compared to placebo/no treatment; indomethacin; or paracetamol (Figure 74). Also, there was no difference in IVH (grade 3-4) when ibuprofen was compared to indomethacin. There were no studies that compared the risks of IVH (grade 3-4) between ibuprofen and paracetamol (Figure 75).

Table 30. Summary of meta-analyses of central nervous system adverse effects following ibuprofen use in preterm neonates with PDA

Outcome	Intervention	Comparator	Studies	Number of participants	RR (95% CI)	P value	I^2 (%)
IVH (any grade**)**	Ibuprofen	Placebo/no treatment	7	868	0.94 (0.77,1.14)	0.52	0
	Ibuprofen	Indomethacin	4	308	0.95 (0.58,1.55)	0.83	0
	Ibuprofen	Paracetamol	4	379	0.87 (0.51,1.49)	0.61	0
IVH (grade 3-4)	Ibuprofen	Placebo/no treatment	1	105	0.81 (0.29,2.25)	0.69	n/a
	Ibuprofen	Indomethacin	5	445	1.28 (0.73,2.23) ¶	0.39	0
	Ibuprofen	Paracetamol	No eligible studies				
PVL	Ibuprofen	Placebo/no treatment	6	899	1.00 (0.60,1.68)	0.99	0
	Ibuprofen	Indomethacin	5	487	0.88 (0.47,1.65)	0.68	1
	Ibuprofen	Paracetamol	2	182	0.83 (0.27,2.62)	0.76	n/a
Neurodevelopmental Impairment	Ibuprofen	Paracetamol	1	61	1.08(0.51,2.27) ¶	0.85	n/a
Mental developmental index (MDI)<70	Ibuprofen	Paracetamol	1	61	0.97 (0.39,2.43)	0.94	n/a
Moderate to severe cerebral palsy	Ibuprofen	Paracetamol	1	61	0.48 (0.10,2.45)	0.38	n/a
Psychomotor developmental index<70	Ibuprofen	Paracetamol	1	61	0.97(0.31,3.01)	0.95	n/a

¶ RR value greater than 1 denotes higher rates of adverse effects with ibuprofen compared with the comparator drug

IVH, Intraventricular haemorrhage; PVL, Periventricular leukomalacia

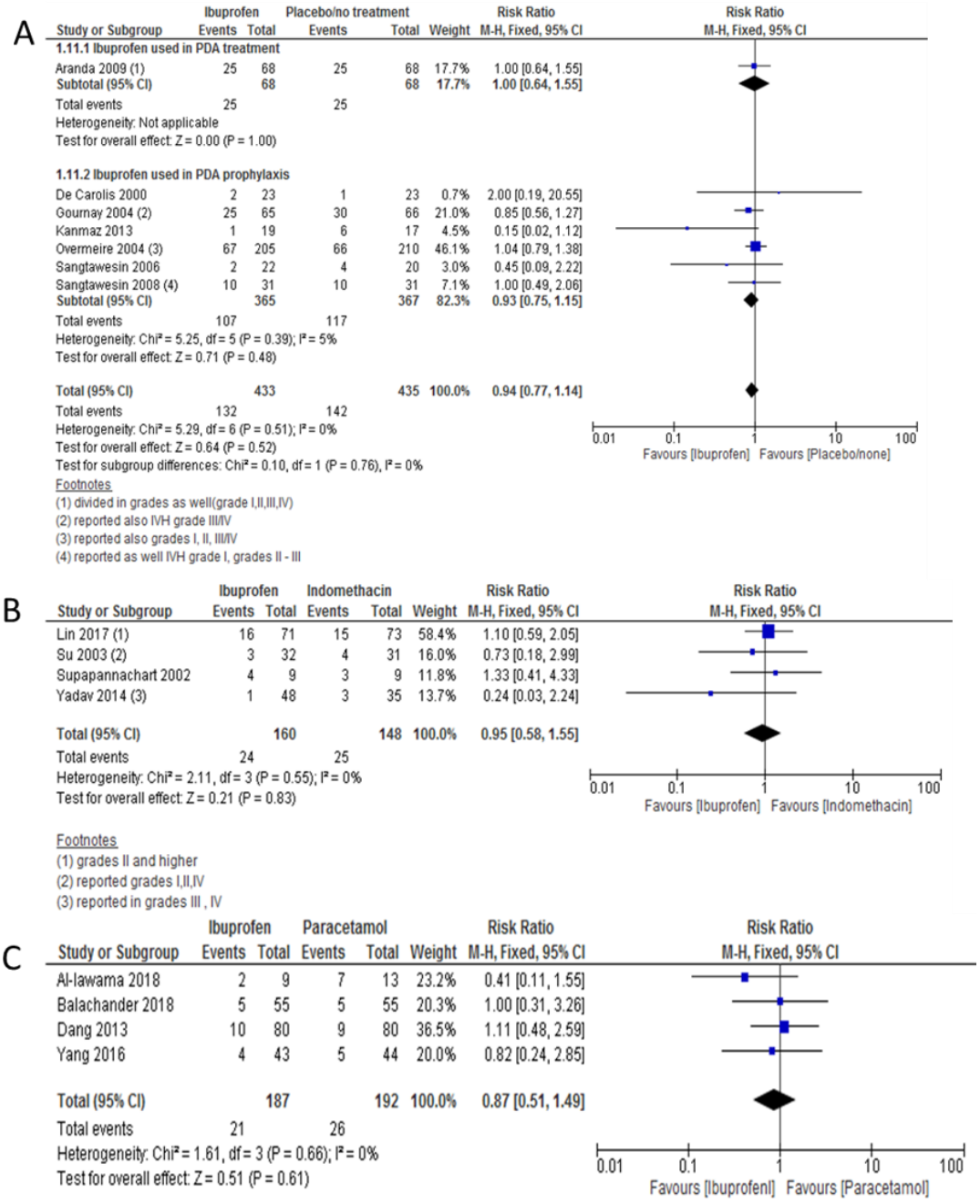


Figure 74. Meta-analyses for the risk of IVH (any grade) comparing ibuprofen to A. placebo/no treatment B. indomethacin C. paracetamol

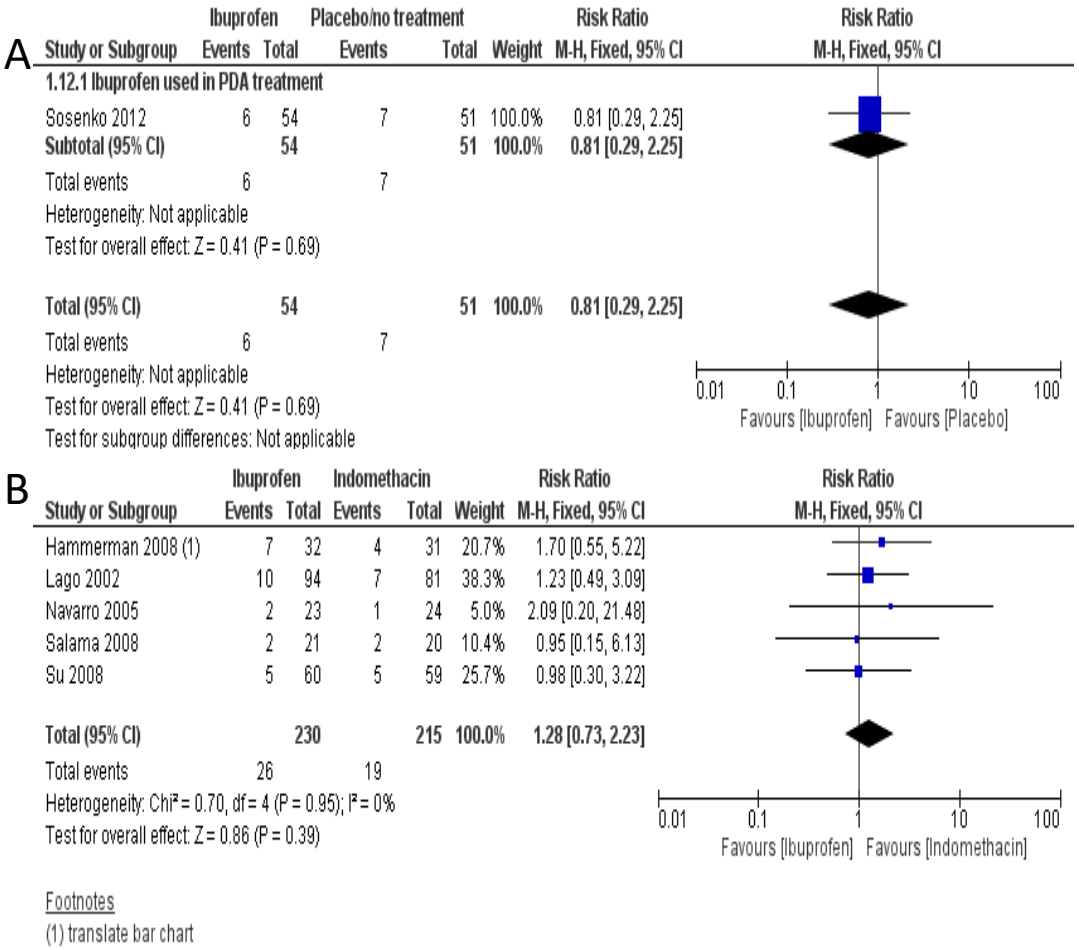


Figure 75. Meta-analyses for the risk of IVH (grade 3-4) comparing ibuprofen to A. placebo/no treatment B. indomethacin

5.3.7.5 All-cause mortality

All-cause mortality was reported by 34 out of 42 RCTs and did not show any difference between ibuprofen as compared to placebo/no treatment; indomethacin; or paracetamol (Table 31, Figure 76).

Table 31. Summary of meta-analyses of all-cause mortality reported in the included studies

Intervention	Comparator	Studies	Number of participants	RR (95% CI)	P value	I^2 (%)
Ibuprofen	Placebo/no treatment	9	1049	0.90 (0.68, 1.19)	0.45	0
	Indomethacin	14	1087	0.90 (0.65, 1.25)	0.55	0
	paracetamol	4	372	1.00 (0.61, 1.62)	0.99	0
Oral ibuprofen	IV ibuprofen	3	240	0.91 (0.36, 2.30)	0.85	0
Ibuprofen (standard dose)	Ibuprofen (high dose)	2	130	0.75 (0.28, 2.01)	0.57	0
Oral ibuprofen	Rectal ibuprofen	1	72	1.00 (0.15, 6.72)	1	n/a
Ibuprofen (standard doses)	Ibuprofen (Echo guided doses)	1	49	0.56 (0.14, 2.25)	0.42	n/a

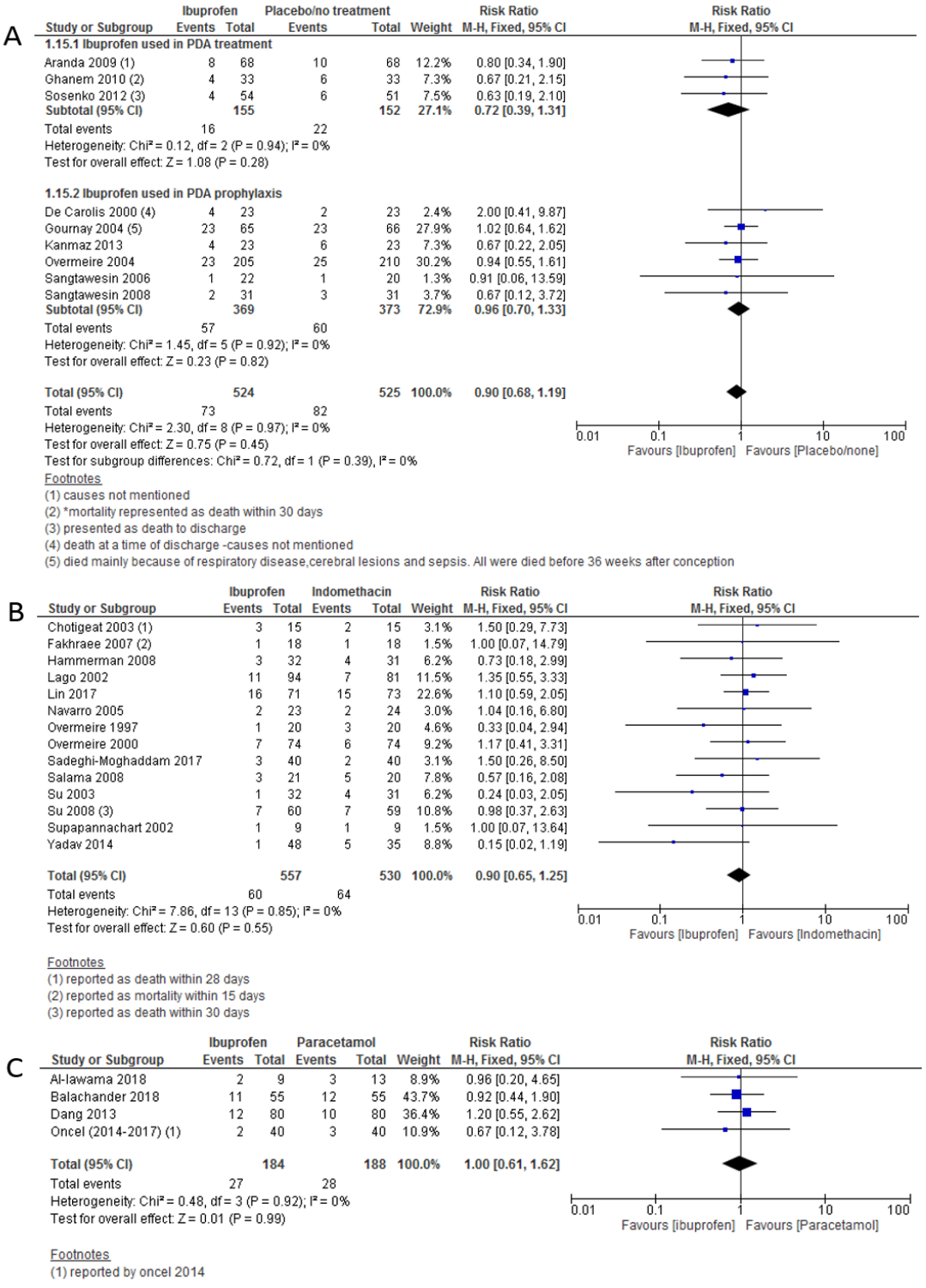


Figure 76. Meta-analyses for the risk of all-cause mortality comparing ibuprofen to A. placebo/no treatment B. indomethacin C. paracetamol

5.3.7.6 Other adverse effects

This includes adverse effects that are not classified under previous sections and were reported by individual RCTs such as, those related to the blood system (e.g. thrombocytopenia, hypoglycaemia, etc.) (Table 32).

Table 32. Summary of meta-analyses of other adverse effects reported in the included studies

Outcome	Intervention	Comparator	Studies	Number of participants	RR (95% CI)	P value	I^2 (%)
Thrombocytopenia	Ibuprofen	Indomethacin	1	47	2.09 (0.20,21.48) ¶	0.54	n/a
Hypoglycaemia	Ibuprofen	Indomethacin	1	119	0.88 (0.67,1.17)	0.38	n/a
Hyper bilirubinaemia	Ibuprofen	Paracetamol	1	160	1.75 (1.03,2.97) ¶	0.04	n/a
Bleeding manifestation	Ibuprofen	Paracetamol	1	110	0.92 (0.44,1.90)	0.81	n/a
Gastrointestinal complications	Ibuprofen	Paracetamol	1	50	11.00 (0.64,188.95) ¶	0.10	n/a
Thrombocytopenia	Ibuprofen	Paracetamol	1	110	0.94 (0.53,1.67)	0.84	n/a
Jaundice	Ibuprofen	Paracetamol	1	110	0.78 (0.54,1.13)	0.19	n/a
Cholestasis	Ibuprofen	Paracetamol	1	110	1.00 (0.15,6.85)	1	n/a

¶ RR value greater than 1 denotes higher rates of adverse effects with ibuprofen compared with the comparator drug

5.3.7.7 Evidence of adverse effects from RCTs comparing ibuprofen in different regimen, routes, and indications

5.3.7.7.1 Oral ibuprofen vs. IV ibuprofen

Four RCTs compared ibuprofen administered via oral and IV routes when used in PDA management (Table 33). There was no significant difference in any of the adverse effects.

5.3.7.7.2 Ibuprofen used in different regimen

Four RCTs compared ibuprofen in different regimens; two RCTs compared standard dose vs. high dose of ibuprofen (309,363), one RCT compared IV ibuprofen when given as bolus vs. continuous infusion (310), and one compared ibuprofen given in standard doses vs. Echocardiography guided doses. Overall, there was no significant difference in any of the adverse effects (Table 34).

5.3.7.7.3 Ibuprofen (prophylaxis) vs. ibuprofen (treatment)

Only one RCT compared ibuprofen when used as prophylaxis vs. as treatment in neonates with PDA (44) (Table 35). Overall, there was no difference in any of the adverse effects.

5.3.7.7.4 Oral ibuprofen vs. rectal ibuprofen

One RCT compared ibuprofen given via the oral route with the rectal route of administration (313) (Table 36). Overall, there was no difference in any of the adverse effects.

Table 33. Summary of meta-analyses of adverse effects in studies comparing oral vs. IV ibuprofen used in preterm neonates with PDA

Outcome	Intervention	Comparator	Studies	Number of participants	RR (95% CI)	P value	I^2 (%)
GI adverse effects							
NEC	Oral ibuprofen	IV ibuprofen	4	304	0.98 (0.43,2.23)	0.95	0
GI bleeding	Oral ibuprofen	IV ibuprofen	3	240	4.60 (0.55,38.72) ¶	0.16	0
Intestinal perforation	Oral ibuprofen	IV ibuprofen	2	134	0.32 (0.01,7.48)	0.48	n/a
Renal adverse effects							
Oliguria	Oral ibuprofen	IV ibuprofen	4	304	0.14 (0.01,2.66)	0.19	n/a
Increase in serum creatinine after treatment	Oral ibuprofen	IV ibuprofen	1	64	0.1 (0.01,2.6)	0.19	n/a
Serum creatinine levels after treatment*	Oral ibuprofen	IV ibuprofen	3	240	-1.80 (-8.27,4.67)	0.59	0
Respiratory adverse effects							
BPD (oxygen requirement at 36 weeks)	Oral ibuprofen	IV ibuprofen	3	236	0.82 (0.56,1.20)	0.31	0
Pulmonary haemorrhage	Oral ibuprofen	IV ibuprofen	2	138	0.15 (0.02,1.25)	0.08	0
Pulmonary HTN	Oral ibuprofen	IV ibuprofen	2	172	Not estimable as zero events in both groups		
Central nervous system adverse effects							

IVH (any grade)	Oral ibuprofen	IV ibuprofen	2	132	0.97 (0.62,1.52)	0.90	0
PVL	Oral ibuprofen	IV ibuprofen	1	64	1.00 (0.15, 6.67)	1	n/a
Moderate to severe cerebral palsy at 18-24 months	Oral ibuprofen	IV ibuprofen	1	57	1.35 (0.24, 7.48) ¶	0.73	n/a
mental developmental index (MDI) <70	Oral ibuprofen	IV ibuprofen	1	57	1.13 (0.34, 3.76) ¶	0.85	n/a
Psychomotor developmental index<70	Oral ibuprofen	IV ibuprofen	1	57	0.68 (0.27,1.7)	0.40	n/a

* Mean difference (95% CI) is used instead of RR (95% CI) and serum levels (mmol/l) measured at 72 hours following the intervention

¶ RR value greater than 1 denotes higher rates of adverse effects with ibuprofen compared with the comparator drug and a value less than 1 denotes vice versa

BPD, Bronchopulmonary dysplasia; GI, gastrointestinal bleeding; IVH, Intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, Periventricular leukomalacia

Table 34. Summary of the meta-analyses of adverse effects of studies comparing ibuprofen in different regimen

Outcome	Studies	Number of participants	RR (95% CI)	P value	I^2 (%)
Ibuprofen (standard dose) vs. ibuprofen (high dose)					
NEC	2	130	1.00 (0.40, 2.50)	1	0
GI bleeding	1	60	0.50 (0.05,5.22)	0.56	n/a
Oliguria	2	130	0.56 (0.12, 2.50)	0.44	0
Renal failure	1	60	Not estimable as zero number of events in both groups		
Increase in serum creatinine after treatment	1	70	0.33 (0.01, 7.91)	0.50	n/a
BPD (oxygen requirement at 36 weeks)	1	70	0.63 (0.33, 1.18)	0.15	n/a
IVH (any grade)	1	70	1.50 (0.46, 4.86) ¶	0.50	n/a
PVL	1	70	0.67 (0.12, 3.75)	0.65	n/a
IV ibuprofen (bolus) vs. IV ibuprofen (continuos infusion)					
GI bleeding	1	111	1.96 (0.63, 6.15) ¶	0.25	n/a
NEC	1	111	2.29 (0.62, 8.41) ¶	0.21	n/a
Intestinal/ bowel perforation	1	111	0.49 (0.05, 5.26)	0.56	n/a
Oliguria	1	111	4.91 (0.24, 100.05) ¶	0.30	n/a
BPD (oxygen requirement undefined)	1	111	0.91 (0.45, 1.81)	0.78	n/a
IVH (any grade)	1	111	1.38 (0.46, 4.07) ¶	0.57	n/a
IVH (grade 3-4)	1	111	2.95 (0.12, 70.82) ¶	0.51	n/a
PVL	1	111	1.96 (0.18, 21.04)	0.58	n/a

Ibuprofen (Echo guided) vs. ibuprofen (standard dose)					
NEC	1	49	0.38 (0.08, 1.86)	0.23	n/a
Oligo-anuria	1	49	5.31 (0.29,97.57)	0.26	n/a
BPD (oxygen requirement at 36 weeks)	1	49	1.35 (0.53, 3.44)	0.53	n/a
IVH (any grade)	1	49	1.50 (0.60, 3.74)	0.38	n/a
Severe ICH	1	49	0.75 (0.05, 11.31)	0.84	n/a
Serum creatinine after treatment *	1	49	-11.60 (-29.64, 6.44)	0.21	n/a
Increase in serum creatinine after treatment	1	49	2.28 (0.10, 53.23)	0.61	n/a

* Mean difference (95% CI) is used instead of RR (95% CI) and serum levels (mmol/l) measured at 72 hours following the intervention

¶ RR value greater than 1 denotes higher rates of adverse effects with ibuprofen compared with the comparator drug and a value less than 1 denotes vice versa

BPD; Bronchopulmonary dysplasia, GI; gastrointestinal bleeding, IVH; Intraventricular haemorrhage, ICH; Intracranial haemorrhage, NEC; necrotising enterocolitis; PVL, Periventricular leukomalacia

Table 35. Summary of results of the study comparing ibuprofen (prophylaxis) vs. ibuprofen (treatment)

Outcome	Studies	Number of participants	RR (95% CI)	P value	I^2 (%)
NEC	1	80	Not estimable as zero number of events in both arms		
GI bleeding	1	80	3.00 (0.13, 71.51) ¶	0.50	n/a
BPD (oxygen requirement undefined)	1	80	0.67 (0.12, 3.78)	0.65	n/a
IVH (any grade)	1	80	3.00 (0.64, 13.98)	0.16	n/a

¶ RR value greater than 1 denotes higher rates of adverse effects with ibuprofen compared with the comparator drug

BPD; Bronchopulmonary dysplasia, GI; gastrointestinal bleeding, IVH; Intraventricular haemorrhage, NEC; necrotising enterocolitis; PVL, Periventricular leukomalacia

Table 36. Summary of results of the study comparing oral ibuprofen vs. rectal ibuprofen

Comparison: Intervention, oral ibuprofen vs. comparator, rectal ibuprofen					
Outcome	**Studies**	**Number of participants**	**RR (95% CI)**	**P value**	**I^2 (%)**
NEC	1	72	1.50 (0.27, 8.45) ¶	0.65	n/a
GI bleeding	1	72	3.00 (0.13, 71.28) ¶	0.50	n/a
Intestinal/ bowel perforation	1	72	3.00 (0.13, 71.28) ¶	0.50	n/a
Oliguria	1	72	3.00 (0.13, 71.28) ¶	0.50	n/a
BPD (oxygen requirement undefined)	1	72	1.20 (0.40, 3.58) ¶	0.74	n/a
IVH (any grade)	1	72	1.75 (0.56, 5.46) ¶	0.34	n/a

¶ RR value greater than 1 denotes higher rates of adverse effects with oral ibuprofen compared with rectal administration

BPD; Bronchopulmonary dysplasia, GI; gastrointestinal bleeding, IVH; Intraventricular haemorrhage, NEC; necrotising enterocolitis

5.3.8 Adverse effects from cohort studies

5.3.8.1 Adverse effects from prospective cohort studies

A total of 309 adverse effects were extracted from seven prospective cohort studies (Figure 77). Three out of the seven included prospective cohort studies had a comparison group (321,324,361) while four studies did not (322,323,325,360). Characteristics of prospective cohort studies and the reported adverse effects are summarised in 9.38.

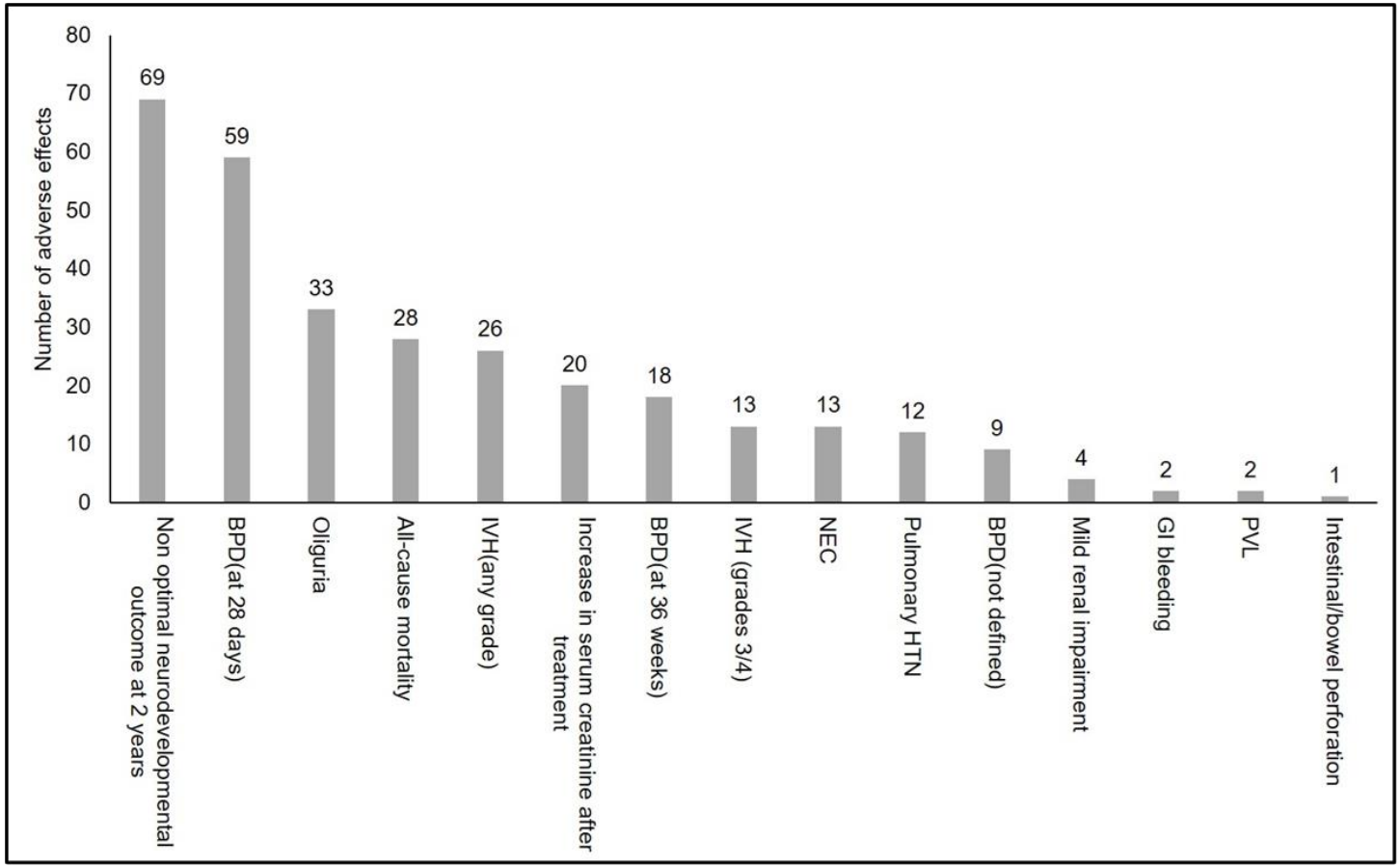


Figure 77. Adverse effects following ibuprofen use in preterm neonates with PDA reported in, prospective cohort studies (seven studies; 309 adverse effects; 681 patients received ibuprofen)

5.3.8.2 Adverse effects from retrospective cohort studies

A total of 2,264 adverse effects were extracted from 26 retrospective cohort studies (Figure 78). Sixteen studies out of 26 compared ibuprofen to other treatment strategies, six studies compared different ibuprofen groups and four studies had no comparison group. Characteristics of retrospective cohort studies and the reported adverse effects are summarised in 9.39.

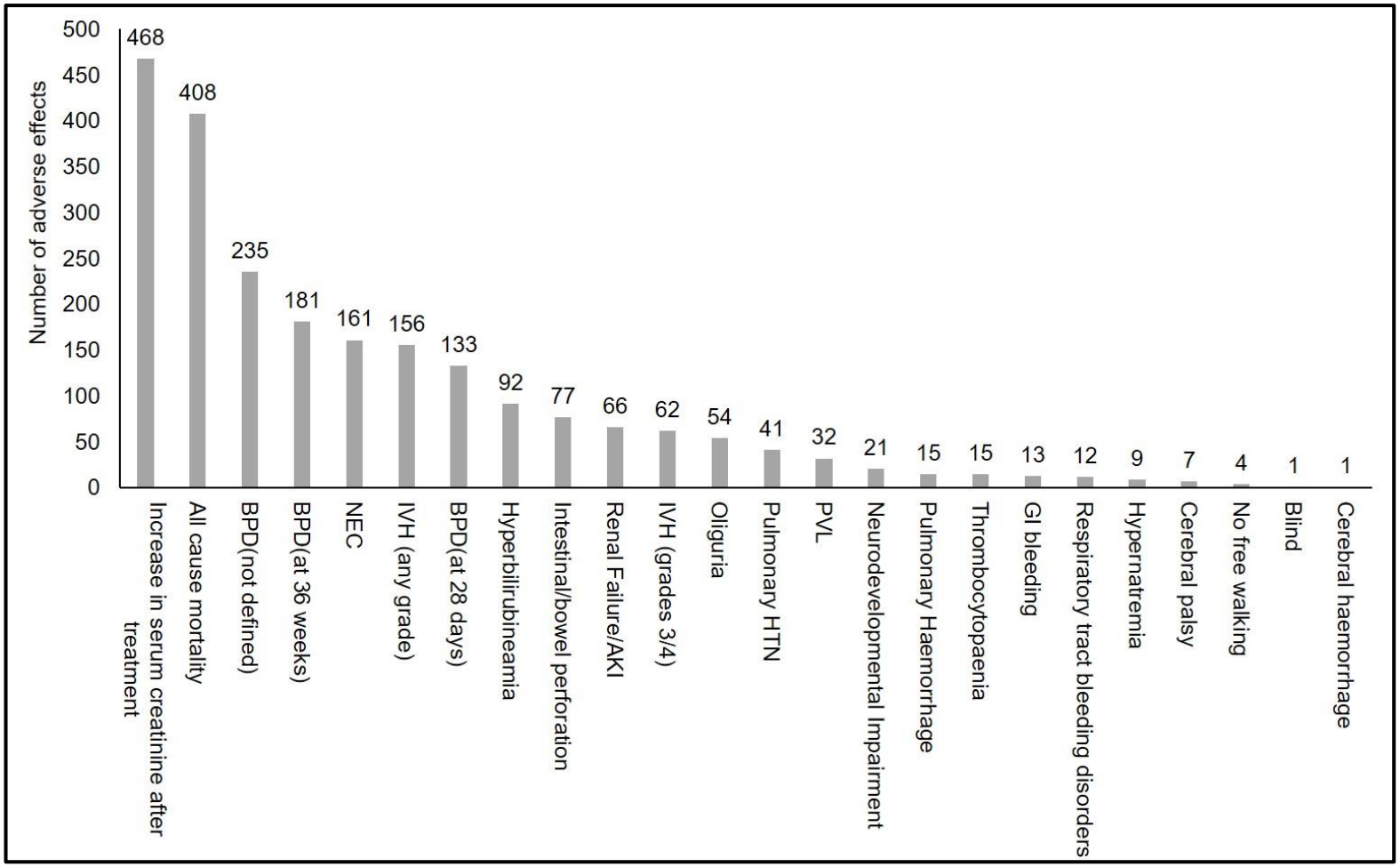


Figure 78. Adverse effects following ibuprofen use in preterm neonates with PDA in retrospective cohort studies (26 studies; 2,264 adverse effects; 3,831 patients received ibuprofen)

5.3.9 Adverse effects from case series

There were four case series [one prospective (320) and three retrospective (43,318,319) which reported adverse effects of ibuprofen when used in PDA management (Table 37). BPD (defined at 28 days) was the most frequently reported adverse effect in these studies (24/99 adverse effects), followed by BPD (defined at 36 weeks) and acute kidney injury/ renal failure (17/99 and 15 /99 respectively).

Table 37. Characteristics of the included case series and the number of reported adverse effects

Study ID	Setting	Participants received ibuprofen	Intervention (ibuprofen protocol)	Number of adverse effects	Notes
Prospective case series (one study)					
Heyman (2003) **(320)**	Single centre Israel Nov 2000 to Apr 2002	N=22 Premature neonates <32 weeks gestation and birth weight < 1500g with RDS and ECHO confirmed PDA	Oral ibuprofen via feeding tube Three doses (10-5-5 mg/kg) every 24 hr	7	
Retrospective case series (three studies)					
Pedersen (2009) **(319)**	Single centre Denmark Dec 2006 to July 2008	N=18 Premature neonates< 34 weeks gestation	IV ibuprofen Three doses (10-5-5 mg/kg) every 24 hr for PDA treatment	4	Reported as a poster abstract
Bolat (2013) (43)	Single centre Turkey Jan 2009 to Jan 2011	N=35 35 out of 1992 neonates have received ibuprofen	Not mentioned	15	The aim of this study is to examine the prevalence of AKI
Chan (2014) **(318)**	Single Centre Hong Kong Jan 2008 to Dec 2011	N=43 Premature neonates < 37 weeks gestation	IV ibuprofen Three doses (10-5-5 mg/kg) every 24 hr for PDA treatment	80	--

AKI, acute kidney injury; ECHO, echocardiography; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome

5.3.10 Adverse effects from case-control studies

Two case-control studies reported 99 adverse effects following ibuprofen use (316,317) (Table 38). One was a single centre study in Italy which reported 22 cases of acute renal failure (ARF). The second study was a multi-centre study in France which compared ibuprofen to control group (not receiving any treatment) in PDA treatment (317) and reported 77 adverse effects with 37 of them were BPD (at 28 days).

Table 38. Characteristics of the included case-control studies and the reported adverse effects

Study ID	Setting	Neonates receiving ibuprofen	Intervention (ibuprofen protocol)	Number of adverse effects	Notes
Cataldi (2005) **(316)**	Multicentre Italy March 2000 to March 2003	22	Not mentioned	22 cases of ARF	This study looked at risk factors of developing ARF in neonates
Vieux (2010) **(317)**	Multicentre France October 2004 to August 2006	74	Ibuprofen used for PDA treatment Regimen: 10 mg/kg in first day; two following days: 5 mg/kg	77	Urine output values could not be extracted as values presented as a line graph with circles represents mean (SD) of the mean.

ARF, acute renal failure; PDA, patent ductus arteriosus; SD, standard deviation

5.3.11 Adverse effects from case reports

Nine case reports (50,52–54,350–353,362) reported 11 adverse effects following ibuprofen use (Table 39). There were five cases of pulmonary hypertension, three cases of intestinal perforation, two cases of reversible renal failure, and one case of GI haemorrhage.

Table 39. Reported adverse effects from individual case reports

Study ID	Gestational age and birth weight	Adverse effect	Indication of ibuprofen	Onset of adverse effect	Dose and frequency	Prognosis
Amendolia (2012) USA **(50)** (two cases)	24 weeks and 4 days 690 g	Severe Pulmonary hypertension	PDA treatment	After third dose	IV L-Lysine preparation Three doses (dose not mentioned) given 24 hr apart	Death on day 14 of life reason: refractory hypotension and hypoxemia
	26 weeks and 3 days 439 g	Severe Pulmonary hypertension	PDA treatment	After second dose	IV L-Lysine preparation Three doses Does not mentioned given 24 hr apart	Death on day 11 of life reason: refractory hypotension and hypoxemia
Bellini (2006) Italy **(52)**	32 weeks 1600 g	Severe pulmonary hypertension	PDA treatment	within an hour after second dose of ibuprofen which was administered at 72 hours of life	IV L-Lysine preparation Three doses Dose: 10 mg/kg then 2 doses of 5 mg/kg after 24h & 48h respectively	Death on day 5 because of progressive worsening of clinical conditions attributed to generalized sepsis not ibuprofen side effects
Erdeve (2008) Turkey (54)	31 weeks 1330 g	Acute renal failure	PDA treatment	Ibuprofen given on day 3 postnatal life, developed symptoms on day 5	Oral ibuprofen 10mg/kg followed by 2 doses of 5mg/kg at 12h intervals	Treated with IV fluids, dopamine infusion. Oliguria resolved on day 9 and renal function return to normal on day 12

Peitz (2008) USA **(350)**	25 weeks 730 g	Intestinal perforation	PDA treatment	First incident: < 18h after the second dose. Second incident: in the morning following the loading dose of which was given on day 12 due to continued presence of PDA	IV ibuprofen Lysine 10mg/kg followed by 5mg/kg in 24h interval infused over 15 minutes	In both instances, intestinal perforation occurred within 24 hours of ibuprofen administration. Ibuprofen was stopped immediately in both instances.
Rodrigue-Castano (2016) Spain **(351)**	26 weeks 750 g	Severe pulmonary hypertension	PDA treatment	After the third dose of ibuprofen (second course).	IV ibuprofen Lysine Received in total 6 doses of ibuprofen 10mg/kg (first dose) followed by 2 doses of 5 mg/kg /dose at 24 hours interval	Diagnosed with severe bronchopulmonary dysplasia (BPD) at 36 weeks of postconceptional age. Died at age of 6 and half months
Sarici (2012) Turkey (53)	31 weeks 1350 g	GI haemorrhage	PDA treatment	14 hours after the second dose of ibuprofen	IV ibuprofen Lysine 10mg/kg, then 5mg/kg and 5mg/kg with 24 hours intervals	Medication stopped before 3rd dose. Recovered and discharged on 27th day of life on full enteral feeding
Sehgal (2013) Australia **(352)**	26 weeks and 2 days 914 g	Pulmonary hypertension	PDA treatment	After second course of ibuprofen (i.e. after a total of 6 doses.	IV ibuprofen Lysine 10mg/kg, then 5mg/kg and 5 g/kg at 24h intervals infused over 15 minutes	The infant was extubated to nasal CPAP on day 38 and was not given any inhaled nitric oxide or sildenafil
Tatli (2004) Turkey **(362)**	30 weeks 1150 g	Intestinal perforation	PDA prophylaxis	on day 3 of life (8 hours after the last dose of ibuprofen	Oral ibuprofen Three doses 10mg/kg followed by 5 mg/kg at 24h interval	Survived and treated with drain; removed on day 6 and enteral feeding was started 5 days later

(two cases)	29 weeks 1100 g	Intestinal perforation	PDA treatment	in 2 days after the last dose of ibuprofen	Oral ibuprofen Three doses 10mg/kg followed by 5 mg/kg in 24 hours interval	Survived and treated with drain; removed after 10 day and discharged without abdominal discomfort
Tiker (2007) Turkey **(353)**	29 weeks 880 g	Transient renal failure	PDA treatment	on day 3 of treatment (unclear if infant received the third dose of ibuprofen)	Oral ibuprofen Three doses 10mg/kg followed by 5 mg/kg in 24 hours interval	Recovered full renal function after three days

BW, birth weight; GA, gestational age; GI, gastrointestinal; PDA, patent ductus arteriosus.

5.3.12 Adverse effects that led to discontinuation of ibuprofen in preterm neonates with PDA

Treatment of ibuprofen was stopped in 56 neonates as a result of ibuprofen toxicity (Table 40). Most cases (33 neonates) were reported within the included RCTs and were due to GI bleeding and renal adverse effects (303,315,355,356,359). Pulmonary hypertension necessitating the discontinuation of ibuprofen was reported by a prospective cohort study in 11 neonates (360). One RCT (312) was stopped as the interim analysis revealed a high incidence of acute kidney injury (AKI) in the ibuprofen group compared to paracetamol group.

Table 40. Studies where ibuprofen was discontinued because of ibuprofen toxicity (56 cases)

Study ID	Adverse effects that led to ibuprofen discontinuation	Number of neonates with adverse effects	Ibuprofen regimen used	Comments
Randomised controlled trials				
Bravo (2013) **(315)**	Intestinal ischaemia	1	All received 1st dose of ibuprofen (10mg/kg/dose) then randomised to: Echo guided treatment: received additional doses of ibuprofen (5 mg/kg at 24-h intervals) only if the PDA was still 1.5mm at the time of the corresponding ibuprofen dose. Standard treatment: received 2 additional doses of 5 mg/kg of ibuprofen at 24-h intervals after the initial dose of 10 mg/kg	Treatment discontinued and no further treatment given. Except surgical ligation was indicated for one neonate.
	Rising in serum creatinine (above 1.5 mg/dl)	1		
	Severe intracranial haemorrhage	2		
	Total	4		
Dang (2013) **(303)**	Renal failure	1	Oral ibuprofen for PDA treatment :3 doses: 10 mg/kg followed by 5 mg/kg after 24 and 48 hr.	Did not complete the treatment course and were withdrawn from the analysis
	NEC	2		
	IVH grade III-IV	3		
	GI bleeding	8		
	Total	14		

Gournay (2004) **(355)**	Refractory hypoxaemia with pulmonary hypertension	3	IV ibuprofen Lysine for PDA treatment 3 doses: 10mg/kg and then two doses 5mg/kg 24h apart as continuous IV infusion over 20 minutes.	Trial was halted
Kanmaz (2013) **(359)**	GI bleeding	2	Oral ibuprofen for PDA prophylaxis: 10mg/kg within 12-24 h after birth followed by 5mg/kg at 24 and 48 h.	Trial was terminated earlier than planned
	SIP	2		
	Acute renal failure	2		
	Total	6		
Overmeire (2004) **(356)**	Oliguria/rising creatinine	5	IV ibuprofen lysine for PDA prophylaxis: 3 doses 10mg/kg within 6 hr of birth followed by 2 doses of 5mg/kg at 24 hr and 48 hr	Did not comple the full course
	Severe IVH	1		
	Total	6		
Prospective cohort studies				
Bersani (2011) **(360)**	Pulmonary hypertension	11	IV ibuprofen for PDA prophylaxis within the first 2 hours of life (10-5-5 mg/kg at 24h interval) over 20 min	-
Tantawy(2011) **(325)**	NEC	1	Oral ibuprofen via feeding tube for PDA treatment at 48 to 120 hr as 3 doses: 10mg/kg followed by two doses of 5mg/kg	-
Case-control studies				

Vieux (2010) **(317)**	Renal insufficiency	2	IV ibuprofen: 3 doses (10-5-5 mg/kg) 24 hrly	Did not complete the 3 doses
	Oliguria	3		
	Total	5		
Retrospective cohort studies				
Olgun (2017) **(340)**	Thrombocytopenia	1	Oral ibuprofen for PDA treatment. Each course :10-5-5 mg/kg every 24 hr	-
	Thrombocytopenia with renal impairment	1		
	Renal impairment	1		
	Total	3		
Case reports				
Peitz (2008) **(350)**	Intestinal perforation	2	IV ibuprofen Lysine for PDA treatment 10-5-5 mg/kg at 24h interval infused over 15 min	treatment stopped immediately
Sarici (2012) (53)	GI haemorrhage	1	Oral ibuprofen for PDA treatment Given as 3 doses: 10-5-5mg/kg at 24h interval	Second dose not given
No cases of ibuprofen discontinuation were found in case series studies in this review				

GI, gastrointestinal; h, hour; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; SIP, spontaneous intestinal perforation.

5.4 Discussion and conclusion

The present systematic review provides the first comprehensive review of ibuprofen adverse effects following its administration in preterm neonates for management of PDA.

5.4.1 The advantage of performing a comprehensive adverse effects review over that of the traditional Cochrane reviews

Systematic reviews of adverse effects are of similar importance as systematic reviews of efficacy, and must be conducted with similar rigour (269). They are considered the determinant type of reviews in cases where different effective treatment strategies exist, or where the controversy includes the option to offer no pharmacological treatment as in the case of PDA management in preterm neonates (366).

Inclusion of non-randomised studies is the distinctive characteristic of systematic reviews that focus on adverse effects as compared to those that are primarily designed to study the efficacy of an intervention such as the Cochrane reviews for ibuprofen. Unlike non-randomised (observational) studies, RCTs are known to be less useful in detecting uncommon/rare adverse effects/ADRs. This is due to their restrictive nature in the number of enrolled participants, time frame, and poor reporting of adverse effects/ADRs as most RCTs focus on efficacy outcomes (367). Among non-randomised studies, prospective study designs (including prospective cohort studies) are ranked higher in the hierarchy of evidence compared to retrospective designs (368). Both prospective and retrospective cohort studies are set to

explore the association between multiple exposures and multiple outcomes. However, retrospective cohort studies are limited due to potential incompleteness of records (i.e. adverse effects in this review). This is because of the nature of retrospective studies in which the outcomes are identified and analysed from previously collected records (369). Prospective cohort studies involve follow up of cohorts with an objective of investigating the association between exposure and the outcomes that are recorded as they occur and hence there is less chance of missing outcomes of interest (370). Hence prospective cohort study designs are useful in providing information about the incidence and the risk factors of common adverse effects/ADRs (371–373). Despite these advantages, prospective cohort studies are known to be limited by a loss to follow up and selection bias (367).

New and rare adverse effects/ADRs can be only captured from individual case reports and case series. Their inclusion in any adverse effects systematic reviews is therefore crucial to paint the complete picture of potential harm form the use of any medicine (367).

5.4.2 Summary of the results

Adverse effects from randomised controlled trials: The most frequently reported GI and renal adverse effects were NEC and oliguria respectively. The most frequently reported respiratory and nervous system adverse effects cases were BPD, (including all definitions) and IVH respectively.

It can be argued that these adverse effects were due to prematurity or were complications of PDA and may not be attributed to the direct effect of

ibuprofen. Several reviews pointed that PDA complications are due to two main reasons; fluid overload and the steal phenomenon (374). Prolonged ventilation, needed as a consequence of fluid overload, can lead to an increased risk of BPD and nosocomial infections. The steal phenomenon is a change in the blood flow movement in splanchnic and renal vessels due to left-to-right shunting. This phenomenon can result in an increased risk of NEC, bowel perforation, worsening in renal impairment and even intracerebral haemorrhage (ICH)/IVH (374,375).

Adverse effects from non-randomised studies: The majority of adverse effects were captured within the retrospective cohort studies (2,264 adverse effects) as compared to prospective cohort studies (309 adverse effects). Among retrospective cohort studies, there are two studies reporting around 40% of the total adverse effects extracted from all other retrospective cohort studies (1102 adverse effects /2264 total adverse effects) (327,329). This high number of adverse effects reported can be attributed to the fact that they were large multicentre studies that captured adverse effects, respectively. It is important to highlight that one retrospective cohort study by Gulack et al. reported an ambiguous outcome ‘any adverse event’ in 802 neonates receiving ibuprofen compared to 3,395 in neonates receiving indomethacin (329). These data were not included in this review as the nature and type of these adverse effects could not be classified.

Another important finding is the discontinuation of ibuprofen because of toxicity which was reported in 56 neonates. The majority of adverse effects that led to discontinuation of treatment in RCTs were GI bleeding and renal

adverse effects (including renal insufficiency, oliguria and an increase in serum creatinine) (303,315,355,356,359). Eleven neonates had pulmonary hypertension following ibuprofen administration in a prospective cohort study which necessitate discontinuation of the drug (360).

5.4.3 Comparison with existing systematic reviews

There are three recent Cochrane reviews assessing effectiveness and safety of ibuprofen in preterm neonates with PDA. Two were published in 2018 where ibuprofen was used for PDA treatment with different comparators (47,244) whereas one published in 2019 where ibuprofen was used for PDA prophylaxis (57).

There were some differences in the studies included between this systematic review and the Cochrane reviews. Four RCTs that were included in this review and were not included in the Cochrane reviews (287,311,312,314). Those studies with the reasons for their exclusion were not stated in the Cochrane reviews. In contrast, there were 13 RCTs included in the Cochrane reviews and were not included in this review. Reasons for excluding these studies in this review are tabulated below (Table 41).

Table 41. Studies included in Cochrane reviews but not in the current review

Study ID (Ref)	Reason for inclusion in Cochrane reviews	Reason for exclusion from this review
Ding (2014) **(376)**	Included in Ohlsson 2018 (47); PKPD study measure PDA closure only.	Did not report any adverse effects outcomes.
Patel (2000) **(261)**	Included in Ohlsson 2018 (47); measure physiologic effect of ibuprofen only (changes in cerebral blood volume, cerebral blood flow, and cerebral oxygen delivery).	Did not report any adverse effects outcomes.
Mosca (1997) **(377)**	Included in Ohlsson 2018 (47); measure physiologic effect of ibuprofen only (cerebral blood flow velocity)	Did not report any adverse effects outcomes.
Patel (1995) **(378)**	Included in Ohlsson 2018 (47); measure physiologic effect of ibuprofen only (cerebral perfusion, and cerebral mitochondrial Oxygenation)	Did not report any adverse effects outcomes.
Plavka (2001) **(379)**	Included in Ohlsson 2018 (47); measure physiologic effect of ibuprofen (cerebral blood flow velocities, blood pressure).	Although mortality and serum creatinine were listed as outcome measures; no information was provided in the original publication about these outcomes. Therefore, it was excluded.
Akar (2017) **(380)**	Included in Ohlsson 2018 (47); measure physiologic effect of ibuprofen only (effect of different forms of ibuprofen treatment on the antioxidant and oxidant status of the patients)	Did not report any adverse effects outcomes.
Lin (2012) **(381)**	Included in Ohlsson 2018 (47); measure both efficacy and adverse effects outcomes.	Article in Chinese. Could not obtain it in English language.
Akisu (2001) **(382)**	Included in Ohlsson 2018 (47); measure both efficacy and adverse effects outcomes.	Article in Turkish. Could not obtain it in English language.
Fesharaki (2012) **(383)**	Included in Ohlsson 2018 (47); measure both efficacy and adverse effects outcomes.	Article in Persian. Could not obtain it in English language.
Adamaska (2005) **(384)**	Included in Ohlsson 2018 (47); measure both efficacy and adverse effects outcomes.	Article in Polish. Could not obtain it in English language.
Dani (2005) **(385)**	Included in Ohlsson 2019 (57); measure IVH (grade 2 to 4) at 7 days of life, PDA on day 3, BPD at 36 weeks', NEC, sepsis (confirmed with positive blood culture)	Ibuprofen was used to prevent IVH in preterm neonates and not PDA closure.

Kalani (2016) **(386)**	Included in Ohlsson 2019 (57); measure IVH, PDA, NEC, GI bleeding, mortality, hospitalisation (days).	Ibuprofen was used to prevent IVH in preterm neonates and not PDA closure.
Bagnoli (2013) **(387)**	Included in Ohlsson 2018 (47); measure failure to close a PDA, need for surgical ligation of the PDA, oliguria, NEC, creatinine and BUN before and after treatment, mortality at 28 days of life	The original paper did not report the results of the adverse effects outcomes. Therefore, it was excluded.

BPD, bronchopulmonary dysplasia; BUN, blood urea nitrogen; GI, gastrointestinal; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus

Despite these differences in the number of studies included, the overall meta-analyses result of this review are very similar to those of the Cochrane reviews.

With regards to GI adverse effects, the meta-analyses in this review concluded that ibuprofen has a lower risk of NEC compared to indomethacin [16 studies; 1125 patients; RR: 0.66, 95% CI: 0.47 to 0.93, p=0.02] with no difference in this outcome when ibuprofen was compared to placebo or paracetamol. These results are consistent with the Cochrane reviews when comparing ibuprofen to indomethacin [18 studies; 1292 patients; RR: 0.68, 95% CI: 0.49 to 0.94, p=0.02], placebo [nine studies; 1,028 patients; RR: 0.96, 95% CI: 0.61 to 1.50] and paracetamol [five studies; 559 patients; RR: 0.88, 95% CI: 0.46 to 1.70].

In this review ibuprofen was found to have higher risk of GI bleeding when compared to placebo [three studies; 140 patients; RR: 2.09, 95% CI: 1.20 to 3.66, p=0.010] and paracetamol [two studies; 240 patients; RR: 7.00, 95% CI: 1.91 to 25.61, p=0.003] with no difference in this outcome when compared to indomethacin. This was similarly reported in the Cochrane reviews when comparing ibuprofen to placebo [5 studies; 282 patients; RR:

2.05, 95% CI: 1.19 to 3.51, p<0.001], paracetamol [4 studies; 537 patients; RR: 0.28, 95% CI: 0.12 to 0.69, p<0.001] with no difference when compared to indomethacin.

Among renal adverse effects, meta-analyses of this review concluded that there was no significant difference of oliguria when comparing ibuprofen to placebo or paracetamol. However, a significant difference of oliguria was found when ibuprofen was compared with indomethacin, with lower risks in the ibuprofen group [five studies; 626 patients; RR: 0.38, 95% CI: 0.25 to 0.56, p<0.001] was similarly reported in the Cochrane review [6 studies; 576 patients; RR: 0.28, 95% CI: 0.14 to 0.54, p<0.001].

Finally, there was no difference in the risk of IVH when comparing the three pharmacological agents in this review and in the Cochrane reviews.

5.4.4 Comparisons with other adverse effects systematic reviews

Previous adverse effects systematic reviews in paediatrics have highlighted that most adverse effects are reported in prospective cohort studies rather than RCTs (277,388). For instance, a safety systematic review on the use of lamotrigine in paediatrics identified 12 prospective cohort studies (1,524 adverse effects) and nine RCTs (549 adverse effects) (388). The other review that explored the safety of use of levetiracetam in paediatrics also reported more adverse effects from 20 prospective cohort studies (897 adverse effects) vs. six RCTs (415 adverse effects) (277). Contrary to these expectations, the present systematic review revealed that most adverse effects were found in RCTs rather than prospective cohort studies. Thirty-nine RCTs reported forty per cent (1,841 adverse effects) of the total number

of adverse effects whereas only seven prospective cohort studies reported five per cent (232 adverse effects) of the total adverse effects in this review.

While different to the trend in paediatric studies, this distribution is similar to other systematic reviews in neonates (389). A recent systematic review with an aim to investigate the safety of azithromycin in neonates yielded more adverse effects in RCTs compared to cohort studies. Four RCTs in this review reported 340 adverse effects following azithromycin use compared to three cohort studies that reported only 16 adverse effects (389). This may be because in neonatal medicine, there is possibly a move towards more RCTs with fewer publications of prospective cohort studies. Additionally, a number of recent RCTs have adopted the recommendation of more carefully reporting adverse effects of the intervention as compared to older RCTs. This is due to the updates on the Consolidated Standards of Reporting Trials (CONSORT) statement to include harms which was published in 2010 (390). This update has added ten further new recommendations into the original CONSORT statement to address harms-related issues and improve the quality of reporting harms in RCTs (391). Despite this, change is slow. A recent systematic review highlighted the inconsistency in reporting of harms in RCTs with an obvious heterogeneity between the included studies for each recommendation(390). This review pointed out that almost half of health research journals (19/41 (46%)) provided online instructions to authors about the CONSORT guideline without a referral to the CONSORT-harms statement. This would suggest a need for further adherence to the CONSORT-harms by both researchers and editorial team of medical/health journals.

The improvement in the practice of reporting adverse effects should make an assessment of the toxicity of new drugs easier to perform and more robust. This can be useful when assessing ADRs in neonates (especially premature neonates) where a definite conclusion about the causality of the events as a result of a drug or prematurity might be difficult to differentiate.

The high number of adverse effects captured from retrospective cohort studies in this review is due to the larger number of patients than those included in RCTs. Such large retrospective database derived reports are expected to be published more and more due to the establishment of large neonatal databases of routinely collected data such as the National Neonatal Research Database in the UK. These data, although a wealthy repository of very useful information, must be interpreted with caution because retrospective studies are more prone to reporting bias when compared to prospective studies.

The methodology followed in this systematic review is consistent with the framework proposed by Loke et al. for conducting systematic reviews of adverse effects. A recent systematic review of levetiracetam toxicity in children followed a similar methodological approach (277). Unlike the levetiracetam systematic review, this review has included all non-randomised studies following quality assessment without any requirements to fulfil certain quality criteria. This is in keeping with the recommendation for using the JBI tool for quality assessment which has been used here. This assessment is subjective and it is considered appropriate to include all the data of adverse effects from non-randomised studies (279). Until a validated tool for non-

randomised studies is developed, it is better to include all the non-randomised studies when conducting adverse effects systematic reviews.

5.4.5 Strengths and limitations

In addition to inclusion of all types of study designs and a comprehensive documentation of all reported adverse effects of ibuprofen in preterm neonates, the strengths of this systematic review include the clear definition of the research question (using PICO model), and adherence to an explicit protocol that was developed and registered prior to the analysis (Prospero [CRD 42018067600]). The robust nature of the search strategy also added strength to the review. This included expert input into selecting the search terms, searching several electronic databases and the grey literature, and including all study designs with no restriction of languages. Another strength is that all studies (RCTS and non-RCTs) were reviewed by two reviewers (and a third one where there was a conflict).

There are some limitations that need to be highlighted. First, some studies were retrieved in non-English language (Chinese, Turkish, Polish, and Iranian) that could not be translated (384,382,383,381,392,393). Another limitation is that the tool used for quality assessment of non-randomised studies is not standardised. However, currently there is no perfect tool for assessment of non-randomised studies and the tool developed by JBI was used. This is used widely to assess the quality of many types of study designs (cohort, case-control, case report) (279) and was therefore selected for this review. A new tool, the ROBINS-I, which is under assessment by Cochrane group, may provide a more rigorous conclusion when assessing

risk of bias of non-randomised studies compared to the tool used in this review (394).

It must also be noted that this systematic review is limited by the difficulty of assessing adverse effects in preterm neonates. This is due to the fact that those events may be attributed to prematurity or the haemodynamic consequences of PDA or they might have been due to the direct effect of ibuprofen (273).

5.4.6 Conclusion

There are still many unanswered questions about the best available treatment strategy when managing PDA, especially in extremely preterm neonates who are more resistant to treatment and more prone to harm. This systematic review has identified the most common and some rare adverse effects encountered following ibuprofen administration in preterm neonates with PDA across all study designs, with quantification of their risks in RCTs and prospective cohort studies. This can assist neonatologists and other healthcare providers in their daily clinical judgement making when it comes to weighing the risks and benefits associated with ibuprofen use and prevent unnecessary exposure to ibuprofen in a cohort of neonates who may be managed conservatively and who have a high risk of adverse outcomes.

Combined results from RCTs and prospective cohort studies in our review show that oliguria is the most commonly reported adverse effect among the renal adverse effects. However, the high number of rising serum creatinine after treatment from retrospective studies should also be considered when treating preterm neonates with ibuprofen for PDA.

Following the count of ibuprofen and indomethacin adverse effects in retrospective cohort studies that compared both agents, ibuprofen was associated with a smaller number of adverse effects compared to indomethacin (1691 vs. 3586 adverse effects). So, this can highlight the fact that ibuprofen might be favourable to indomethacin in terms of its safety.

Paracetamol, a new emerging pharmacological option, might be favoured when compared to ibuprofen as it is found to be associated with less risk of GI bleeding. However, there is a need for more studies that aim towards its' long-term benefits when used in preterm neonates with PDA.

CHAPTER 6 REVIEW OF NEONATAL DRUG FORMULARIES AND OTHER PRACTICE GUIDELINES USED IN NEONATAL UNITS IN THE UK

6.1 Introduction

In the previous chapters, I have focussed on the *pattern* of drug use in neonatal units in England and Wales by applying quantitative methods on data in a national database. These analyses; however, do not give any insight into how these drugs are used, e.g. there is no information in the National Neonatal Research Database (NNRD) about the indications and recommended doses for any of these drugs. *Quality,* which is a determinant of irrational practice, can be assessed through an evaluation of current practices by investigating the use of local guidelines. This will enable us to identify whether prescribing information in the drug formularies and available practice guidelines are consistent across different units.

Tools to detect inappropriate prescribing have been developed widely in the elderly. However, there are few in paediatrics and none in neonates. After scoping the literature, only three tools were found to be developed for the paediatric population (395–397). The first was proposed in France and was named Pediatric: Omission of Prescriptions and Inappropriate Prescriptions (POPI) to identify inappropriate prescribing in this population (395). However, the use of this tool would be inappropriate to aid prescribers in neonatal medicine, as most of the criteria are for children, not neonates. Another study in UK and Ireland attempted to develop indicators of potentially inappropriate

prescribing in children (PIPc) in a primary care setting (396), which also have not included criteria for neonates. The most recent tool in the paediatric population was conducted in the UK by Corrick et al. with the aim of evaluating the applicability of the POPI tool to UK practice and modified, where necessary, to apply it in paediatric practice (397). This tool is also inappropriate to be used for the neonatal population as it was mainly directed for infants and children. It is worth considering the creation of such a tool to tackle irrational prescribing in the neonatal population, especially with the inconsistencies that are found across the collected neonatal drug information resources.

This study will aim to explore the information held in current neonatal formularies and practice guidelines used in the UK and compare prescribing information extracted from them. The British National Formulary for Children (BNF-C) is considered the standard dosing information that meets the WHO standards for national formularies (28) and is widely used in the UK. However, it is worth exploring if there are any further resources used across neonatal units in the UK and whether prescribing information in those formularies and other clinical practice guidelines is similar or different.

6.1.1 Study aim and objectives

The aim of this study was to review the neonatal drug formularies and any other existing neonatal practice guidelines used in different neonatal units in the UK.

This was a multi-centre observational study conducted over 12 months from 1st April 2018 to 1st April 2019 and set out to address two main questions with the following objectives:

- Objective 1: Is the prescribing information of the frequently prescribed drugs stated in neonatal drug formularies and or local practice guidelines used in UK neonatal units similar, or do they differ?
- Objective 2: Is the prescribing information of the drugs used in PDA management (indomethacin, ibuprofen, and paracetamol) stated in neonatal drug formularies and or local practice guidelines used in UK neonatal units similar, or do they differ?

6.2 Methods

6.2.1 Study design

A prospective multi-centre study was conducted over 12 months (1/4/2018 to 1/4/2019) to obtain drug formularies and or practice guidelines used in neonatal units in the UK, or drug formularies that are exclusively aimed for the use of prescribing in older children were excluded.

This study was reviewed and approved by the Faculty of Medicine and Health Sciences (FMHS) Research Ethics Committee (FMHS Ref no: 283-1803) (attached in 9.40).

6.2.2 Data collection

Drug resources were requested electronically via two main networks; the Neonatal and Paediatric Pharmacists Group (NPPG) and the British Association of Perinatal Medicine (BAPM). NPPG is a professional network formed in 1994, to improve the care of neonates, infants and children by advancing the personal development of pharmacists and the provision of quality pharmacy services. BAPM is the UK's leading organisation of clinicians in perinatal medicine and has representation in every neonatal unit in the UK, founded in Bristol since 1976.

Data collection was done by the researcher of the study (myself). This was conducted by circulating an invitation letter electronically to the members of those two networks. A copy of the participation invite letter is attached in 9.41. However, because the NPPG network is an establishment of the UK

National Health Service (NHS) network, it was necessary to contact a member of the NPPG as an initial step to prompt the post of the invite letter at the NPPG network message board. The initial message was posted by Dr Sharon Conroy (SC) (associate professor at school of medicine, UoN) who is also an active member at the NPPG network. The initial invite letter was posted on 28th April 2018 by SC and resulted in two responses from the members by May 2018. Following this initial step, I then followed the data collection process. Since there were no further responses by June 2018, an attempt was made to contact the NNPG network administrator, Peter Polland, to circulate the invite letter. The invite letter was then emailed to all NPPG members by the network administrator, which resulted in nine further responses by mid-November 2018. At that time, an email was sent to BAPM to circulate the invite letter to their members; there was no response so a reminder was sent in March 2019 and again no response was received. A final contact was made with the NPPG to collate further responses. However, an email received from the administrator indicated that the timing was difficult to resend an email to all members (Figure 79).

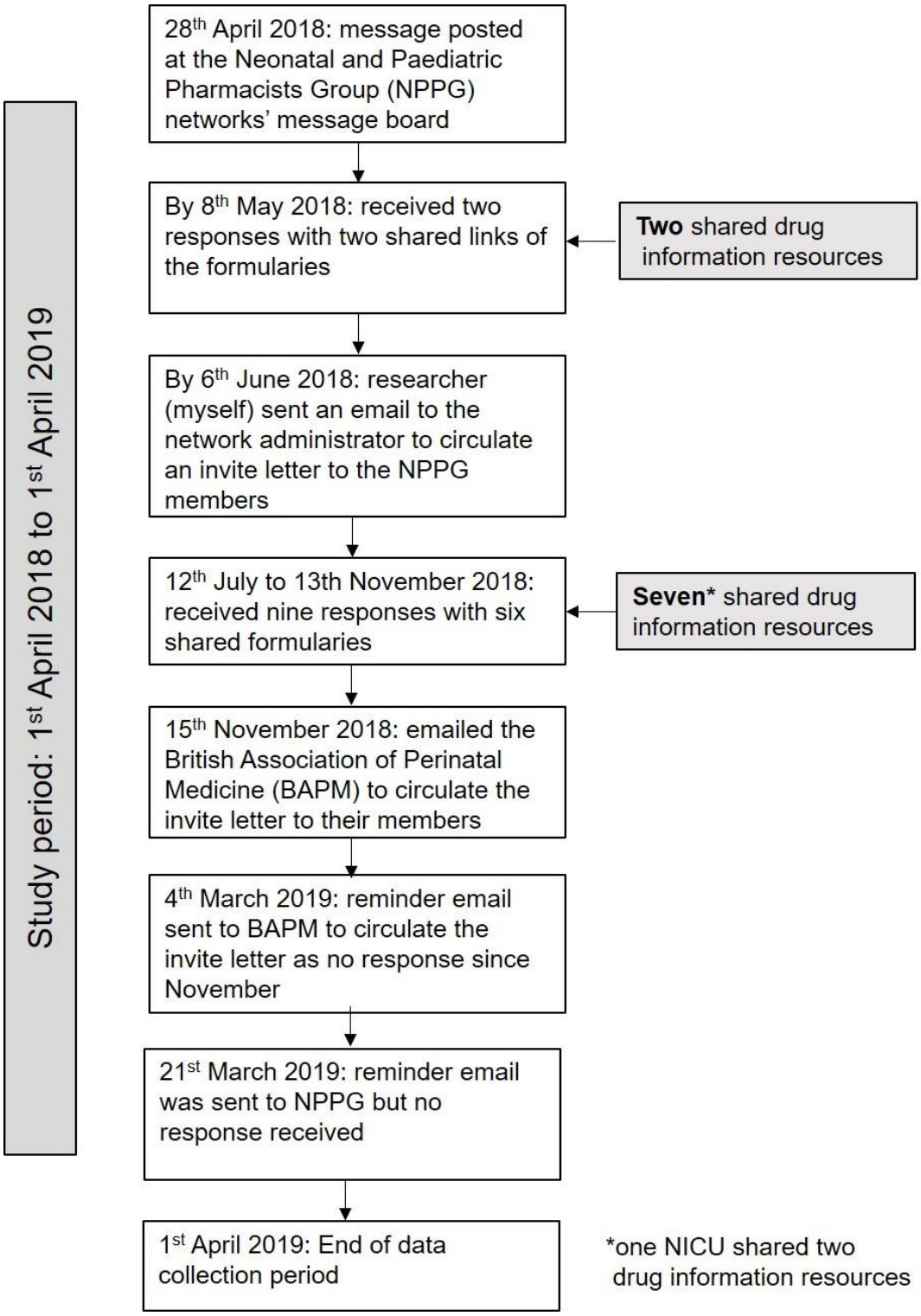


Figure 79. Data collection during the study period and the responses gained

6.2.3 Data extraction and analysis

The contents of all collected drug resources were analysed descriptively using Microsoft Excel (version 16, 64 bit).

For objective 1: relevant information about the most frequently prescribed drugs were extracted. The drugs were chosen based on the results of Chapter 3. These drugs were the ten most frequently prescribed drugs identified across neonatal units in England and Wales: benzylpenicillin, gentamicin, cefotaxime, caffeine, morphine (IV), flucloxacillin and pulmonary surfactants. However, sodium, phosphate and iron, which are also amongst the ten frequently prescribed drugs were not included in this analysis, as they are used in neonatal units as supplements. The data extracted from the formularies were the following:

- Indication of use
- Dosing regimen
- Instruction for administration
- Contraindications
- Cautions
- Monitoring for adverse effects

Similarly, this was also done for objective 2, with the above categories of information on the drugs used in PDA (ibuprofen, indomethacin, and paracetamol) extracted.

6.3 Results

6.3.1 Participating units' characteristics

Eleven neonatal units responded to the participation letter during the study period. Only eight units shared their neonatal drug formularies or guidelines or both. The total number of shared neonatal formularies/guidelines was nine, as one unit shared two local formularies (Table 42).

As can be seen from the table, seven out of eight responding units were from different places in England, and one was from West-Scotland. Four of the units were level three neonatal units (NICUs), while two were level two (LNU) units. However, two participants shared the formularies/ guideline of the trust or several hospitals, so the level of the unit cannot be assigned. Most of the units shared electronic links to their formularies/neonatal guidelines. However, three out of eight units shared an electronic copy of their formularies.

A total of nine shared documents that include six drug formularies, and three clinical practice guidelines were received and included for the descriptive analysis.

Table 42. Characteristics of the participating neonatal units and an overview of the neonatal formularies/drug guidelines

	Unit 1	Unit 2	Unit 3	Unit 4	Unit 5*	Unit 6*	Unit 7	Unit 8
Region	England (London)	England (Yorkshire and the Humber)	England (Yorkshire and the Humber)	England (south-eastern)	England (London)	West of Scotland	England (East-midland)	England (Cambridge)
Level of unit	NICU	NICU	LNU	NICU	-	-	LNU	NICU
Type of document shared	Electronic link to the paediatric formulary (includes neonates) with drugs monographs	Electronic link to the network of Leeds formulary	Electronic link to the Yorkshire-Humber-neonatal-ODN guidelines/ Formularies and PDF document of some drugs monographs	Electronic link to the local hospital prescribing guidelines and drugs monograph	Two local neonatal drug formularies in an electronic PDF document	Two electronic links of the neonatal drug formulary and clinical practice guidelines	Local neonatal guideline (Microsoft Word document)	Neonatal handbook guideline and an electronic link of the east region guidelines
Other comments	Guidelines could be only accessed through the trust intranet	-	Neonatal Formulary Book, BNFC and Drugs in Pregnancy & Lactation are used as a resource	Uses an electronic prescribing system developed collaboratively by pharmacists and neonatologists	Numbered the formularies as formulary (a) and formulary (b)	-	-	-

LNU, local neonatal unit; NICU, neonatal intensive care unit; ODN, operational delivery networks
*The unit level cannot be determined as the shared document covers a trust or several hospitals in that region

6.3.2 Objective 1: Is the prescribing information of the frequently prescribed drugs stated in neonatal drug formularies and or local practice guidelines used in the UK neonatal units similar?

Antibiotics included in the list of ten most frequently prescribed drugs were: benzylpenicillin, gentamicin, cefotaxime, and flucloxacillin.

6.3.2.1 Benzylpenicillin

Benzylpenicillin is the most frequently prescribed drugs across neonatal units in England and Wales. This drug was cited across all the collected formularies and practice guidelines as being used for sepsis or meningitis. According to the BNF-C, this antibiotic is prescribed for neonatal sepsis as 25 mg/kg every 12 hours (increased every 8 hours) in those up to 7 days and as 25 mg/kg every 8 hours (increased to 50 mg/kg every 8 hours) in neonates 7 to 28 days (398).

Five out of the nine shared drug resources stated its use in sepsis. However, there are different dose regimens used which varied between 25 to 100 mg/kg either twice or three times per day depending on the severity of the infection and the gestational age of the neonate. Resources from four units have mentioned the dosage regimen according to the postnatal age of the neonate (Table 43) whereas the fifth unit did not state the specific dose for sepsis. Three units out of four (units 2,3, and 6) use 50 mg/kg twice daily for neonates < seven days and 50 mg/kg three times daily for neonates seven to 28 days. The fourth unit halved the above-mentioned dosage regimens for those ages.

Similarly, for meningitis different dose regimens were cited across the shared drug information resources, which varied between 50 to 100 mg/kg twice or three times per day.

The detailed prescribing information of benzylpenicillin obtained from the participating units is in 9.42.

Table 43. The dosage regimen of benzylpenicillin in sepsis

Unit	Indication	Neonatal age	Dosage regimen
Unit 2	Sepsis (suspected at birth)	<7 days of age	50mg/kg 12 hourly
		7 to 28 days of age	50mg/kg 8 hourly
		>28 days of age	50mg/kg 6 hourly
Unit 3	Sepsis (suspected at birth)	<7 days of age	50mg/kg 12 hourly
		7 to 28 days of age	50mg/kg 8 hourly
		>28 days of age	50mg/kg 6 hourly
Unit 6	Early-onset sepsis	Preterm	50mg/kg/dose 12 hourly
		Term < 7 days	50mg/kg/dose 12 hourly
		Term 7 to 28 days	50mg/kg /dose 8 hourly
Unit 7	Early-onset sepsis	< 7 days	25 mg/kg every 12 hours; change to 25mg/kg every 8 hours
		7 to 28 days	25 mg/kg every 8 hours; increased if necessary, to 50 mg/kg every 8 hours in severe infection

6.3.2.2 Gentamicin

Gentamicin is usually administered with benzylpenicillin for the management of neonatal sepsis, particularly early-onset sepsis (EOS). According to the BNF-C, the recommended dose is 5 mg/kg every 36 hours in neonates up to 7 days of age, and every 24 hours in neonates 7 to 28 days of age (399). It was the second most frequently prescribed drug in neonatal units in England and Wales. Four out of nine shared drug information resources stated the use of gentamicin for sepsis, with three of them in EOS. The remaining five indicated the use of gentamicin in infections as general without specifying the type of infection. Also, similarly to benzylpenicillin, various doses were found to be used that ranged between 3 to 5 mg/kg every 24 or 36 hours and started at different gestational ages. However, two units used the same regimen of gentamicin in sepsis for neonates < seven days of age (5mg/kg/dose once every 36 hours) and neonates ≥ seven days (5mg/kg/dose once every 24 hours).

Gentamicin requires regular therapeutic drug monitoring due to its potential ototoxicity and nephrotoxicity. Eight out of the nine information resources stated the gentamicin therapeutic monitoring protocol. All of the eight resources indicated that trough levels should be taken with seven of them stated that this should be before the second dose. Peak levels were required by five out of the eight formularies while three of them indicated that it is required only if there was no response to the treatment (Figure 80).

The detailed prescribing information of gentamicin obtained from the participating units is in 9.43.

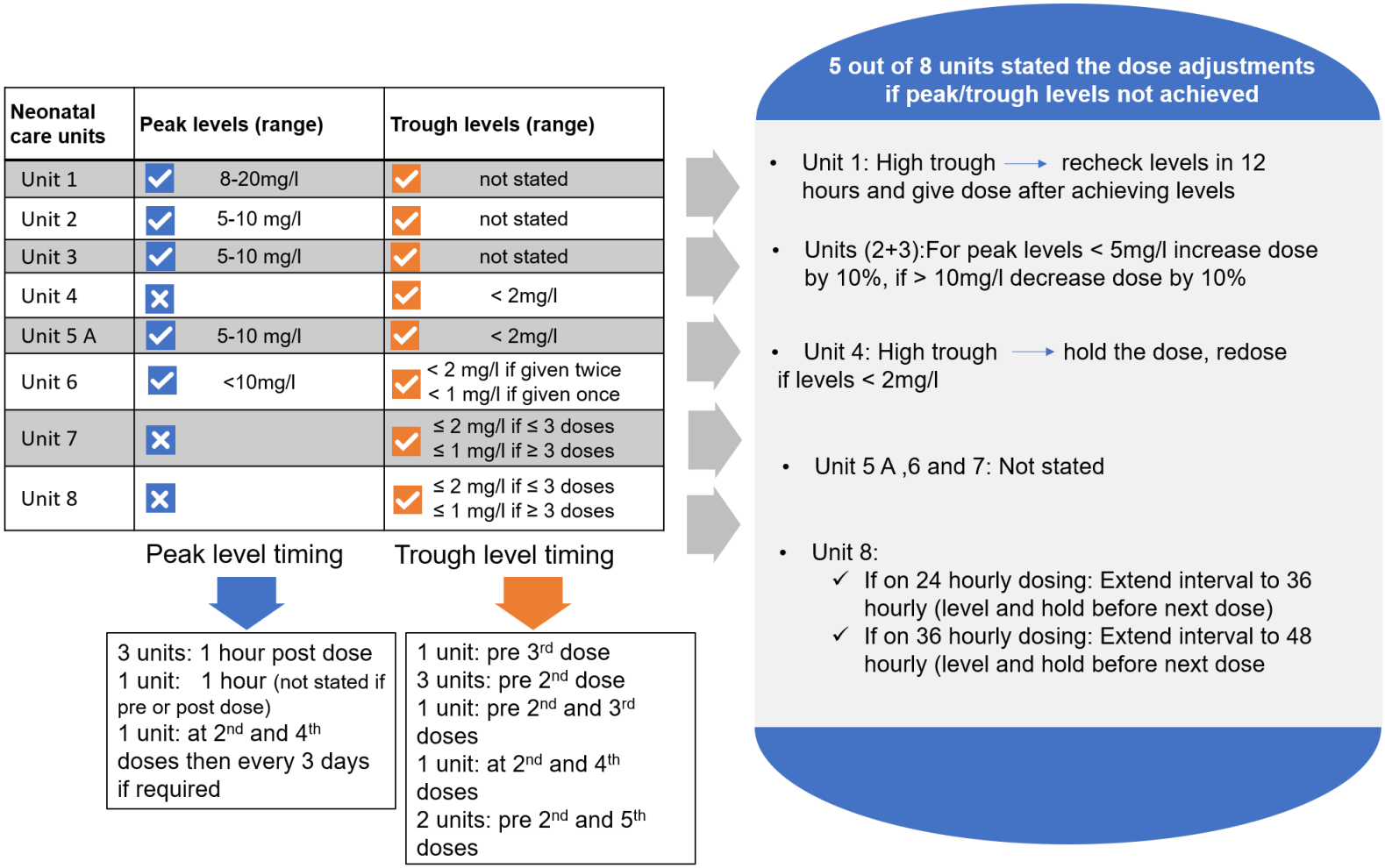


Figure 80. Therapeutic gentamicin monitoring from eight neonatal care units

6.3.2.3 Cefotaxime

Cefotaxime is a third-generation cephalosporin frequently used among neonates. According to the BNF-C, this antibiotic is used in infections sensitive to Gram-positive and Gram-negative bacteria and severe infections/meningitis. The doses vary according to neonatal age and type of infection, for example, 25mg/kg every 12 hours is prescribed for neonates up to 7 days in Gram-positive and Gram-negative infections and increased to 50 mg/kg every 12 hours in severe infections and meningitis (400).

One out of the nine resources indicated the use of cefotaxime as first-line in late-onset sepsis, three stated its broad term use in infections, four indicated its use in infections and meningitis, and one indicated its use only in meningitis. The doses were stated by seven units and were mostly similar, with six units using it at 50 mg/kg at different hours based on the neonatal age (Figure 81).

The detailed prescribing information of cefotaxime obtained from the participating units is in 9.44.

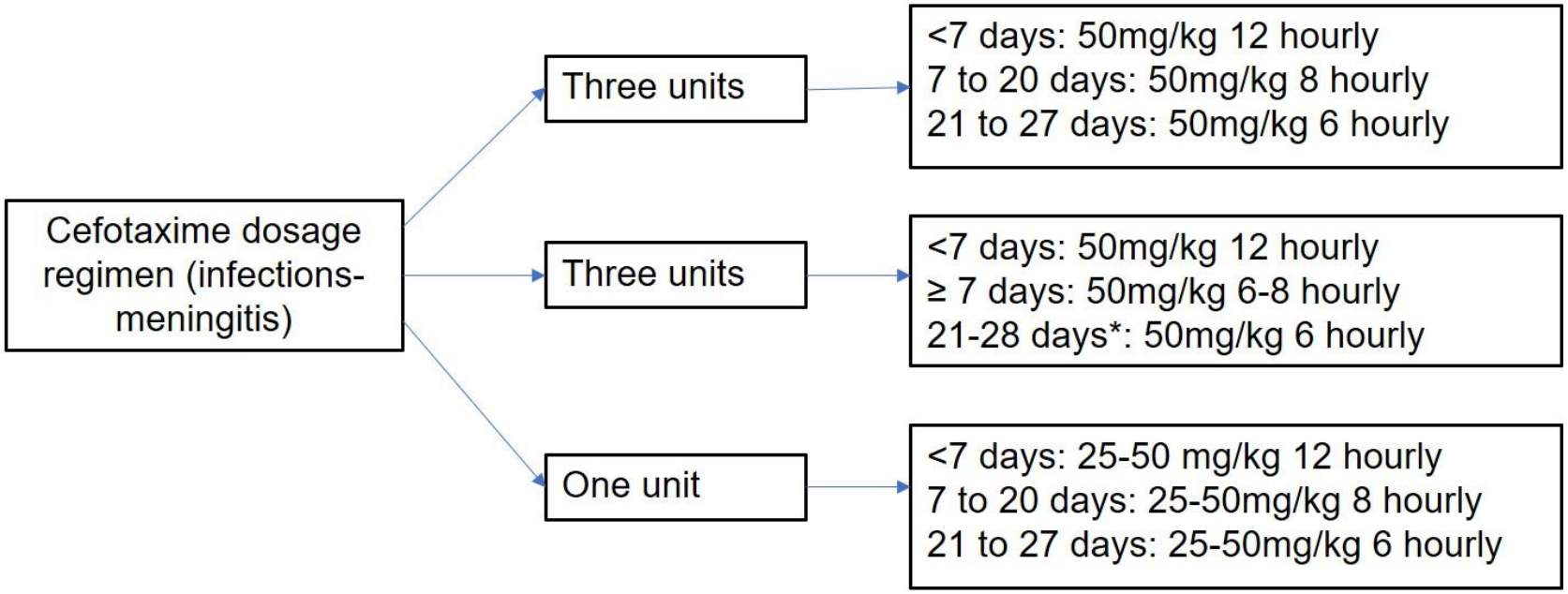


Figure 81. Cefotaxime variability in dosage regimen (stated by seven units)

6.3.2.4 Flucloxacillin

According to the BNF-C, flucloxacillin is indicated for use in neonates with infections related to staphylococcal (e.g. meningitis), skin (e.g. impetigo), and osteomyelitis. The doses vary according to the neonatal age and the type of infection. For instance, the recommended dose in neonates up to 7 days of age with osteomyelitis is 50-100 mg/kg every 12 hours (every 8 hours in neonates 7 to 20 days). Whereas in neonates up to 7 days of age with impetigo, the recommended dose is 25mg/kg every 12 hours (every 8 hours in neonates 7 to 20 days) (401).

Four out of the nine drug information resources stated the use of flucloxacillin in infections, whereas four were more specific and stated its use in staphylococcal infections, and one indicated its use in skin and systemic infections. The doses of flucloxacillin also varied between units, ranges between 25 to 100 mg/kg administered at different intervals based on different neonatal gestational ages (Figure 82).

The detailed prescribing information of flucloxacillin obtained from the participating units is in 9.45.

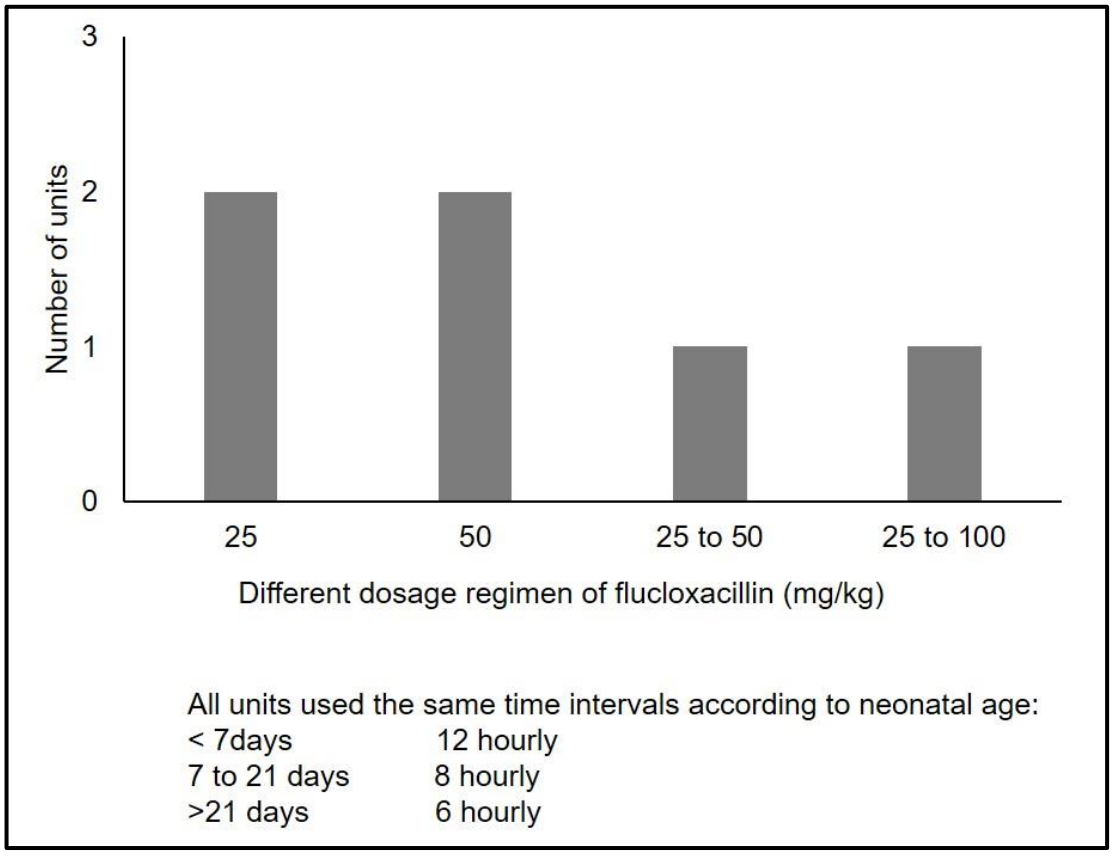


Figure 82. Number of units using different dosage regimen of flucloxacillin to treat infection

6.3.2.5 Caffeine (citrate)

Caffeine is a respiratory stimulant used for apnoea of prematurity. As per BNF-C, the recommended dose of caffeine citrate in neonatal apnoea is 20mg/kg (loading dose), then maintenance dose of 5mg/kg once daily (may increase above 20mg/kg) and started 24 hours post the loading dose (402). As of August 2013 and due to safety information, all licensed preparations of caffeine are required to be labelled as caffeine citrate to minimise the risk of dosing errors as a recommendation by the Medicines and Healthcare products Regulatory Agency (MHRA) (193). All units participating in this study have stated caffeine as caffeine citrate in their formularies and or clinical practice guidelines and had the same indication for its use which is apnoea of prematurity. Eight out of the nine resources stated the doses of caffeine citrate as a loading and maintenance dose, whereas one resource did not state any dose recommendation for caffeine citrate. The loading dose is given as 20 mg/kg in all the participating units. However, the maintenance dose varied between units (Figure 83).

Also, all the resources highlighted the fact that monitoring of caffeine levels is unnecessary unless adverse symptoms persist, or there is evidence of toxicity. An interesting observation is that caffeine is usually advised to be given via intravenous (IV) infusion as a bolus injection is associated with sudden changes in blood pressure. Most of the resources have stated that the direction for its use is via slow IV infusion. However, one practice guideline stated a direction of using bolus infusion of caffeine citrate when given as a maintenance dose.

The detailed prescribing information of caffeine obtained from the participating units is in 9.46.

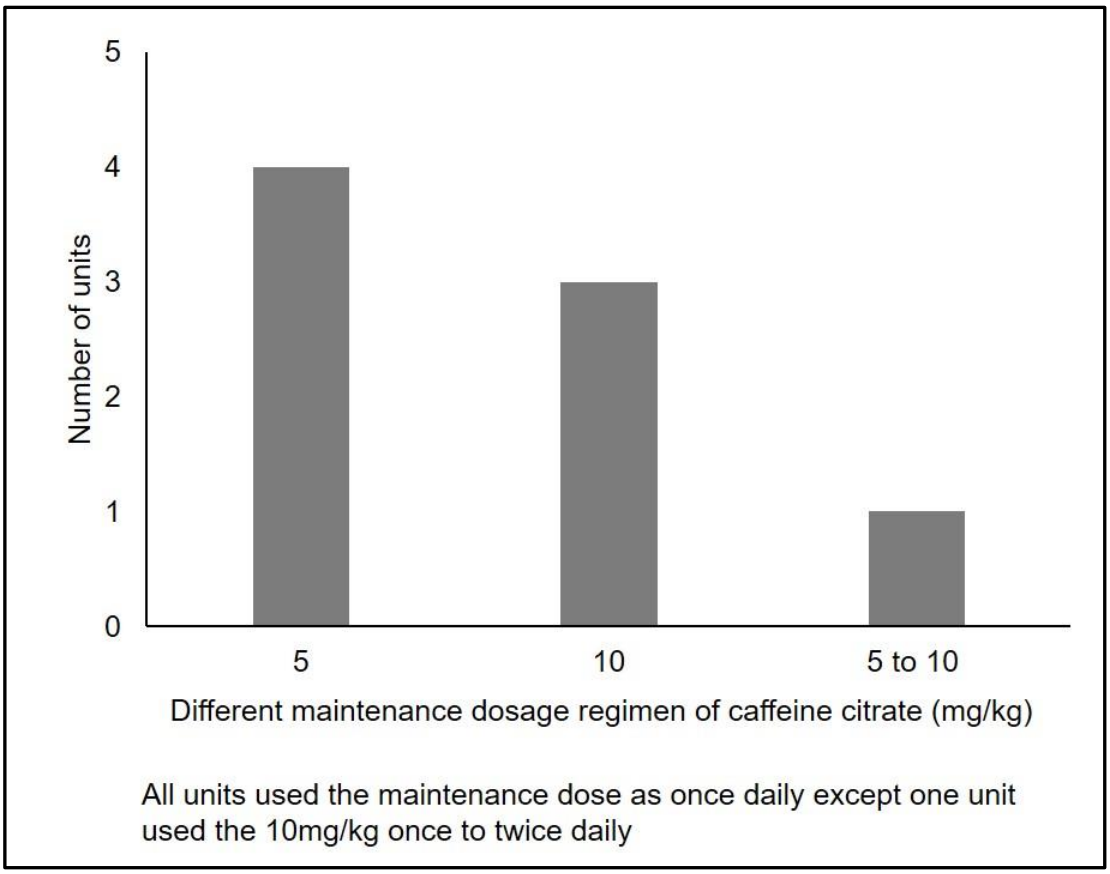


Figure 83. Number of units using different maintenance dosage regimen of caffeine citrate

6.3.2.6 Morphine (IV)

Morphine (sulphate) has a few different indications in the neonatal population. It is used primarily as a sedative and analgesic. Also, it has been used to treat neonates with Neonatal Abstinence Syndrome (NAS), which refers to a collective set of withdrawal symptoms that neonates can develop following birth if their mothers have taken addictive drugs such as narcotics, antidepressants, or potentially addictive drugs. According to the BNF-C, the recommended dose of IV morphine as analgesic is 50 mcg/kg every 6 hours and adjusted later according to response. Whereas, if used for NAS, the recommended dose of morphine is 40 mcg/kg every 4 hours (orally), and increased if necessary (403).

Seven resources out of nine have reported the dosage of morphine according to the indication, whereas the remaining two stated general dosing. The dosing for morphine, when used as pre-medication for intubation, was similar in four out of seven resources given as 100 mcg/kg. However, the loading dose of morphine when indicated for analgesia or sedation varied between 50-100 mcg/kg (Figure 84).

Regarding Neonatal Abstinence Syndrome (NAS), the doses were mostly given at 40 mcg/kg every 4 hours, and morphine was given as an oral preparation in most of the formularies for this indication.

The detailed prescribing information of morphine obtained from the participating units is in 9.47.

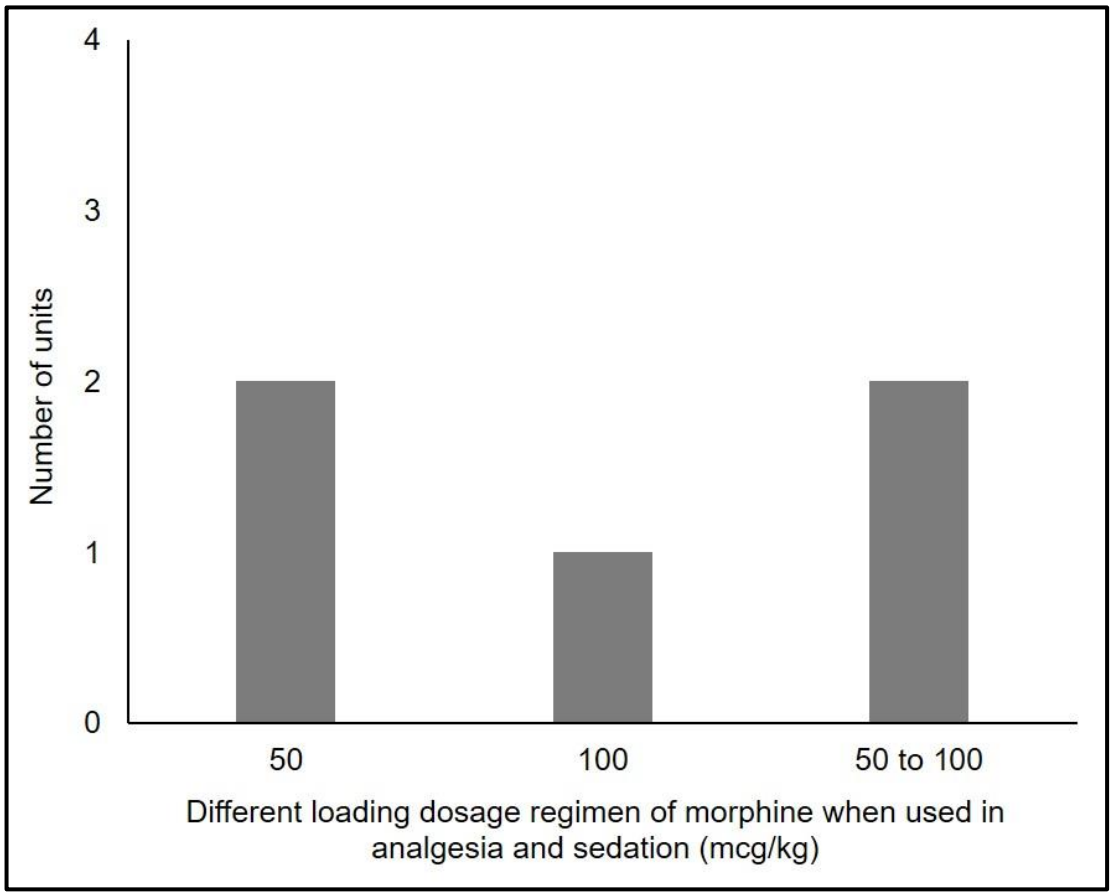


Figure 84. Number of units using a different loading dose of morphine when used as analgesic or sedation

6.3.2.7 Pulmonary surfactants

Pulmonary surfactants are used primarily in preterm neonates who develop respiratory distress syndrome (RDS) as a result of their lungs' immaturity, which affects surfactants production (196). Six out of the nine shared documents cited poractant as a pulmonary surfactant used in their units for preterm neonates with RDS. According to the BNF-C, the recommended dose of poractant alfa when treating RDS in neonates is 100-200 mg/kg, then 100 mg/kg every 12 hours if required (404). The remaining three units had no information regarding pulmonary surfactants in their shared documents. Doses were similar and ranged from 100 to 200 mg/kg/dose as an initial dose for RDS treatment.

The detailed prescribing information of poractant obtained from the participating units is in 9.48.

6.3.3 Objective 2: Is the prescribing information of the drugs used in PDA management (indomethacin, ibuprofen, and paracetamol) stated in neonatal drug formularies and or local practice guidelines used in UK neonatal units similar?

6.3.3.1 Indomethacin

Five out of nine drug information resources included indomethacin prescribing information when used in PDA. Indomethacin is one of the drugs used in PDA closure. However, BNF-C does not list any doses for its' use in PDA closure.

One resource indicated that indomethacin is used as a second-line agent after ibuprofen, whereas another one stated its use as a first-line drug. Three resources out of five listed the dose regimen of indomethacin used in PDA with two of them (UNIT-1 and UNIT 5-A) using the same regimen of either 100mcg/kg every 24 hours intravenously for six doses or as a short courses regimen detailed in (Figure 85).

The detailed prescribing information of indomethacin obtained from the participating units is in 9.49.

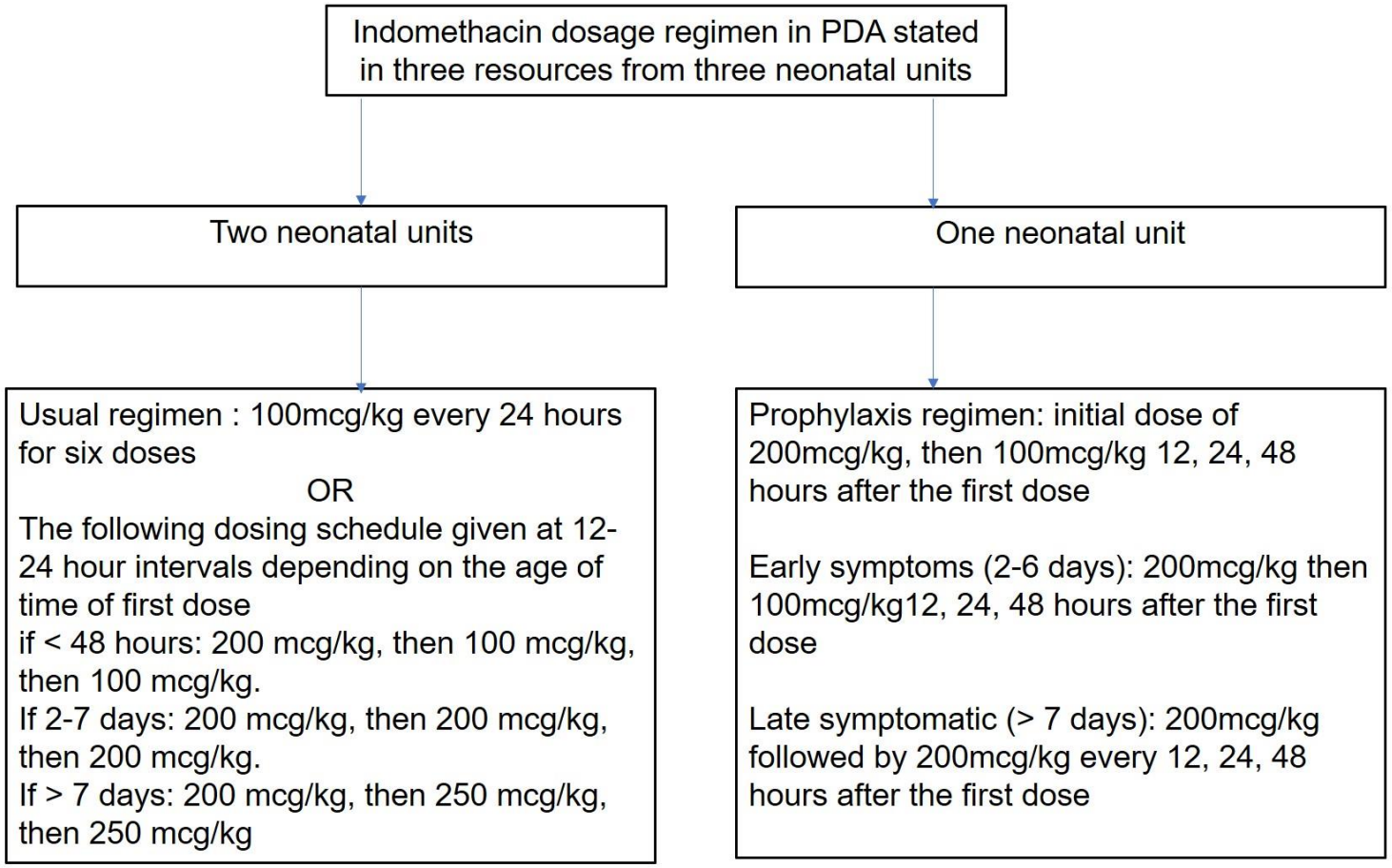


Figure 85. The dosage regimen of indomethacin for PDA treatment as stated in the drug information resources

6.3.3.2 Ibuprofen

Eight out of nine shared drug information resources had information about ibuprofen use in PDA. According to the BNF-C, ibuprofen is used in PDA closure at an initial dose of 10mg/kg, followed by 5mg/kg every 24 hours for two doses and the course maybe repeated after 48 hours if necessary (405).

One of the resources indicated the use of ibuprofen as a second-line drug instead of indomethacin for PDA. Interestingly, all of the shared resources had unified dosage regimens for ibuprofen in PDA, which is: three doses given as slow IV infusion of 10-5-5 mg/kg at 24 hours intervals. Also, they all suggested a repeated course in case the ductus reopens or has not closed after 48 hours after the first course. Monitoring for renal, hepatic function and urine output were amongst the monitoring parameters during ibuprofen treatment that were cited in the shared resources.

The detailed prescribing information of ibuprofen obtained from the participating units is in 9.50.

6.3.3.3 Paracetamol

Only two out of the nine shared resources listed paracetamol to be used for PDA in addition to its use as an analgesic. The other seven resources listed the indication of paracetamol as an analgesic only.

In the BNF-C, there are no doses listed for paracetamol when used in PDA. However, there are doses listed when it is used for pain/pyrexia with discomfort. Paracetamol is indicated at a dose of 7.5 mg/kg every 8 hours for neonates of 32 weeks corrected GA and above as IV infusion (406).

The doses were different as one has specified the doses per neonatal age at the time of the treatment, whereas the other listed one fixed-dose for all age groups (Table 44).

Table 44. Paracetamol comparison when used in PDA as stated in neonatal formularies

Comparison	UNIT-6	UNIT-8
Dose regimen	Five day course; given as IV infusion. Gestation and age based • 23 0/7 to 25 6/7 and ≤ 7days at time of treatment: 12.5mg/kg every 6 hours • 23 0/7 to 25 6/7 and > 7days at time of treatment: 15mg/kg every 6 hours • ≥ 26 0/7: 15mg/kg every 6 hours • Maintenance dose to commence six hours after loading dose	15mg/kg 6 hourly for 5-7 days
Instruction for administration	Check Paracetamol trough level, immediately before the third maintenance dose. Given by IV infusion over 15 minutes	Not stated
Contraindications	Not stated	Not stated
Cautions	Caution in hepatic impairment	Not stated
Monitoring for adverse effects	Monitor hepatic function	Liver function tests should be checked daily

6.4 Discussion

In neonatal medicine, the use of drug formularies and clinical practice guidelines is vital to provide comprehensive guidance on the safe and effective use of drugs in this population. This is due to the vast array of neonatal ages and birth weights, in addition to the immaturity of their organs if born preterm that could affect their response to medicines. All of this can add challenges to clinicians when prescribing and requires referral to such resources, in addition to their clinical judgment, to provide the best therapeutic plan to their patients.

The results of this study have shown that there are some similarities in the extracted drug information from the obtained resources, as well as some inconsistencies and these are discussed in the following sections.

6.4.1 Antibiotics

I found several differences in the prescribing recommendations for the most frequently prescribed antibiotics, benzylpenicillin and gentamicin. Benzylpenicillin and gentamicin are used as a first line for sepsis and were stated in four resources to be explicitly used for sepsis. The dosage regimen of benzylpenicillin reported in three out of these four resources was double that recommended by the National Institute for Health and Care Excellence (NICE) clinical guidelines for the treatment of early-onset sepsis/suspected sepsis at birth. One unit only had the same dose recommended by NICE, which is 25 mg/kg 12 hourly for neonates less than a week of age and increased to 8 hourly for neonates between 7 and 28 days (407).

The gentamicin starting dose for early-onset neonatal sepsis is 5mg/kg and repeated every 36 hours in which the interval can be shortened depending on the severity of the illness and the results of the blood culture as per NICE guidelines (407). Four obtained resources from the neonatal units have stated the use of gentamicin for sepsis with two of them indicating the starting dose of 5mg/kg as per NICE guidelines but with different dosing intervals depending on the neonatal age. All units have stated the use of gentamicin as a once daily dosage regimen, which is supported by the literature. The most recent Cochrane systematic review by Rao et al. conducted with the aim of comparing and safety of once-daily regimen to multiple dosage regimen of gentamicin in suspected or proven sepsis (408). This systematic review has supported the superiority of the 'once-daily regimen' of gentamicin compared to the 'multiple daily regimen' based on the pharmacokinetic profile. PK of gentamicin varies widely in neonates with a longer half-life and smaller clearance in preterm neonates compared to term ones (409). The general recommendation is to attain lower troughs and higher peaks to reduce the toxicity and achieve the efficacy. This can be attained by the 'one dosage regimen' with a high loading dose to increase the peak concentration (409). However, the review suggested the need for further studies that investigates the clinical safety and efficacy of gentamicin. Gentamicin is known to be nephrotoxic and ototoxic with severe toxicity seen after 7 to 10 days of use. Hence, a trough concentration level must be measured, which must be less than 2 mg/l to avoid the toxicity. All units have recommended trough levels of gentamicin to be measured and where stated the level was suggested to be < 2mg/l before commencing the next dose.

Cefotaxime is known to be used for late-onset sepsis (LOS) or meningitis in neonates. The participating units have listed the dosage regimen of cefotaxime for meningitis and severe infections. Only one resource stated the use of cefotaxime for LOS with a dose of 50mg/kg at different frequencies, according to GA. According to the NICE guidelines on neonatal infections, there is still uncertainty and lack of evidence-based guidelines to treat LOS (410). However, the BNFc stated the dose of cefotaxime for LOS as 25mg/kg at different frequencies, according to GA. The latest national surveillance from the UK indicated that 95-97% of isolated organisms from LOS blood samples were susceptible to gentamicin and flucloxacillin/ penicillin (411). Cefotaxime dosage regimen in neonatal meningitis and severe infections were stated in all units per the BNFc and National Institute for Health and Care Excellence (NICE) as 50mg/kg at different frequencies, according to GA.

6.4.2 Caffeine

The prescribing of caffeine as caffeine citrate with a loading dose of 20 mg/kg was standardised across sources. This loading dose is equivalent to the dose used in several studies across the literature, and it is the licensed loading dose as per the summary of product characteristics of caffeine citrate for the treatment of apnoea of prematurity (AOP) (203). Apnoea of prematurity, defined as a cessation of breathing for 20 seconds or longer or a shorter pause accompanied by bradycardia, cyanosis, or pallor in preterm neonates (194). The maintenance dose of caffeine citrate varied between units. One resource stated higher maintenance dosage regimen of caffeine of 10 mg

twice daily compared the other units stating the maintenance dose of caffeine as once daily. The BNFc stated that the maintenance dose of caffeine citrate up to 20mg/kg daily can be considered if therapeutic efficacy was not achieved, taking into consideration the toxicity levels (412). To date, inconsistencies in the dosage regimen for caffeine citrates still exist. A recent review by Moschino et al. summarised the available evidence about the different dosage regimen of caffeine citrate (192). Moschino et al. pointed out that based on the suggestions of the available evidence from recent systematic reviews, a higher dosage regimen of caffeine citrate may be better in improving neonatal outcomes which include reducing episodes of apnoea, extubating failure, and BPD at 36 weeks. However, higher rates of tachycardia were observed. The range of dosage regimen stated in the systematic reviews varied for the loading dose between 10 to 80 mg (or > 20mg) and for the maintenance dose between 5 to 30 mg (or > 10mg) (413–415). What is less clear is the long-term outcomes and safety data on the high dosage regimen of caffeine which may have led to the continual use of the standard dosage regimen of caffeine citrate (loading dose: 20 mg/kg, maintenance dose: 5-10 mg/kg). This dosage regimen has been used in one of the landmarks randomised controlled trials of caffeine when used in preterm neonates, which is the ‘Caffeine for Apnoea of Prematurity’ (CAP) (203). None of the resources indicated the duration of caffeine citrate when used in AOP, but one unit has stated that the treatment should be held for five days before the actual date of the discharge. This is done to allow for the continuous monitoring for the toxicity of caffeine as the half-life of caffeine in neonates is between 60-140 hours. All units highlighted the importance of

labelling and prescribing caffeine as caffeine citrate as this can avoid dosing errors. This is due to the fact that the dose of caffeine citrate is equivalent to twice that of caffeine when expressed as caffeine base (193).

6.4.3 Pulmonary surfactants

Pulmonary surfactants are vital in the management of neonates with RDS. There were three different animal-derived surfactant preparations licensed in Europe in 2016. Two are bovine minced pulmonary surfactant (beractant and bovactant), and one is porcine minced pulmonary surfactant (poractant alfa) (416). Evidence has shown that those preparations also differ in their clinical outcomes. Recent Cochrane Systematic review concluded that poractant alfa is associated with a better survival rate and improved pulmonary outcomes when compared with beractant (417). This could explain the use of poractant alfa as a surfactant and not beractant across the collected resources in the present study. The recent European Consensus guidelines on the management of RDS have recommended the use of poractant alfa as an initial dose of 200mg/kg as it is also found to be associated with better clinical outcomes when compared to the 100mg/kg of beractant or proactant alfa (416). However, there is uncertainty whether this advantage is related to the dose or the source of surfactant preparations. Despite the available evidence and recommendations, only one resource in the present study stated the initial dosage regimen of poractant alfa as 200mg/kg whereas others stated the initial dos as a range of 100-200mg/kg. A recent systematic review and meta-analysis by Foligno and Luca (2020) have compared the porcine and bovine surfactant therapy on extra-pulmonary outcomes (418). Interestingly,

this meta-analysis showed a lower risk of PDA with porcine preparation when compared with bovine preparation [12 studies; 1472 patients; OR: 0.655; 95% CI: 0.460 to 0.931; p = 0.018]. No differences were observed in other extra-pulmonary outcomes.

6.4.4 PDA drugs

Generally, indomethacin and ibuprofen are used in preterm infant only as agents to close the PDA. This study demonstrates this consistency. Also, the dosing of ibuprofen was found to be similar in the collected resources and was given as three doses 24 hours apart. This dosage regimen is the recommended and licensed dose of ibuprofen to be used for PDA (45). The findings from the systematic review of ibuprofen adverse effects presented in this thesis (Chapter 5) also indicated that nearly all studies have used the same dosage regimen of ibuprofen in PDA. However, the doses of indomethacin varied across the units. This is was not unexpected as the dosage regimen of indomethacin when used in PDA differs widely across the literature (245). So, until a consensus regarding the optimal dose of indomethacin for PDA closure to be used, the variety in doses used across several drug formularies will remain. Paracetamol was used by most of the units as an analgesic rather than for PDA, despite the lack of evidence of using it as an analgesic and the latest evidence of using it for PDA as detailed in Chapter 4.

6.4.5 Limitations of the presented study

The study has captured a small number of drug information resources. Only eight units (with nine drug information resources) responded to the letter of

participation to the study out of approximately 195 neonatal units across the UK (22,23). This can affect the generalisability of the data and hinder, reaching a definite conclusion about the actual practice in neonatal unit settings. Even with such small numbers, I found inconsistencies in practice for the use of frequently used medicines. This is of particular note for those drugs that have a potential to cause harm if used inappropriately such as gentamicin and caffeine.

In conclusion, despite the limitations of this study, this is an attempt to provide an initial overview of the available neonatal drug formularies and clinical practice guidelines in the UK. This initiative highlights the need to reach consensus in the prescribing information of some drugs (e.g., benzylpenicillin and caffeine), and reinforces the similarities of others (e.g., ibuprofen in PDA). Future implications of the findings are discussed in Chapter 7.

CHAPTER 7 DISCUSSION

The main goal of this thesis was to assess the rational use of drugs in neonates admitted to neonatal units in the UK. This was done by exploring the *patterns* and *quality* of prescribing. To further explore the complexities of rational drug use in neonates, one example, i.e. patent ductus arteriosus (PDA) in preterm neonates was explored further. As a result, several findings of the work presented have emerged. I found some answers but in addition, my work has raised several questions that need to be addressed in future research. These are discussed at the end of each chapter. Here, I provide a summary of my findings and put them together to give a combined view obtained from the work and the wider implications of the findings.

7.1 Summary of findings

The complexity of prescribing in neonates necessitates essential measures to ensure safe and effective use of drugs in neonates. Drug utilisation research is considered an explorative key tool used to investigate the patterns of drug prescribing and the extent to which the drugs are used. This, in turn, will provide an overall picture of the impact of guidelines' implementation and whether they can affect the prescribing behaviour of the clinicians. The up-to-date literature review detailed in *chapter two* of drug utilisation studies has highlighted the similarities and differences of drug prescribing patterns on a global scale. It has concluded that antibiotics remain the most frequently prescribed drugs globally and a need to rationalise the use of those agents worldwide due to the ongoing concerns of anti-microbial resistance. Also, this review found similarities of prescribing

patterns in some regions like Europe and highlighted a lack of drug utilisation studies in others such as Africa and China. The review also revealed the paucity of drug utilisation research in the UK with so far three studies conducted with limitations that hinder an overall conclusion of the prescribing patterns across neonatal units in the UK (28,29,63). These limitations triggered the need for the study described in Chapter 3, which explored the drug utilisation patterns across the neonatal units in England and Wales. This was done using a retrospective data analysis approach of a national database (NNRD). Several points were highlighted from this study that was either related to the drug use profile or the usefulness of the NNRD database in drug utilisation research.

My findings support the evidence from two studies in the USA that similarly utilised large databases in investigating drug utilisation patterns in their NICUs (66,185). All have reported penicillin and gentamicin to be the most frequently prescribed drugs in their NICUs. Consistent with Clark et al., caffeine was amongst the most frequently prescribed drug in preterm neonates (gestational age (GA) < 37 weeks) and the most frequently prescribed drugs in low, very low and extremely low birth weight neonates. Drug use in preterm neonates is challenging due to the burden of co-morbidities that lead to polypharmacy, consequently exposing them to a higher risk of adverse effects. I found a high burden of drug use with extremely preterm and very preterm neonates exposed to a median of 17 and 8 unique drugs, respectively. Interestingly, I found a large group of neonates who were admitted to a neonatal unit but did not have records of having received drugs. These neonates were more mature and had a greater

BW at birth and had shorter length of stay compared to those who received drugs. This group has not been looked at previously.

Drug use over time can undergo change and I found some interesting variations over the study period. Across the entire cohort, ranitidine, domperidone and ocular chloramphenicol use decreased while the use of benzylpenicillin, gentamicin, amikacin, and pulmonary surfactants increased. Some of these changes may be explained by the changing demographics of the population included in the NNRD – from 2010 to 2017 there is an increase in the number of term born neonates whose data are entered into the NNRD which may inflate the number of those who received drugs such as benzyl penicillin. The NNRD, a rich repository of real-life data, allows large national studies such as mine possible. However, it has some limitations and I have discussed them in detail in the chapter.

In my exploration of drugs used for management of PDA in very and extremely preterm neonates, I found that ibuprofen was the most frequently used. However, a firm conclusion about paracetamol use in PDA could not be reached as NNRD data available to me did not allow me to make a direct linkage between the drugs and its indication for use. It is therefore possible that some use of paracetamol may be for its analgesic effect or its indication for preterm neonates for post-immunisation.

The popularity of ibuprofen compared to indomethacin is due to the evidence that ibuprofen is safer to use, However, this relative safety does not preclude the fact that it too has several adverse effects. My systematic review of ibuprofen adverse effects when used in preterm neonates with PDA captured all new and rare adverse effects that are usually found in observational studies rather than randomised trials. I found that half of the total reported adverse effects were in retrospective cohort studies. Although results of such studies should be interpreted with caution as they are more prone to bias, these large numbers of adverse effects are worthy of note.

As a final step in my journey to explore rational drug use in neonates in the UK, I explored the current neonatal drug formularies and practice guidelines in the UK. Despite the descriptive nature of this study and the small number of the drug information resources I was able to access, the results are interesting. They revealed some inconsistencies in prescribing information most notably in those drugs which have the potential of causing harm such as gentamicin and caffeine. To continue the theme, I also looked at the drugs used in PDA. While the recommendations for ibuprofen were fairly uniform, indomethacin doses and regimens varied. The dosing regimen of paracetamol, interestingly, was listed for analgesic in most of the units.

7.2 Implications of findings and caveats for future research

This thesis has re-asserted the adage that 'it requires much to treat the too little'. The implications of my findings and the caveats for future research can be broadly described below.

7.2.1 Towards a better understanding of drug utilisation research in neonates through the usage of large databases

Drug utilisation research is an eclectic discipline that gathers quantitative and qualitative measures to answer specific questions about drug use in a healthcare setting. In the UK, such large studies can be conducted easily and at low cost by using the NNRD. However, there are some gaps that need to be filled to allow this. Firstly, the way in which prescribed drugs are recorded should be standardised so that clinicians can enter the drug names uniformly. Use of a standardised classification system of the drugs and diseases will allow aggregation of data and meaningful comparison and analysis at national and international levels. The most preferred system is the Anatomic Therapeutic Classification (ATC) as this system provides one unique code for each drug (419). The application of such a system in neonatal drug utilisation studies has been observed in several studies across the literature (5,420–422). However, these studies were all prospective using primary data sources and hence laborious and expensive to replicate. Incorporation of such standardisation into databases such as the NNRD will facilitate DUR without the need for such resource-intensive prospective studies. A recent expert review published by Allegaert et al., reported that the application of this classification is possible in neonates with the availability of specific

indication for each drug (423). With this step, the data related to the drugs can be aggregated easily. Another system that can be used in the UK to facilitate unified coding of drug nomenclature is the use of an existed unified dictionary of drugs named the 'dictionary of medicines and devices (dm+d)' (424). This electronic dictionary of unified codes represents medicines and devices in use across the NHS in a consistent way to facilitate sharing of information pertaining to medicines and devices between organisations. This dictionary is contained within a widely used database in the UK, the Clinical Practice Research Database (CPRD), which contains data routinely recorded in primary care. Incorporating such a system into Badger.net, and hence into the NNRD, will aid clinicians in prescribing, sharing information, and facilitating the analysis process when used by researchers through those standardised codes (425).

Another point that can be used to improve the NNRD for drug utilisation research purposes is having records of the timing of the drugs, dosage regimen and concurrent drugs used. This may be achieved by linking electronic prescribing software with NNRD platforms such as Badger.net. The availability of such information will allow for better evaluation and assessment of the adverse effects of the drugs, especially in preterm neonates, where polypharmacy exists.

Record linkage to other electronic databases is another area that could be applied to improve the quality of the NNRD when used in DUR. For example, Hospital Episode Statistics (HES), as mentioned in Chapter 3, does not capture any neonatal drug information, but does captures some data items

related to a neonate's time in hospital that might be useful for record linkage to the NNRD. This includes NHS maternity statistics, such as data from the Maternity Service Data set (MSDS) (426) which captures records of each stage of the maternity service and have been updated lately to include more neonatal data items. Some of those are related to birth complications, admission and transfer dates, and diagnosis details. However, it must be noted that this data captures information in England only.

My findings also suggest the importance of establishing neonatal networks in regions such as Africa and Middle East, in addition to those in Europe (e.g. Task Force in Europe for Drug Development for the Young (TEDDY)), with the aim of conducting drug utilisation research to evaluate the current prescribing practices, to develop and implement guidelines, and finally to monitor their success (10). This suggestion emerged as per the DUR review in Chapter 2, only two studies were found to be conducted in Africa; one aimed towards exploring most frequently prescribed antibiotics in Zimbabwe (132) whereas the other one was conducted to assess the prevalence of off-label and unlicensed drugs in an Ethiopian NICU (140). This paucity of research in Africa, known to have the highest neonatal mortality rate warrants further research to explore the pattern of drug use across their NICUs. Similarly, the paucity of drug utilisation studies in the Middle East was found in Chapter 2 prompting such networks or research groups to be established.

Another point to note is that I was unable to include data from Scotland and Northern Ireland. While the data from Scotland were not available to me due to research governance rules, data from Northern Ireland is not included in

the NNRD. Also, an additional problem with the current NNRD is that some neonates are transferred between the UK nations for the purpose of receiving care in different units and this may result in incomplete records of their care in the current database. Any further study claiming to be representative of all of the UK needs to take data from devolved nations into consideration, and research governance around access to these data should be streamlined.

Some interesting clinical questions also arise from my work. My findings re-iterate the need for improvement in prescribing practices to tackle the high usage of antibiotics across different neonatal settings worldwide. Neonatal sepsis and other severe infections contribute to large numbers of neonatal morbidity and mortality (9). This somewhat justifies the high use of antibiotics in but there remains a need to establish some measures to rationalise antibiotics use to avoid unnecessary drug exposure to vulnerable neonates. The results of my NNRD data analysis and systematic review of global DUR both show that antibiotics are, by far, the largest group of drugs given to neonates. Turner et al. (28) highlighted gaps in knowledge of therapeutic treatment of bacterial sepsis, and further work might be useful in this area. There should be an attempt to investigate and monitor the management of sepsis and implement strategies to reduce irrational use. Several strategies can be implemented, such as anti-microbial stewardship to promote safe and effective use of antibiotics and reduce possible anti-microbial resistance (10). These programs should focus on education, continuous monitoring of the current prescribing and resistance patterns, and antibiotics surveillance to promote the use of antibiotics (4,9,78).

Another area for future research is expanding the use of surfactants. My analyses miss out surfactant use in the delivery suite. In addition, more recently, new methods of administering surfactant such as the least invasive surfactant administration have become popular and such details should be recorded and analysed.

The rational use of caffeine in very and extremely preterm neonates also needs attention. Caffeine was entered in three different ways in the database; caffeine, caffeine base, and caffeine citrate. This is concerning, from a pharmacology point of view, caffeine base and citrate differ greatly in terms of their dosage, prompting warnings from the Medicine and Healthcare Products Regulatory Agency (MHRA) (193). Caffeine use should, therefore, be standardised and monitored to avoid unintended adverse effects.

In research, especially drug utilisation studies, combining both quantitative and qualitative methods, complement each other and enhance the interpretation of the findings. Providing an in-depth understanding of clinicians' prescribing behaviour in neonatal medicine is vital, as prescribing in this population is not only guided by rational decisions but also psychosocial factors (7,427). This area is rarely explored in drug utilisation research in neonates, and there is scope for qualitative research, including methods such as focus group discussions, open-ended questionnaires, and in-depth interviews to explore these.

7.2.2 Pharmacological management of PDA: Room for improvement

Taken together, my findings from studies in Chapters 4, 5, and 6 suggest a need for continued research in PDA therapeutics. Ibuprofen is the preferred agents across neonatal units. I was unable to explore whether the use was as a treatment or prophylactic, or if it was guided by ECHO. Using ibuprofen prophylactically is not recommended (55–58,428) due to the increased risk of adverse effects without any benefit in long term outcomes. The patterns of paracetamol prescribing in PDA could also be analysed in more details if linkage between the drugs, and their indications was available.

The systematic review of adverse effects of ibuprofen highlighted in an analytical and quantitative method all the adverse effects of this drug when used in PDA highlighting the need to continue to monitor drug use and the search of alternatives with fewer side effects and trials comparing treatment with no treatment and/or placebo. Further systematic reviews of ibuprofen adverse effects, which take stratification according to different gestational age groups into account, will provide a full picture of ibuprofen adverse effects and will aid neonatologists to weigh the risks and benefits before prescribing ibuprofen.

Another future area of research is the causality assessment of adverse effects in neonates. Surprisingly, none of the studies included in this review has assessed the causality of the adverse effects reported. Assessing the causality of adverse effects in neonates is an ongoing challenge, especially in premature ones. This is due to the difficulty in differentiating the 'true' adverse effects from the confounding variables (e.g. organ dysfunction and

immaturity) in such sub-population of neonates. A new validated algorithm consisting of 13 scored items have been suggested to detect ADRs in neonatal population by Du et al. which may be reliable and tailored to neonates as compared to Naranjo algorithm (268,429). Although not yet tested in a larger neonatal population, the adaptation of such an algorithm in future neonatal studies would be beneficial.

Research questions that could be asked include the factors that affect the response of preterm neonates with PDA to cyclooxygenase (COX) inhibitors, including ibuprofen. There are several predicting factors highlighted in the literature that affect PDA response to COX inhibitors (256) such as gestational age and birth weight, antenatal glucocorticoids, respiratory distress syndrome, and infections. However, there are no large multi-centre trials that address this to help avoid unnecessary pharmacological treatment (256). With the emergence of the perception that paracetamol may be as effective as ibuprofen in PDA management in a recent Cochrane review (244), a further systematic review with more focus on adverse effects of paracetamol is suggested as a future area for research.

7.2.3 Neonatal formularies

Finally, the findings in Chapter 6 has shown inconsistencies in the recommended dosage regimens of indomethacin and paracetamol when used in PDA in the drug information resources. There is a need to reach a consensus in terms of dosage regimen of those agents. This can be possibly addressed by using randomised trial or consensus and expert opinion such as the Delphi method (430). Even with the small numbers available to me, I

found important inconsistencies in prescribing recommendations highlighting the need for a rational prescribing tool for neonates. A larger, more comprehensive review of neonatal formularies could help gather more information to support this. Several tools have been developed for inappropriate prescribing in the elderly population (431). The fact that many tools have been designed for the elderly is due to the burden of comorbidities and polypharmacy in this population (395), characteristics that the elderly, rather interestingly, share with preterm neonates. There are few tools to detect inappropriate prescribing in paediatrics and none in neonates (432,433). A large body of work, including evidence synthesis incorporated into consensus building with the Delphi technique, will be needed to tackle this difficult but essential task. A national, or ideally, international collaboration is required to do this. A summary of all those discussed caveats for future research that came to light following the findings of this thesis is shown in Figure 86.

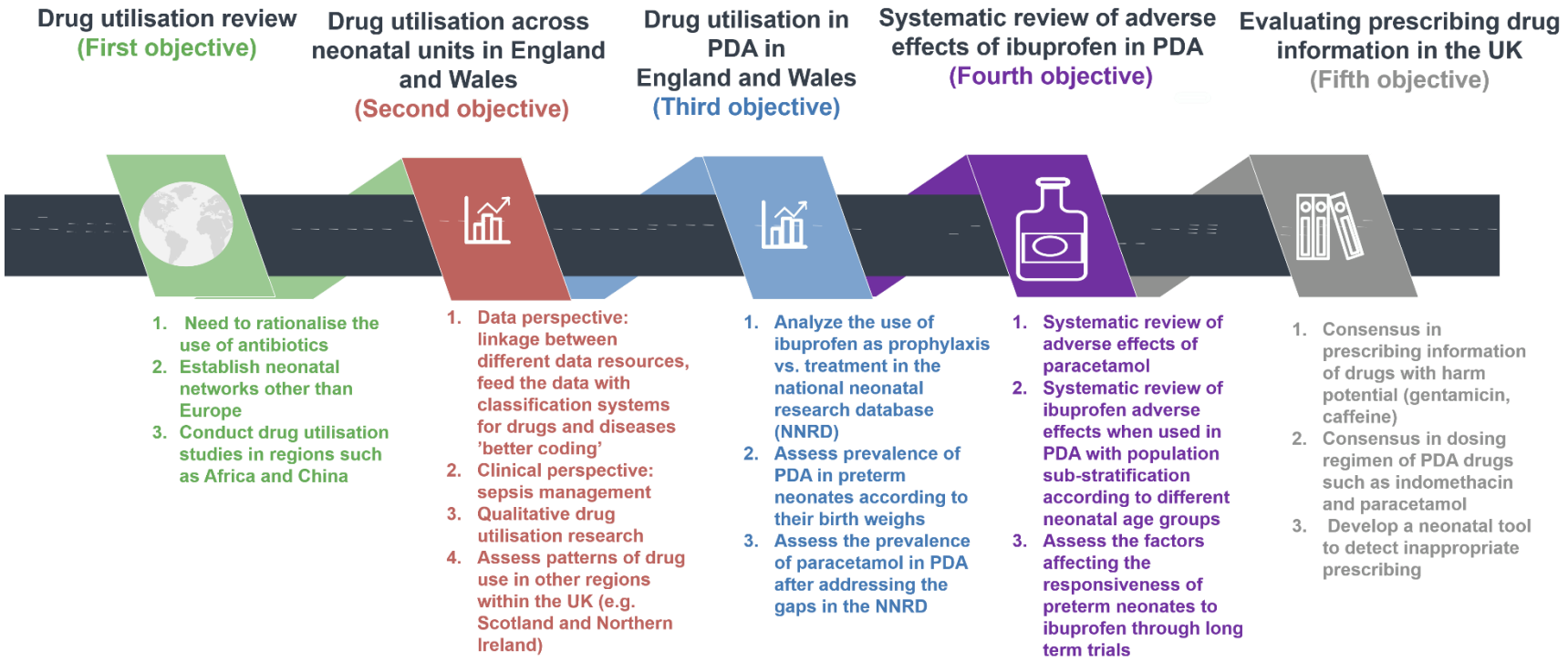


Figure 86. Summary of the caveats for future research emerged from this thesis

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CHAPTER 9 APPENDICES

9.1 Copy of the published paper: Review of drug utilisation studies in neonatal units: A global perspective

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MDPI

Review

Review of Drug Utilization Studies in Neonatal Units: A Global Perspective

Asma Al-Turkait [1], Lisa Szatkowski [2], Imti Choonara [1] and Shalini Ojha [1,3,*]

1 Division of Graduate Entry Medicine, School of Medicine, University of Nottingham, Nottingham NG7 2RD, UK; asma.al-turkait@nottingham.ac.uk (A.A.-T.); imti.choonara@nottingham.ac.uk (I.C.)
2 Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham NG7 2RD, UK; lisa.szatkowski@nottingham.ac.uk
3 Neonatal Unit, University Hospitals of Derby and Burton NHS Trust, Derby DE22 3NE, UK
* Correspondence: shalini.ojha@nottingham.ac.uk; Tel.: +44-1332-724691

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Abstract: Rational prescribing is challenging in neonatology. Drug utilization studies help identify and define the problem. We performed a review of the literature on drug use in neonatal units and describe global variations. We searched databases (EMBASE, CINAHL and Medline) from inception to July 2020, screened studies and extracted relevant data (two reviewers). The search revealed 573 studies of which 84 were included. India (n = 14) and the USA (n = 13) reported the most. Data collection was prospective (n = 56) and retrospective (n = 26), mostly (n = 52) from one center only. Sixty studies described general drug use in 34 to 450,386 infants (median (IQR) 190 (91–767)) over a median (IQR) of 6 (3–18) months. Of the participants, 20–87% were preterm. The mean number of drugs per infant (range 11.1 to 1.7, pooled mean (SD) 4 (2.4)) was high with some reporting very high burden (≥30 drugs per infant in 8 studies). This was not associated with the proportion of preterm infants included. Antibiotics were the most frequently used drug. Drug use patterns were generally uniform with some variation in antibiotic use and more use of phenobarbitone in Asia. This study provides a global perspective on drug utilization in neonates and highlights the need for better quality information to assess rational prescribing.

Keywords: infants; newborn; care; neonatal intensive; drug use review; antibiotics

1. Introduction

Prescribing drugs to newborn infants, particularly those born preterm, is a challenge fraught with complexities including lack of evidence-based information about pharmacokinetics and pharmacodynamics of drugs, efficacy and side-effect profiles for some of the most frequently used drugs. Despite this, infants in neonatal care are exposed to many drugs, often off-label, unlicensed and without clear guidance on dosing. The large gaps in knowledge translate into large differences in interpretation of the sparse evidence that is available, leading to wide variations in practice on one hand and the perpetuation of incorrect practices on the other.

Drug-utilization research provides an insight into the pattern of prescribing and is the essential first step towards rational drug use and evidence-based pharmacotherapy [1]. Physicians prescribe drugs not necessarily based on the available evidence but also under influence from psychosocial and circumstantial aspects that impact their decisions [2]. Investigation into the trends and variability of drug use in the neonatal population can provide information that could guide effective strategies to improve prescribing practices and highlight areas for research. Observational studies describing patterns of drug use provide preliminary evidence to support this agenda. Although evidence for

medication use in neonates is limited, studies describing drug use are accumulating [3] and emerging evidence suggests wide variations in practices across the globe.

The aim of this study was to conduct an up-to-date comprehensive review of literature to accumulate information from studies describing patterns of drug use in neonatal units and describe variations in the most frequently prescribed drugs across different regions.

2. Materials and Methods

Three databases (EMBASE, CINAHL and Medline) were searched from their inception to 20 July 2020 based on the following PICo: population, neonates, infants or newborn (all gestational ages); interest, drug use or drug utilization; and context, neonatal intensive care or neonatal care. A combination of free-text and medical subject headings were applied to each database separately. Various free-text keywords were created and used to complement the Medical Subject Headings (MeSH) terms. For the population search terms, infant* or newborn* or neonate* were used and are defined as infants 0–28 days of age. For the interest/intervention search terms, free-text keywords, a combination of drug use and drug utili?ation was applied. The term utilzation was used to include both utilization or utilisation. The context or the setting free-text keywords used for this review were neonatal intensive care unit* and neonatal unit*. This setting was used as the aim of this review was to provide an updated drug utilization literature review at the level of neonatal intensive care units only. All the previously mentioned free-text keywords were used in addition to the MeSH terms identified in each database separately. The full search strategy is detailed in Appendix A (Table A1). Reference lists were searched to identify any relevant articles. Following the retrieval of the records, titles were reviewed to remove any duplicates before starting to screen the abstracts for inclusion.

All observational studies conducted in neonatal units that reported data on the most frequently prescribed drugs, antibiotics or at least therapeutic groups were included. This includes overall frequently prescribed drugs or pharmacological groups, off-label and or unlicensed drugs or specific pharmacological groups. Studies were excluded if data on drug utilization were not available, if the population included children >28 days old, if maternal rather than infant drug use was reported or if the reports were systematic or other reviews.

All included studies were tabulated (using Microsoft Excel, v15, Microsoft Corporation, Redmond, WA, USA) and data on location of study, inclusion and exclusion criteria, demographics of the included population, number of drugs prescribed per infant, length of stay in neonatal care and the ten most frequently prescribed drugs or pharmacological groups were extracted. Screening and data extraction were completed by two authors (AAT and SO). Quality assessment of the studies was not performed as there is no appropriate tool for the type of studies that are included.

Data extracted, where available, included: country (or countries) where neonatal unit(s) was placed, number of neonatal units included in the study, duration of study, number of infants included, proportion of female participants (calculated as total number of participants—number of males, where only number of males was reported), proportion of preterm infants (defined as born at <37 weeks gestational age), inclusion criteria, exclusion criteria for participants, list of excluded medicinal products, gestational age and birth weight of the participants and drugs received per participant (defined as number of individual drugs received per infant during the entire neonatal care reported). Lists of most frequently used drugs were extracted for all drugs, antibiotics and pharmacological groups, where reported. Data, where available, were sought for indication of use, doses, frequency and duration of administration and adverse effects.

The number of studies that reported a drug as one of its 10 most frequently used is reported as counts. Mean and standard deviation (SD) of number of drugs received per infant were extracted from reports were available. Where the SD was not reported, it was imputed from the available summary statistics (mean, median, interquartile range (IQR), range) and sample size using the process described by Hozo et al. [4]. The correlation between proportion of included preterm infants and number of drugs per infant was calculated using the Pearson's correlation coefficient test in Stata v17.0.

3. Results

The search retrieved 715 articles of which 92 were eligible for full-text screening. A description of these studies is given in Tables A2–A10 in Appendix B. Fifteen further studies were excluded and 7 added from a search of reference lists, such that 84 studies were included in the review. The screening process is illustrated in Figure 1.

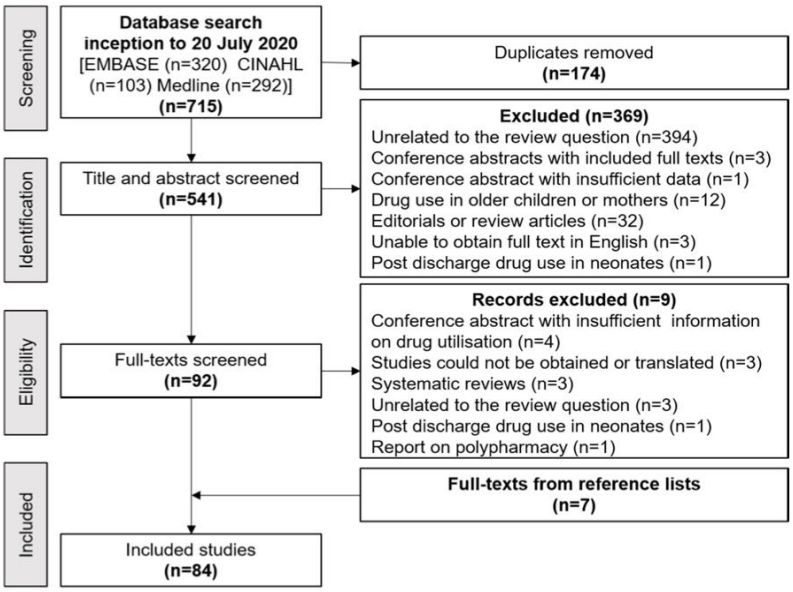

Figure 1. Selection of studies for inclusion.

3.1. Characteristics of Included Studies

Most of the included studies (60/84) evaluated drugs in all drug groups or categories. These 84 included 8 studies that also reported separate analyses of antibiotic use and 20 studies that reported use of off-label medications. In addition, 11 studies reported antibiotic usage only, 6 reported off-label or unlicensed drug use and 7 reported pharmacological groups that were frequently used rather than listing individual drugs. The studies were all observational with 56 prospective and 26 retrospective data collection over a varied time period. Two studies collected both retrospective and prospective data [5,6]. Studies were largely based in a single center (52/84) [5–56]. Thirty-two studies were based in more than one neonatal unit, ranging from 2 centers (7 studies) [57–63] to 341 centers (one study) [64].

Sixty studies, conducted between 1983 and 2020, reported drug use in all therapeutic categories. Most (43 of 60) collected data prospectively while 17 retrieved retrospective data. The studies were conducted in 26 countries (Figure 2) with India and the United States of America (USA) accounting for the largest number of reports, 14 and 13 respectively. There was one study that involved several European countries (21 participated) [65] and one study conducted in Germany and Brazil [66].

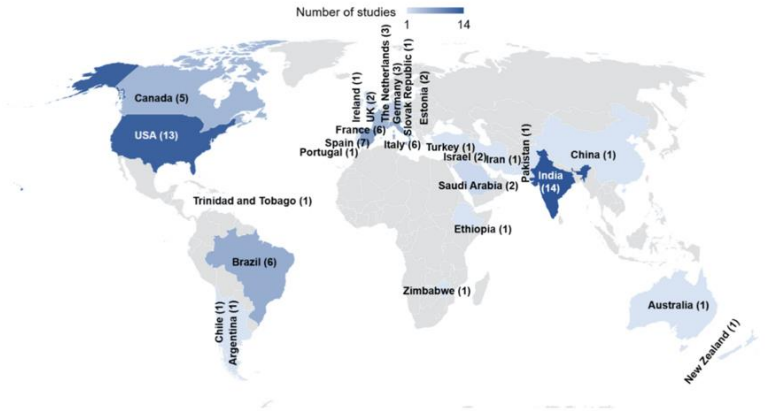

Figure 2. Countries of origin of reports of drug utilization in neonatal units.

The study periods varied from one month [26,55,67,68] to studies spanning over 22 years [33]. The median (interquartile range, IQR) duration of data collection in 79 studies was 6 (3–18) months. Sample size, reported in 77 studies, ranged from 34 [25] to 450,386 [69] infants with a median (IQR) of 190 (91–767) infants. The retrospective studies using large databases with routinely collected data covered the largest span of time and included the largest number of infants, such as Hsieh et al. [69] and Clark et al. [70], who reported data from an administrative electronic database managed by the Pediatrix Medical Group in the USA.

Thirty-four of 60 studies reported the proportion of preterm infants (born at <37 weeks gestational age) among their cohort (range 20% [24] to 87% [71]) in addition to the two studies (34), (31) that included preterm infants only. In addition, one study Puia-Dumitrescu 2020 [72] reported drugs received by infants born at 22–24 weeks gestational age only.

Participants were infants admitted to neonatal units who received at least one drug during their stay. Several studies excluded certain drugs and infusions such as vitamin K, intravenous fluids, parenteral nutrition and fluids used to maintain patency of vascular access. The details of inclusion and exclusion for each included study is given in the tables in Appendix B.

3.2. Number of Drugs Per Infant

The mean and standard deviation (SD) of the number of drugs per infants received during neonatal care was reported in 14 studies [8,13,18,22–24,34,38,43,51,53,63,73,74] and sufficient information was available to impute the SD value in 7 other studies [19,28,32,39,42,69,75] (Figure 3). The pooled mean (SD) of the number of drugs received per infant, calculated from data reported in 29 studies, was 4 (2.4) drugs. There was no correlation (Pearson's r = 0.14; p value = 0.60) between the number of drugs per infant and the proportion of premature infants included in the studies (Figure 4). Several studies (27 studies) [8,11,13,19,20,22,23,26,28,32,34,37–39,42–45,50,59,63,67–69,71,73,75] reported the maximum number of drugs received by at least one infant: Kumar et al. [38] reported the highest drug burden with at least one infant receiving 62 individual drugs, while 8 other studies [13,20,22,23,28,32,43,50] reported that the maximum number of drug per infant was ≥30 in their population.

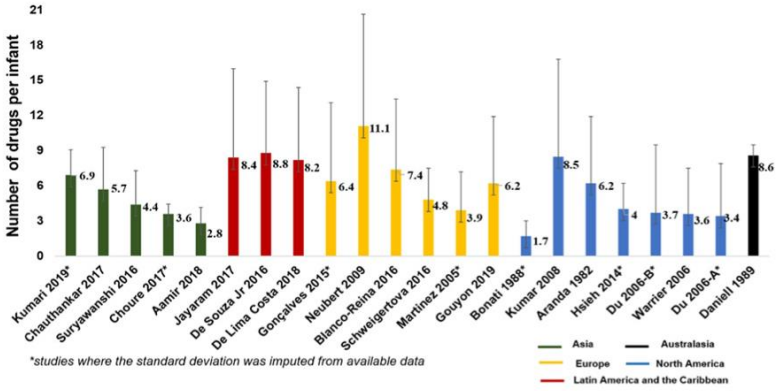

Figure 3. Number of unique drugs per infant reported in drug utilization studies in neonatal units.

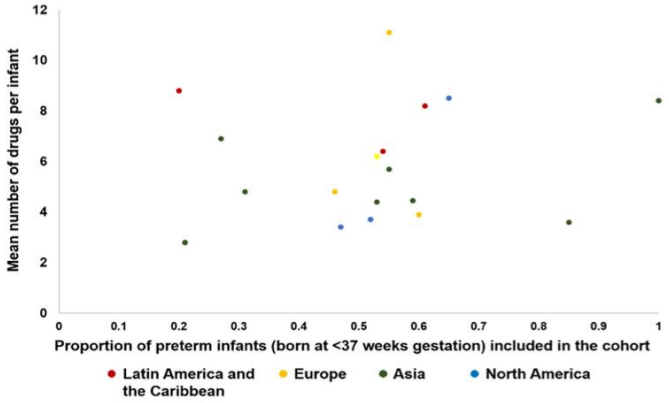

Figure 4. Number of drugs per infant and proportion of preterm infants included in the study.

3.3. *Most Frequently Prescribed Pharmacological Groups*

Thirty out of the 60 included studies reported the most frequently prescribed pharmacological groups, using different methods in their classification. Most used the WHO-Anatomical Therapeutic Chemical (ATC) classification system (19 of 30 studies) [7,13,23–25,30,32,34,42,43,50,51,59,63,71,73,76]. Four studies listed the pharmacological class of the drugs [10,19,39,47] while Kumar et al. (2008) [26] classified the pharmacological groups based on the most frequent indication and the physiological effects of the drug (38). The remaining six studies did not state their classification method [14,21,33,61,75,77].

Among the studies that used the WHO-ATC system, anti-infectives for systemic use were the most frequently prescribed pharmacological group in the majority (14 studies) [13,23–25,30, 34,42,43,50,51,59,71,73,76]. This was followed by agents for the alimentary tract and metabolism (4 studies) [7,63,65,74] and agents for the central nervous system (1 study) (32). Among the four studies that listed the pharmacological groups according to their pharmacological class, three studies reported that antimicrobials were the most frequently prescribed group [19,39,47] and one study by Ashwin et al. (2018) identified that penicillins were the most frequently prescribed [10]. Kumar et al. (2008) reported that the gastrointestinal agents were the most frequently prescribed pharmacological group [38].

3.4. Most Frequently Prescribed Drugs

Forty-eight studies reported the most frequently prescribed drugs. Figure 5 shows the drugs and the number of studies that reported it among its list of most frequently prescribed drugs and Table 1 gives a summary of the data by geographic region.

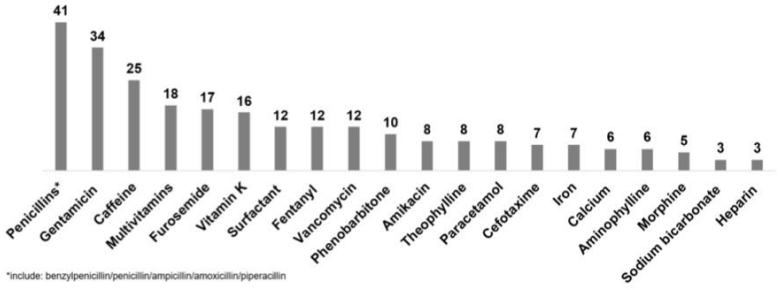

Figure 5. Drugs reported as one of 10 most frequently prescribed in 44 neonatal drug utilization studies. Bars represent the number of studies that reported each drug as one of its 10 most frequently prescribed.

Table 1. Drugs reported to be among the 10 most frequently prescribed in neonatal drug utilization studies in different regions across the world.

Geographic Region (Number of Studies) (Ref)	Most Frequently Prescribed Drugs (Number of Studies Citing the Drug among the 10 Most Frequently Prescribed Drugs)
Europe (24 studies) [7,13,20,25,26,29,31,35,37,42–44,50,59,62,63,65,67,68,71,74–76,79]	caffeine (18 studies), gentamicin (17 studies), ampicillin (11 studies), furosemide (9 studies), multivitamins (9 studies), vitamin K (11 studies), benzylpenicillin (8 studies), amikacin (6 studies), morphine (5 studies), paracetamol (6 studies)
North America (10 studies) [8,9,28,38,53,60,69,70,72,78]	ampicillin (8 studies), gentamicin (8 studies), furosemide (6 studies), surfactant (6 studies), penicillin (5 studies), vancomycin (6 studies), caffeine citrate* (6 studies), cefotaxime (4 studies), dopamine (5 studies), calcium gluconate (4 studies)
Asia (6 studies) [14,17,19,51,55,73]	phenobarbitone (4 studies), vitamin K (4 studies), amikacin (3 studies), aminophylline (3 studies), ceftriaxone (2 studies), ceftazidime (2 studies), gentamicin (2 studies), phenytoin (2 studies), penicillin/sulbactam (2 studies),caffeine (1 study)
Latin America and Caribbean (4 studies) [15,24,32,41]	fentanyl (4 studies), gentamicin (3 studies), vancomycin (3 studies), multivitamins (3 studies), amikacin (2 studies), ampicillin (2 studies), furosemide (2 studies), aminophylline (2 studies), morphine (1 study), metamizole (1 study)
Middle East (2 studies) [11,45]	gentamicin, ampicillin, amoxicillin, vitamins
Australasia (2 studies) [22,46]	vancomycin, gentamicin

Every study had one or more antibiotic in this list with penicillins (41 studies) and gentamicin (34 studies) reported most frequently. Six studies did not have either penicillin or gentamicin in this list. Of these, two reported antibiotics (without specifying which antibiotics were included) [17,19] and the other four [28,35,48,55] had cefotaxime, ceftriaxone, vancomycin, tobramycin, amikacin. cefoperazone-sulbactam and piperacillin-tazobactam amongst their most frequently prescribed drugs.

Most studies did not report the indications of use, dose, frequency or duration of use or adverse effects of the frequently used drugs.

An antibiotic was the most frequently prescribed drug in most studies. Twenty-one studies reported a drug from another therapeutic class as its most frequently used. These were calcium gluconate (2 studies [7,8]), multivitamins (3 studies [44,65,75]), vitamin K (7 studies [14,22,43,45,55,62,76]), caffeine (2 studies [35,71]), chlorhexidine powder (1 study [37]), theophylline (1 study [42]), epinephrine (1 study [78]), parenteral nutrition (1 study [60]), cholecalciferol (1 study [63]), fentanyl (1 study [32]) and vitamin D (1 study [74]). Of the two studies that reported caffeine as the first most frequently prescribed drug, 86.8% of included infants in Cuzzolin et al. (2016) were preterm [71] while Jong et al. (2001) did not report the preterm proportion in their cohort [35].

3.5. Most Frequently Prescribed Antibiotics

Seven studies solely reported the most frequently prescribed antibiotics. In addition, several antibiotics appeared in the list of the most frequently prescribed drugs in studies that did not focus only on antibiotics. In total, 59 studies reported the most frequently used antibiotics. Figure 6 shows the antibiotics and the number of studies that reported it among its most frequently prescribed antibiotic/drug by geographical region. In addition to the data in Figure 6, two studies from Israel [11,45] reported gentamicin, ampicillin and amoxicillin as the most frequently prescribed antibiotics, and one of these [45] also included meropenem among the most frequently prescribed. The two Australasian studies [46,71] included gentamicin, vancomycin, ampicillin and benzylpenicillin in both lists. One African study [6] reported gentamicin, amoxicillin and ceftriaxone as the top three most frequently prescribed antibiotics. The single study from China [55] reported use of cefoperazone-sulbactum, and piperacillin-tazobactum as the most frequently used for all gestational age groups.

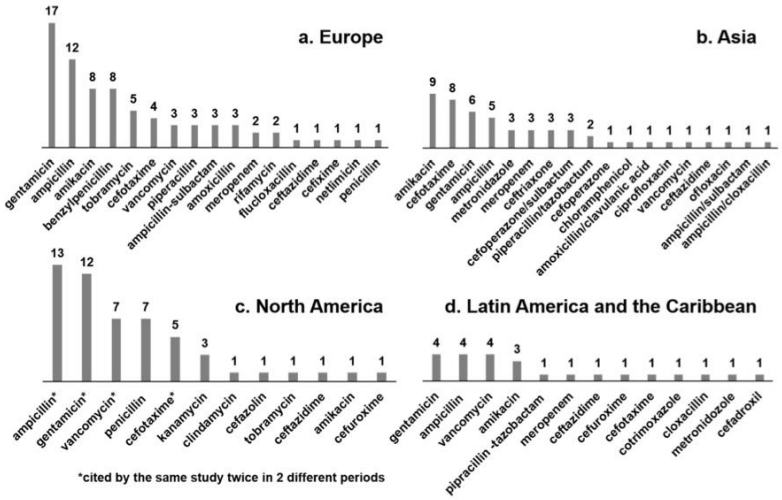

Figure 6. Drugs reported as one of 10 most frequently prescribed antibiotics in neonatal drug utilization studies. (Bars represent the number of studies that reported each drug as one of its 10 most frequently prescribed antibiotic).

4. Discussion

This review presents a comprehensive global perspective of neonatal drug utilization research. Over 15 million infants are "born too soon" every year and provision of essential newborn care is imperative for meeting the United Nations' target to reduce neonatal mortality rates, a key component of the Sustainable Development Goals. Pharmacotherapy plays a large role in neonatal care, particularly intensive care. This role is complicated by several factors including the developmental immaturity of newborn infants, paucity of evidence-base for efficacy, dosing and adverse effects information and the lack of licensed formulations. It is therefore not unsurprising that there is an explosion of interest in this area as reported by Allegaert et al., who found an increasing number of studies investigating drug utilization in newborns [3]. We found drug utilization studies from most parts of the world. Some regions are however sparsely represented—we found only one study from China and one from Africa, both published in the year 2020. India, which has the largest number of preterm births, contributed the largest number of studies, closely followed by the USA. The heightened interest in this area in India is interesting in view of the WHO-led concern that the WHO South-East Asia Region, which includes India, is likely the most at-risk part of the world for the emergence of resistance to microorganisms [80]. Although an increasing number of studies from Europe, and from South America and Australasia, also add to the volume of publications suggesting a world-wide interest, there remains a distinct lack of any collaborative international effort to explore the problem.

Methodologically, the studies remain limited to assessing the most common prescribed drugs either in general, or those that are off-label or unlicensed. Details required to assess the rational use of medications such as indication, dose or duration of use are lacking. Most studies were restricted to single centers and included a limited sample size. Larger studies such as those from the Peadiatrix Medical group in the USA [69,70] are powered by electronic patient records. It is plausible that the use of electronic patient records may enable further large-scale evaluations of drug utilization. This requires efforts to improve electronic patient records such as use of standardized nomenclature and categorization of drugs, collection of data on indications, dosage, adverse effects and medication errors which empower unraveling the yarn of rational prescribing (or the lack of rational prescribing) in neonatal medicine.

The populations included in the studies within this review are quite heterogeneous. Most studies include all neonatal unit admissions with a varied proportion of premature infants. However, it is likely that the composition of the premature cohort is not uniform as studies from high-income countries are likely to include a much more immature population compared to the preterm cohorts in the more resource-limited settings. We found wide variation in the number of medications used per infant ranging from 1.7 drugs per infants reported by Bonati et al. [75] to 11.1 per patient as reported by Neubert et al. [43]. However, we did not see a relationship between the proportion of premature infants included in the study with the average number of drugs prescribed per patient. This is likely to be because of the heterogeneity in the populations and variations in which drugs were excluded from the study. The burden of medication exposure in newborn infants was also well demonstrated by the maximum number of drugs per patient reported in some studies—62 in the most extreme example [38] with several others reporting use of more than 30 drugs in some infants.

We found that the drug utilization pattern is similar across most regions and nations, with a predominance of antibiotics use in all reports. Few studies reported drugs other than an antibiotic as the one in most common usage e.g., caffeine featured at the top of the list in 2 studies. This could be because of the high proportion of premature infants in the study, however we could only confirm this is one study [71] where 87% of included infants were born preterm. Variations in which drugs were excluded from analysis in each study accounts for some other drugs which were not antibiotics appearing as the most frequently prescribed, such as parenteral nutrition, vitamin K and multivitamins which, due to their ubiquitous use, were excluded from most studies. We saw some regional variations: in studies from Asia, specifically India, phenobarbitone was frequently reported. This may reflect the high prevalence of birth asphyxia which, along with prematurity and infections, is one of the

three causes reported to account for 0.79 million of 1.01 million neonatal deaths in India in the Million Death Study [81].

The results of this review clearly demonstrate that antibiotics remain the most frequently used drug in neonatal medicine. This is not unexpected as the burden of infections remains high; neonatal sepsis or meningitis accounted for 16% neonatal deaths globally in 2015 [82]. High risk of death and poor outcomes in survivors warrants the reliance on empirical antibiotic usage based on the sensitive but nonspecific clinical diagnosis of possible infections, particularly in preterm infants, and the antibiotics given to clinically well infants born with risk-factors for early-onset sepsis. Unfortunately, the selective pressure exerted by this widespread use is driving antimicrobial antibiotic resistance. Although this is a global problem it is unequally spread, with data from high-income countries such as the UK showing that 95% of pathogens were susceptible to the most commonly used empirical antibiotic regimens, while in low-and middle-income countries up to 70% of pathogens isolated in neonatal sepsis may not be susceptible to the recommended first-line regimens [83]. Many neonates in hospitals in south Asia are now treated with carbapenems as a first-line therapy for sepsis or presumed sepsis [84]. This is reflected in our findings with the more frequent appearance of antibiotics such as third generation cephalosporins and meropenem, and tazobactum in studies from Asia and Latin America. Data from South Asia reflect a high burden on neonatal sepsis and a distinct pathogen profile with predominance of Gram-negative organisms and lower prevalence of group B streptococci as compared to high income countries [85]. In a review of neonatal sepsis in South Asia, Chaurasia et al. reported that 50–88% of common isolates from health facilities are resistant to first-line antibiotics ampicillin and gentamicin and often to third-generation cephalosporins such as cefotaxime. However, most remain susceptible to meropenem and vancomycin, antibiotics that are on the WHO-specified "watch group" [85]. The choice of antibiotics in China as reported by Yue et al. [55] is also unusual when compared to most other countries. Authors suggest that this is driven by the high levels of ampicillin resistance and prohibition of gentamicin use due to the high risk of hearing loss in the population. Against this backdrop, the widespread availability and antimicrobial use in neonates and the contribution of antimicrobial resistance as a complicating factor in neonatal sepsis becomes extremely important and rather than increasing use of antibiotics, infection prevention measures such as hand hygiene, surveillance cultures, contact precautions and antibiotic stewardship should be implemented [86].

Our findings are in keeping with previous reviews. Allegart et al.(2019) [3] which updated the review by Rosli et al. 2017 [87] focused on research objectives, methodology and patterns of drug use across neonatal units. This review also highlighted that antimicrobials such as penicillins and aminoglycosides are amongst the most frequently prescribed drugs to hospitalized infants which is consistent with our findings. Krzyzaniak et al. (2016) also highlighted the frequent report of antibiotics in their included studies [88]. They concluded that patterns of drug utilization were similar across the globe. Our findings, although broadly consistent with this, do demonstrate some variations which may be explained by the difference in disease burden and pattern of antibiotic use in different regions of the world. This difference may be explained by the limited number of studies included in Krzyzaniak et al. In addition, although individually several studies do report this plausible relationship [18,23,32,34,38,43], we did not see a consistent relationship between the proportion of premature infants included in the studies with the number of drugs prescribed per infant as reported by Krzyzaniak et al.. This variation may be because the relationship between prematurity and drug utilization is not straightforward. Moderate to late preterm infants are often well with minimal medical needs while some term infants suffer significant morbidities requiring multiple drugs and prolonged intensive care. The large proportion of term infants who do not require any medications are not admitted to neonatal units and hence are not included in studies where the population is restricted to those in the neonatal unit. In this population, the number of drugs per infant may be more affected by the criteria for admission, range of gestational ages admitted and morbidities in those infants.

Although the included studies have all reported use of medicines prescribed to infants admitted to neonatal units, the studies do not report the admission criteria for their units. Variations such as those

in types of neonatal units (for example those providing high levels of intensive care or surgical units vs. special care nurseries) and difference in survival of extremely preterm infants (who form a large part of the work in high-income countries but may not survive beyond a few hours in low-income settings) could account for variations that make any cohesive analysis difficult. The analysis of data extracted from the included studies is limited by the heterogeneity of the included populations, variations in study designs and different methods of reporting the findings. In addition, our review is limited by exclusion of non-English-language studies which may be the reason for missing data or very few reports from some parts of the world.

5. Conclusions

We found that the pattern of drug utilization in neonatal units is largely similar across global regions. A few exceptions reflect the patient population included in the study, differences in the burden of neonatal pathologies and the variations in antibiotic usage reflect the global burden of antimicrobial resistance. The review also highlights the lack of details such as paucity on information indication, dose and duration of use or adverse effects, calling for improved collection and analysis of drug utilization data in neonatal medicine. Such research, particularly when conducted collaboratively across national and continental boundaries, is imperative to promote rational use of medicine in neonates.

6. Patents

Not Applicable.

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9.2 Search strategy for drug utilisation review

Database (Total hits 715)	Search terms	Combination of search terms (A combination between title abstract free text keywords and Mesh terms was done for a compressive search from the inception of the database to July 2020 using OR , AND)
EMBASE (provided by Ovid) From 1974 to July 2020 **Number of hits** **320**	Population search terms: Free text words: Infant*-newborn*-neonate* MeSH terms: INFANT-NEWBORN Drug utilisation search terms: Free text words: “drug use”- drug utili?ation MeSH terms: DRUG UTILIZATION-“DRUG USE” Setting search terms: Free text words: neonatal intensive care unit*-neonatal unit* MeSH terms: NEWBORN INTENSIVE CARE- NEONATAL INTENSIVE CARE UNIT	~"(((infant*).ti,ab OR (newborn*).ti,ab OR (neonate*).ti,ab OR *INFANT/ OR exp INFANT/ OR *NEWBORN/) AND (("drug use").ti,ab OR ("drug utili?ation").ti,ab OR *"DRUG UTILIZATION"/ OR exp "DRUG UTILIZATION"/ OR *"DRUG USE"/ OR exp "DRUG USE"/)) AND (*"NEWBORN INTENSIVE CARE"/ OR *"NEONATAL INTENSIVE CARE UNIT"/)"
Medline (provided by ProQuest)	Population search terms: Free text words: Infant*-newborn*-neonate* MeSH terms: INFANT-INFANT, NEWBORN	~"(((infant*).ti,ab OR (neonate*).ti,ab OR (newborn*).ti,ab OR *INFANT/ OR exp INFANT/ OR *"INFANT, NEWBORN"/ OR exp "INFANT, NEWBORN"/) AND (("drug use").ti,ab OR (drug utili?ation).ti,ab OR *"DRUG UTILIZATION"/ OR exp "DRUG UTILIZATION"/ OR *"DRUG UTILIZATION REVIEW"/ OR exp "DRUG UTILIZATION REVIEW"/)) AND ((neonatal intensive care unit*).ti,ab OR (neonatal unit*).ti,ab OR *"INTENSIVE CARE UNITS, NEONATAL"/ OR exp "INTENSIVE CARE UNITS, NEONATAL"/)"

From 1946 to July 2020 **Number of hits** **292**	Drug utilisation search terms: Free text words: “drug use”- drug utili?ation MeSH terms: DRUG UTILISATION Setting search terms: Free text words: neonatal intensive care unit*- neonatal unit* MeSH terms: Care,neonatal intensive- intensive care units,neonatal infant,newborn,intensive care- neonatal intensive care-neonatal intensive care units	
CINAHL (provided by EBSCO) From 1937 to July 2020 **Number of hits** **103**	Population search terms: Free text words: Infant*-newborn*-neonate* MeSH terms: INFANT- INFANT,NEWBORN Drug utilisation search terms: Free text words: “drug useinfa”- drug utili?ation MeSH terms: DRUG UTILIZATION Setting search terms: Free text words: neonatal intensive care unit*- neonatal unit* MeSH terms: INTENSIVE CARE UNITS,NEONATAL	Combination of search terms (A combination between title abstract key words, and Mesh terms was done for a compressive search from inception of the database to February 2019 using OR , AND) ~"(((infant*).ti,ab OR (newborn*).ti,ab OR (neonate*).ti,ab OR *INFANT/ OR exp INFANT/ OR *"INFANT, NEWBORN"/ OR exp "INFANT, NEWBORN"/) AND (("drug use").ti,ab OR (drug utili?ation).ti,ab OR *"DRUG UTILIZATION"/)) AND ((neonatal unit*).ti,ab OR (neonatal intensive care unit*).ti,ab OR *"INTENSIVE CARE UNITS, NEONATAL"/ OR exp "INTENSIVE CARE UNITS, NEONATAL"/)"

9.3 Description of drug utilisation studies on drug use in general (60 studies studies)

Studies of drug utilisation in Europe (27 studies)						
Study ID	**Study period**	**Inclusion and exclusion criteria**	**Number of neonates (%female)**	**Gestation age (weeks) Birth weight (grams)**	**Number of drugs prescribed per neonate**	**Hospital stay (in days)**
Italy (six studies)						
Bonati 1988 **(75)**	One year (year not stated)	Inclusion: All admitted neonates Exclusion: Fluids and electrolytes, glucose, oxygen, vitamin K and prophylactic ophthalmic preparation	N=706 (47%)	GA (mean, range): 33.3, 26-36 BW (mean, range): 2013, 510-3600	Mean (SD): 1.7 (0-8)	Mean (range): 26 (0-142)
Dell' Aera 2007 **(83)**	Jul-Aug 2004	Inclusion: All admitted neonates Exclusion: Not stated	N=34 (not stated)	Not stated	Not stated	Not stated
Dessi 2010 **(84)**	Mar 2007 (one month)	Inclusion: All admitted neonates receiving drugs Exclusion: Saline, blood transfusions, oxygen	N=38 (not stated)	Not stated	Range: 1-4	Not stated
Laforgia 2014 **(91)**	May 2011 (one month)	Inclusion: All admitted neonates with at least one drug Exclusion: Not stated	N=126 (not stated)	GA (median, range): 31, 23-36 BW: not stated	Median (range): 3 (1-7)	Not stated
Cuzzolin 2016 **(80)**	May-Jul 2014	Inclusion: All admitted neonates with at least one drug Exclusion: Not stated	N=220 (41%)	Not stated	Median (range): 4 (1-9)	Not stated
Girardi 2017 **(113)**	Jan 2009-Dec 2011 (3 years)	Inclusion: All admitted neonates with GA < 37 weeks and BW ≤1500 g	N=159 (not stated)	1000-1500 g group: Average (range): 30 (27-36) <1000g group:	Not stated	Not stated

		Exclusion: Died within first 48 hours after birth		26 (22-33)		
Spain (four studies)						
Martinez 2005 **(122)**	Oct-Dec 2003	Inclusion: All admitted neonates Exclusion: Not stated	N=48 (not stated)	Not stated	Mean (range): 3.9 (1-14)	Not stated
Payares 2010 **(100)**	Eight months (year not stated)	Not stated	N=52 (48%)	GA: 0-48 days BW (range): 550-3920	Not stated	Not stated
Blanco-Reina 2016 **(74)**	Jul-Nov (year not stated)	Inclusion: Admitted neonates with at least one drug Exclusion: Not stated	N=48 (41%)	GA (mean (SD)): 34.5 (4.2) BW (mean (SD)): 2335 (949)	Mean (SD): 7.4 (6)	Not stated
Alonso 2019 **(70)**	Apr-Sept 2018	Inclusion: All admitted neonates Exclusion: Blood products, TPN, fluids and oxygen	N=84 (38%)	Not stated	Not stated	Not stated
France (four studies)						
Gouyon 2019 **(68)**	Jan 2017-Dec 2018	Inclusion: All neonates with first prescription before 28th day of life and at least one electronic medical prescription Exclusion: No prescriptions, or none in first 28 days	N=27382 (55%)	GA (mean (SD)): 35.4 (4.3) BW (mean (SD)): 2457.8 (944.5)	Mean (SD): 6.2 (5.7)	Mean (SD) : 14.6 (19.5)
Gortner 1991 **(86)**	Aug 1989 -May 1990 (10 months)	Inclusion: Premature neonates with a need of intubation and mechanical ventilation Exclusion: Vitamin K and heparin for flush	N=164 (46%)	GA (mean (SD)): 27.2 (1.2) BW (mean (SD)): 970 (145)	Not stated	Not stated
Nguyen 2011	Jan-Apr 2009	Inclusion: All admitted neonates	N=65 (not stated)	GA median(range)): 34 (27-41)	Median (range):	Median (range):

(96)		Exclusion: TPN, IV fluids, oxygen and drugs used in research studies		BW median(range)): 1930 (810–4520)	4 (1-7)	15 (1-47)
Riou 2015 **(101)**	One year (2012)	Inclusion: All admitted neonates with at least one drug Exclusion: Blood products, oxygen, enteral and parenteral nutrition, and standard IV replacement solutions	N=910 (43%)	GA (median (IQR)): 34 (31-37) BW (median (IQR)): 2040 (1530 -2270)	Median (IQR): 8 (5-13)	Median (IQR): 18 (8-38.7)
The Netherlands (three studies)						
Jong 2001 **(88)**	Feb-Mar 1999	Inclusion: All admitted neonates Exclusion: Blood products, TPN, oxygen therapy, IV fluids	N=64 (50%)	Not stated	Not stated	Not stated
Flint 2014 **(110)** Poster abstract	Jan 2007-Jun 2013	Not stated	N=4054 (45%)	GA (median, range): 32 ,23^{+6} - 42 $^{+2}$ BW (median, range): 1800, 360 -5400)	Not stated	Not stated
Flint 2018 **(111)**	Sept 2014-Aug 2015 (one year)	Inclusion: All admitted neonates Exclusion: Electrolytes, TPN, vaccines, dermatological products, contrast media	N=1491 (48%)	GA (median, IQR): 32^{+5}, 29^{+6} to 37^{+6} BW (median (IQR)): 1865,1253 -3000	Median (IQR): 5 (3-10)	Median (IQR): 12 (5-32)
Germany (two studies)						
Lindner 2008 **(93)**	Study period not stated (Germany)	Inclusion: All neonates with GA<32 Exclusion: Not stated	N=113 (44%)	GA (mean (SD)): 26.9 (1.65) BW (mean (SD)): 930 (253)	Not stated	Not stated
Neubert 2009 **(95)**	Dec 2004-Oct 2005 (11 months)	Inclusion: All admitted neonates for > 24 hours Exclusion: IV infusions (glucose or chloride), TPN and oxygen	N=183 (44%)	GA (mean (SD)): 33.6 (4.66) BW (mean (SD)): 2134 (935)	Mean (SD): 11.1 (9.56) Range: 0-45	Mean (SD): 19.3 (25)

UK (two studies)						
Conroy 1999 (29)	Feb-May 1998 (13 weeks)	Inclusion: All admitted neonates Exclusion: IV fluids, flushes of sodium chloride 0.9% or heparin, blood products (other than albumin) and oxygen	N=70 (not stated)	GA of preterm only (median, range): 33 (26 to 36)	Median (range): 3.5 (0-42)	Not stated
Turner 2009 (28)	Dec 2007-Apr 2008	Inclusion: All admitted neonates Exclusion: Blood products, IV fluids, TPN	Not stated	Not stated	Not stated	Not stated
Ireland (one study)						
Kieran 2013 **(89)**	Feb-Mar 2012	Inclusion: All admitted neonates Exclusion: Not stated	N=110 (not stated)	GA (mean (SD)): 35 (5) BW (median (IQR)): 2615 (1601 -3500)	Median (IQR): 4 (3-11)	Not stated
Portugal (one study)						
Silva 2015 **(118)**	Jan-Jun 2013	Inclusion: All admitted neonates Exclusion: Oxygen, IV fluids and flushes, drugs used in surgeries, contrast agents, vaccines, blood products (except albumin and immunoglobulins), basic creams, research drugs	N=218 (45%)	GA (mean (SD)): 36.07 (4.0) BW (mean (SD)): 2554 (910.5)	Median (range): 3 (0-34)	Median (range): 7 (1-210)
Estonia (one study)						
Lass 2011 **(92)**	Feb-Aug 2008	Inclusion: All admitted neonates Exclusion: IV fluids, blood products, oxygen, nutritional and technical products, basic creams and ointments, TPN, vaccines and vitamins	N=490 (not stated)	GA: Not stated BW (mean (SD)): 2446 (1124)	Median (IQR, max): 4 (2-7, 27)	Median (IQR): 10 (5-18.75)
Slovak Republic (one study)						

Schweigertova 2016 **(103)**	Apr-Sep 2012	Inclusion: All admitted neonates Exclusion: IV replacement solutions, TPN, vaccines, blood products and oxygen	N=202 (49%)	GA (mean (SD)): 36 (3.4) BW: Not stated	Mean (SD): 4.8 (2.7)	Mean (SD): 14 (10) Range: 1-51
Turkey (one study)						
Oguz 2012 **(99)**	Dec 2011	Inclusion: All admitted neonates Exclusion: Standard IV solutions, sodium chloride 0.9% infusions, TPN, blood products (except albumin), and oxygen	N=93 (not stated)	GA (mean (SD)): 32.5 (4.7) BW (mean (SD)): 2081 (951)	Median (range): 3 (1-11)	Not stated
Multi-European countries (21 countries)						
Mesek 2019 (63)	Jan–Jun 2012	Inclusion: All neonates in neonatal unit receiving prescription on the day (at 8 AM) Exclusion: Blood products, glucose and electrolyte solutions, vaccines, nursery care topical agents, herbal medicines and enteral nutrition including breast milk fortifiers	N=726 (43%)	GA (median, (IQR)): 34 (30–38) BW (median, (IQR)): 1993 (1356–3006)	Not stated	Not stated
Studies of drug utilisation in Middle East (2 studies)						
Israel (two studies)						
Barr 2002 **(73)**	Apr-Jul 2000	Inclusion: All admitted neonates Exclusion: Saline, heparin flush, blood transfusions, and oxygen	N=105 (not stated)	Not stated	Range: 1-13	Not stated
Nir-Neuman 2018 **(97)**	Dec 2015-Jan 2016	Inclusion: All admitted neonates Exclusion: TPN, blood products, fluids, oxygen therapy, nasal sprays, eye drops, ointments, and local creams	N=134 (49%)	GA (median, IQR): (35,33-38) BW (mean(SD)): 2424 (854)	Median (IQR): 6 (2-17)	Median (IQR): 11.5 (6-24.5)

Studies of drug utilisation in North America (12 studies)						
USA (nine studies)						
Russel 1983 **(102)**	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Lesko 1990 **(116)**	1978-1986	Inclusion: All admitted neonates for > 24 hour Exclusion: Vitamin K and topical products (silver nitrate)	N=2690 (43%)	GA: Not stated BW (median): 2220	8	8
Clark 2006 (65)	February-May 1998 (13 weeks)	Inclusion: All neonates in database Exclusion: Not stated	N=253651 (44%)	GA (median, IQR): 35 (33-38) BW (median, IQR): 2460 (1790-3200)	Not stated	Not stated
Du 2006 **(109)**	Jan 1997-Jun 2004 (7 years) Divided into 2 periods: First period: 1997-1998 Second period: 2001-2004 (USA)	Inclusion: All admitted neonates with at least one drug Exclusion: TPN, oxygen, vitamin K prophylaxis, erythromycin ophthalmic prophylaxis, routine cord care, vaccinations, blood and blood products (except fresh frozen plasma)	• 1997-1998: N=2332 (47%) • 2001-2004: N=2691 (44%)	• 1997-1998: GA (mean): 35.7 BW (mean):2580 • 2001-2004: GA (mean): 35.3 BW (mean): 2499	• 1997-1998: Median (range): 3.37 (2, 1-28) • 2001-2004: Median (range): 3.72 (2,1-36)	• 1997-1998: 13.8 • 2001-2004: 15.4
Warrier 2006 **(119)**	Jan 1997-June 2004	Inclusion: All admitted neonates with at least one drug	N=6839 (46%)	GA (mean (SD)): 35 (5) BW (mean (SD)):	Mean (SD): 3.6 (3.9)	Mean (SD): 15 (24)

		Exclusion: Blood and blood products (except fresh frozen plasma), TPN, oxygen, vitamin K prophylaxis, erythromycin ophthalmic prophylaxis, routine cord care, vaccinations, normal saline except for hypotension		2498 (1000)		
Kumar 2008 **(115)**	Sept 2000-Aug 2003 (3 years)	Inclusion: All admitted neonates Exclusion: TPN, nutritional supplements such as vitamins, standard IV fluids, immunizations, and research drugs	N=2304 (43%)	GA (mean (SD)): 34.1 (4.6) BW (mean (SD)): 2325 (1014)	Mean (SD): 8.5 (8.3)	Mean (SD): 21.1 (24.8)
Hsieh 2014 (66)	2005-2010 (5 years)	Inclusion: All admitted neonates Exclusion: After a day of life 120, and all vitamins (except vitamin A), nutritional supplements, vaccines, eye drops, and topical drugs	N=450,386 (44%)	GA (median, IQR): 35 (33-38) BW (median, IQR): 2490 (1830 to 3191)	Mean (range): 4 (1-14) Extremely LBW: Mean (range): 17 (2-45)	Median (range): 10 (5-21)
Gulati 2016 **(114)**	1990-2011 (22 years)	Inclusion: All VLBW Exclusion: Volume boluses, blood and blood products, TPN, and topical medications	N=5529 (50%)	GA (median, IQR): 28 (26-30) BW (median, IQR): 1017 (745-1271)	Median (IQR): 9 (5-15)	Median (IQR): 42 (25-67)
Puia-Dumitrescu 2020 **(120)**	2006–2016 (10 years)	Inclusion: 22–24 week admitted to NICU Exclusion: Missing or incomplete discharge data or discharge home at GA < 32 weeks. All nutritional supplements, vitamins (except Vitamin A), vaccines, eye drops and topical	N=7578 (47%)	GA: Not stated BW (median, (IQR)): 610 (540–680)	Median (IQR): 13 (8, 18)	Median (IQR): 91 days (7, 119)

Canada (3 studies)						
Aranda 1982 **(71)**	Not stated	Inclusion: All admitted neonates Exclusion: Drugs for routine prophylaxis (e.g. antimicrobial eye drops)	N=293 (not stated)	GA (mean (SD)): 36.4 (0.25) BW (mean (SD)): 2687 (157)	Mean (SD): 6.2 (5.7) Range: 1-26	Not stated
Aranda 1983 **(107)**	Over two periods. First period: Jul1974 – Feb 1975 Second period: Feb 1977– Nov 1977	Inclusion: All admitted neonates Exclusion: Vitamin K, ophthalmic preparations, fluids and electrolytes, IV amino acids/intralipids and/or glucose (except if for neonatal hypoglycaemia, phototherapy and oxygen	Not stated	First period: GA (mean (SD)): 36.9 (0.2); BW (mean (SD)): 2612 (51) Second period: GA (mean (SD)): 36.42 (0.25); BW (mean (SD)): 2686.9 (156.7)	First period Mean (SD): 3.40 (0.20) Second period Mean (SD): 6.19 (0.33)	First period Mean (SD): 14 (1.1) Second period Mean (SD):19.44 (1.6)
Collinge 1988 **(79)**	Not stated	Inclusion: All admitted neonates Exclusion: Not stated	N=1200 (not stated)	Not stated	5.7	Not stated
Studies of drug utilisation in Asia (11 studies)						
China (one study)						
Yue 2020 **(106)**	Mar-Apr 2018	Inclusion: All inpatients Exclusion: IV solutions (0.9% sodium chloride, 5% / 10% glucose, sterile solution for injection), blood products (except albumin), 1% silver nitrate eye drops, parenteral nutrition, heparin for venous access, oxygen, electrolytes (calcium gluconate, sodium bicarbonate, magnesium sulphate, potassium chloride)	N=319 (44%)	GA (mean (SD)): 35.8 (3.9) BW (mean (SD)): 2570 (911)	Median (IQR): 3 (1, 5.5)	median (IQR): 5 (3-10)

India (nine studies)						
Chatterjee 2007 (5)	Mar-Aug 2005 (6 months)	Inclusion: All admitted neonates Exclusion: Not stated	N=176 (37%)	GA: not stated BW (mean (SD)): 2214 (774)	4.8	7
Sharanappa 2014 **(104)**	Jan-Jun 2013	Not stated	N=100 (not stated)	Not stated	Not stated	Not stated
Brijal 2015 (4)	Mar 2013-Feb 2014 (one year)	Inclusion: All admitted neonates Exclusion: Discharged or die within 24 hours of NICU admission	N=650 (38%)	GA (mean (SD)) in days: 3.36 (4.16) BW (mean (SD)): 2160 (600)	4.46	Not stated
Suryawanshi 2016 **(105)**	Apr-Sept 2014	Not stated	N=528 (39%)	GA (mean (SD)): 35 (3) BW (mean (SD)): 2000 (700)	Mean (SD): 4.37 (2.91)	Not stated
Chauthankar 2017 **(77)**	Jul 2014-Mar 2015 (9 months)	Inclusion: All admitted neonates with at least one drug Exclusion: Blood, blood products, vitamin K prophylaxis, prophylactic ophthalmic treatment, vaccines or IV fluids	N=460 (41%)	GA (median, range) in days: 1,1-27 BW (mean (SD)): 2000 (700)	Mean (SD): 5.7 (3.6)	10 (2-78)
Choure 2017 **(78)**	Apr-Sept 2014 (6 months)	Inclusion: All admitted neonates Exclusion: IV fluids, parenteral nutrition, nutritional supplements, blood and blood products, oxygen, phototherapy, and vaccinations	N=220 (46%)	Not stated	Mean (range): 3.6 (1-6)	Not stated

Jayaram 2017 **(87)**	Aug-Jan 2016 (6 months)	Inclusion: All admitted neonates Exclusion: IV fluids, TPN, routine oral nutritional supplements, vaccines, vitamin K, topical anaesthetic, oxygen and blood products	N=154 (46%)	GA (mean (SD)): 34 (2.75) BW (mean (SD)): 1712 (914)	Mean (SD): 8.4 (7.6) Range: 0-17	Mean (SD): 17 (18.5)
Ashwin 2018 **(72)**	6 months (year not stated)	Not stated	N=70 (39%)	GA (mean (SD)): 35 (3.14) BW mean (SD)): 2200 (730)	3	Not stated
Kumari 2019 **(90)**	Oct 2017-Dec 2017	Inclusion: All admitted neonates Exclusion: IV fluids, vaccines, Vitamin K, oxygen, and blood products	N=81 (33%)	GA: Not stated BW (mean): 2261	Mean (range): 6.9 (1-14)	Mean: 6
Pakistan (one study)						
Aamir 2018 **(69)**	Mar-Aug 2005 (6 months)	Inclusion: All admitted neonates Exclusion: Topical medication, oxygen, and IV solution	N=1300 (32%)	GA (median, range): 33, 26-35 BW: Not stated	Mean (SD): 2.85 (1.358) Range: 1-9	Mean (SD): 3.15 (2.8)
Studies of drug utilisation in Latin America and Caribbean (6 studies)						
Brazil (five studies)						
Marino 2011 **(117)** Conference abstract	Jan 2006-Dec 2007	Not stated	N=827 (not stated)	Addressed drug utilisation in neonates with different birth weight Group a (<1000 g) Group b (1000-1499 g) Group c (1500 to 2499) Group d (2500 g or more)	Group a: 11.1 Group b: 6 Group c: 1.7 Group d: 1.2	Not stated

Carvalho 2012 **(76)**	Jul-Aug 2011	Inclusion: All admitted neonates Exclusion: Blood and blood products, parenteral nutrition, oxygen and other gases, vitamin K, silver nitrate, and vaccines	N=61 (41%)	Not stated	5	10
Gonçalves 2015 **(85)**	Jan-Jun 2012	Inclusion: All admitted neonates > 24 hours Exclusion: sodium chloride, 5 % glucose, blood products (except albumin), heparin for venous access, vaccines, phytonadione, 1 % silver nitrate eye drops, TPN, oxygen, and electrolytes	N=187 (42%)	GA (median, IQR): 36.6,33.9-38.3 BW (mean (SD)): 2473 (831)	Mean (range): 6.4 (0-40)	Mean (SD): 20.6 (22.3) Range: 1-128
De Souza Jr 2016 **(108)**	Over 6 months (year not stated)	Inclusion: Neonates with electronic records of > 24 hours with drug Exclusion: Neonates with incomplete clinical data, prescriptions or prescriptions containing only vaccines, blood products, TPN, silver nitrate eye drops or IM administration of phytonadione in the delivery room, or IV fluids	N=192 (50%)	GA (mean (SD)): 33.3 (4.3) BW (mean (SD)): 1909.5 (886)	Mean (SD): 8.8 (6.1)	Mean (SD): 18.8 (18.1)
De Lima Costa 2018 **(82)**	Aug 2015-Jul 2016	Inclusion: All admitted neonates Exclusion: TPN, IV fluids, oxygen, blood products or electrolytes	N=220 (46%)	GA (mean (SD)): 32.4 (4.4) BW (mean (SD)): 1932.7 (1127.6)	Mean (SD): 8.2 (6.2) Range: 1-33	Not stated
Argentina (one study)						
Fungo 2013 **(112)**	Jan-Dec 2011 (Argentina)	Inclusion: Not stated Exclusion: Compounded preparations made by local division of neonatology and drugs	Not stated	Not stated	Not stated	Not stated

		donated or acquired by family members				
Studies of drug utilisation in Australasia (two studies)						
New Zealand (one study)						
Daniell 1989 **(81)**	Nov 1987- Feb 1988	Inclusion: All admitted neonates Exclusion: IV glucose, TPN, oxygen, blood products, sodium chloride flush, expressed milk and milk formula	N=79 (not stated)	GA (mean (SD)): 34 (0.6) BW (mean (SD)): 2185 (112)	Mean (SD): 8.6 (0.9) Range: 0-30	Mean (SD): 18.4 (2.3)
Australia (one study)						
O'Donnell 2002 **(98)**	Dec 2001- Feb 2002	Inclusion: All admitted neonates Exclusion: TPN, IV fluids, oxygen, and research drugs	N=97 (not stated)	GA (median, range): 31, 22.7-41.1 BW (median, range): 1560, 414- 4790	Not stated	Not stated

BW, birthweight; GA, gestation age; SD, standard deviation; TPN, total parenteral nutrition

9.4 Most frequently prescribed drugs in drug utilisation studies (Europe)

Frequently prescribed drugs	Bonati 1988	Conroy 1999	Jong 2001	Martinez 2005	Dell' Aera 2007	Turner 2009	Dessi 2010	Neuburt 2010	Nguyen 2011	Lass 2011-preterm	Lass 2011-term	Oguz 2012	Flint 2014	Kieran 2014	Laforgia 2014	Riou 2015	Schweigertova	Silva 2015	Cuzzolin 2016	Blanco-Reina 2016	Girardi 2017-A*	Girardi 2017-B**	Flint 2018	Alonso 2019	Gouyon 2019	Mesek 2019
Antibiotics																										
Amikacin				√	√							√			√	√			√		√	√				
Amoxicillin									√							√							√		√	
Ampicillin	√			√						√	√	√			√		√	√	√	√	√	√		√		
Ampicillin-Sulbactam					√		√												√						√	√
Benzyl-penicillin		√				√			√		√		√	√									√		√	√
Cefixime							√																			
Cefotaxime				√												√				√					√	
Ceftazidime							√																			
Flucloxacillin		√																								
Gentamicin	√	√		√		√	√			√	√		√	√	√		√	√	√	√			√	√	√	√
Meropenem					√							√														
Netilmicin												√							√							
Penicillin												√														
Piperacillin	√							√																		

Piperacillin and enzyme inhibitor																		√				
Rifamycin													√									√
Tobramycin	√		√		√		√													√		
Vancomycin					√					√					√	√						
Analgesics																						
Fentanyl								√	√						√	√	√	√				
Morphine		√									√	√		√						√		
Paracetamol						√			√				√	√						√		√
Piritramide							√															
Antifungals																						
Clotrimazole														√	√							
Fluconazole								√							√		√	√				
Ketocon-azole														√								
Nystatin			√							√												
Antimuscarinics																						
Atropine																			√			
Cyclo-pentolate												√										
Cardiovascular agents																						
Dobutamine							√		√													
Dopamine																√						
Furosemide	√	√		√			√		√	√			√		√		√	√	√			
Heparin									√	√												

Hydrochlor-thiazide													√		
Spirono-lactone	√												√		
Corticosteroids															
Budesonide			√												
Methyl-prednisolone												√			
Other steriods			√												
Electrolytes and minerals															
Calcium gluconate														√	
Calcium (oral)														√	
Ferrous fumarate					√										
Ferrous sulphate								√	√						
Iron hydroxide poly-maltose											√				√
Endocrine agents															
Methimazole				√											
Pyridoxine										√		√			
Gastro-intestinal agents															
Domperidone					√										
Ranitidine		√													
Simeticone						√	√								

Neurological agents																										
Midazolam									√								√									
Pheno-barbital	√												√		√											
Respiratory agents																										
Amino-phylline	√																									
Caffeine citrate***		√	√	√	√	√		√	√		√	√	√	√	√		√	√		√	√	√		√	√	
Ipratropium and salbutamol			√							√																
Surfactant							√					√		√								√	√			
Theophylline				√			√				√															
Vitamins and supplements																										
Calcifediol																						√				
Calcitriol																					√	√				
Chole-calciferol																√	√						√			
Citicoline	√																									
Folic acid		√														√										
Multi-vitamins	√	√		√	√	√					√			√	√		√							√	√	
Parenteral nutrition solution					√									√											√	
Vitamin D3 and E			√					√																		
Vitamin K	√	√				√		√	√				√		√	√							√		√	√

Vitamin D										√	√
Others											
Albumin	√										
Anti-diarrhoeal								√			
Calcium folinate			√	√			√				
Carnitine		√									
Chlor-hexidine						√					
Dextriferrone					√						
Epoetin alfa				√					√		
Laury sulphate+ sodium citrate					√						
Octeniding wash						√					
Phenyl-ephrine						√					
Sodium chloride				√							

*group A: neonates with birth weight < 1000g
**group B: neonates with birth weight 1000-1500 grams
***some studies reported it as caffeine only

9.5 Most frequently prescribed drugs in drug utilisation studies (North America)

Frequently prescribed drugs in North America	Aranda 1982	Russel 1982	Aranda 1983 (1974 period)	Aranda 1983 (1977 period)	Lesko 1990	Clark 2006	Du 2006 (1996-1998)	Du 2006 (2001-2004)	Warrier 2006	Kumar 2008	Hsieh 2015	Puia-Dumitrescu 2020
Antibiotics												
Ampicillin	√	√	√	√	√	√			√	√	√	√
Cefotaxime						√	√	√	√			
Chloramphenicol			√									
Gentamicin	√	√	√	√	√	√				√	√	√
Kanamycin	√		√	√								
Penicillin	√	√	√	√	√							
Vancomycin						√	√	√	√		√	√
Analgesics												
Fentanyl								√		√	√	√
Cardiovascular agents												
Aldactone									√			
Dobutamine							√	√				
Dopamine		√							√	√	√	√
Epinephrine		√										
Furosemide	√	√	√	√		√				√	√	
Heparin					√					√		
Indomethacin							√	√		√		√
Corticosteroids												

Dexamethasone							√					
Hydrocortisone												√
Electrolytes and minerals												
Calcium gluconate	√	√	√	√								
Calcium					√							
Electrolytes					√							
Potassium chloride					√							
Sodium chloride					√							
Gastro-intestinal agents												
Metoclopramide						√	√	√				
Neurological agents												
Midazolam											√	
Phenobarbital		√					√	√				
Respiratory agents												
Aminophylline							√					
Caffeine citrate*						√		√	√	√	√	√
Surfactant						√	√	√	√	√	√	√
theophylline							√	√	√			
Anti-fungal												
Fluconazole												√
Vitamins and supplements												
Ferrous sulphate						√						
Iron			√	√					√			
Multivitamins	√		√	√		√						

Parenteral nutrition					√				
Vitamin K	√								
Others									
Erythropoietin								√	
Fresh frozen plasma					√				
Fat supplement				√					
Glycerine	√								
Naloxone		√							
Plasma protein							√		
Sodium bicarbonate	√	√	√	√					

*some studies reported caffeine instead of caffeine citrate

9.6 Most frequently prescribed drugs in drug utilisation studies (Asia)

Frequently prescribed drugs in Asia	Chatterjee 2007	Sharanappa 2014	Brijal 2015	Choure 2017	Aamir 2018	Yune 2020
Antibiotics						
Ampicillin					√	
Amikacin		√	√		√	
Ampicillin/sulbactam			√			
Antibiotics	√			√		
Ceftriaxone		√			√	
Ceftazidime					√	
Cefotaxime			√			
Gentamicin			√		√	
Metronidazole			√			
Cefoperazone-sulbactam						√
Pipracillin/tazobactam						√
Analgesics						
Paracetamol					√	
Pentazocin				√		
Anti-Fungals						
Fluconazole						√
Cardiovascular agents						

Adrenaline				√			
Captopril						√	
Furosemide							√
Electrolytes and minerals							
Calcium gluconate				√			
Neurological agents							
Phenobarbitone		√	√		√	√	
Phenytoin					√	√	
Respiratory agents							
Aminophylline		√			√	√	
Caffeine							√
Vitamins and supplements							
Vitamin K	√	√	√		√		√
Vitamin AD							√
Others							
carnitine			√				
IV fluids	√						
Others					√		
Hepatitis B vaccine							√
Endocrine agents							
levothyroxine							√

9.7 Most frequently prescribed drugs in drug utilisation studies (Latin America and Caribbean)

Frequently prescribed drugs in Latin America and Caribbean	Marino 2011 (group a: bw<1000g)	Marino 2011 (group b: bw: 1000-1499 g)	Marino 2011 (group c: Bw:1500-2499g)	Marino 2011 (group d: >2500 g)	Carvalho 2012	Goncalves 2015	De Souza 2016
Antibiotics							
Amikacin	√	√	√	√	√		
Ampicillin	√	√	√	√	√		√
Gentamicin					√	√	√
Vancomycin	√				√		√
Analgesics							
Fentanyl				√	√	√	√
Morphine					√		
Metamizole				√			
Paracetamol					√		
Cardiovascular agents							
Dobutamine							√
Furosemide	√			√			
Heparin							√
Indomethacin		√					
Gastro-intestinal drugs							
Domperidone			√				
Gastrointestinal drugs	√	√					

Ranitidine			√					
Neurological agents								
Midazolam				√				
Phenobarbital					√			
Aminophylline	√	√						√
Caffeine	√	√	√					
Surfactant	√	√	√					
Vitamins and supplements								
Folinic acid								√
Multivitamins					√	√		√
Vitamin K								√
Glycerine					√			
Filgrastim	√							

9.8 Description of drug utilisation on antibiotics only (11 studies)

Study ID	Study period	Inclusion and exclusion criteria	Number of neonates (% female)	Gestation age (weeks) Birth weight (grams)	Number of drugs prescribed per neonate
Asia -India (four studies)					
Gandra 2018 **(128)**	Feb 2016-Feb 2017 (one year)	Inclusion: All admitted neonates with active antimicrobial prescriptions Exclusion: Not stated	N=403 (32%)	GA (median, IQR): 34.5 (31-38) BW (median (IQR): 1737 (1210-2710)	Not stated
Hauge 2017 **(130)**	Apr 2008-Mar 2010 (3 years)	Inclusion: Neonates with sepsis Exclusion: Not stated	N1 (teaching hospital): 217 (63%) N2 (non-teaching hospital): 1572 (49%)	Not stated	Teaching: 7 Non-teaching: 4
Shinde 2017 **(134)**	Oct 2011- Sept 2012	Inclusion: Neonates with sepsis Exclusion: Discharged or transferred to other hospital or died within 2 days in NICU	N= 84 (29%)	GA: Not stated BW (mean (SD)): 2000 (620)	Not stated

Subash 2015 **(131)**	Feb-Apr 2013	Inclusion: Neonates with suspected or confirmed sepsis Exclusion: Neonates with surgical problems, major congenital malformations, on antibiotics or those whose mothers received antibiotics before delivery	N= Not stated (42%)	Not stated	Not stated
Latin America and Caribbean-Trinidad and Tobago (one study)					
Hariharan 2013 **(125)**	Sept-Nov 2008	Inclusion: All neonates receiving antimicrobials Exclusion: Not receiving antimicrobials	N=353 (not stated)	GA: < 40 days BW (mean (SD)): 2960 (940)	Not stated
Latin America and Caribbean-Chile (one study)					
Jimenez 2017 **(126)**	Four years	Inclusion: All neonates admitted within study period Exclusion: Not stated	N=5,619 (46.5%)	GA (mean (SD)): 36.2 (3.6) BW: Not stated	Not stated
North America-USA (two studies)					
Cantey 2015 **(127)**	Oct 2011-Nov 2012 (4 months)	Inclusion: All neonates admitted to NICU Exclusion: Not stated	N1 (retrospective period) = 593 (57%) N2 (prospective period) = 1014 (43%)	Retrospective: GA (median, IQR): 38 (34.5-39.4) BW (median, IQR): 2860 (2145-3457) Prospective: GA (median, IQR): 37.4 (34.1-39.1) BW (median, IQR): 2793 (2070-3435)	Not stated

Grohskopf 2005 **(129)**	Aug 1999 -Feb 2000	Inclusion: Neonates admitted at NICU at each participating hospital on study dates Exclusion: Not stated	N=1580 (45%)	Not stated	Median (range): 2 (1-5)
Middle East-Saudi Arabia (one study)					
Balkhy 2019 **(133)**	Oct 2012–Jun 2013 (33 months)	Inclusion: <16 years (data on neonates reported separately) received at least one antimicrobials Exclusion: Antimicrobial by route other than parenteral or oral routes	N=1813 (not stated)	Not stated	Not stated
Africa-Zimbabwe (one study)					
Chiminhi 2020 **(132)**	May–Nov 2018	Inclusion: All admitted neonates Exclusion: Not stated	N=459 (49%)	GA: Not stated BW (median, (IQR)): 2800 (2–3.4)	Not stated
Europe-Brazil and Germany (one study)					
Silva 2020 (64)	Jan–Dec 2018 (Brazil) May–August 2016 (Germany)	Inclusion: Neonatal or paediatric ICU admissions, had antimicrobial for >24hours Exclusion: Topical and inhaled antibiotics	N=2567 (not stated)	Not stated	Not stated

BW, birthweight; GA, gestation age; NICU; neonatal intensive care unit; SD; standard deviation

9.9 Description of drug utilisation on off-label and/unlicensed drugs only (six studies)

Study ID	Study period	Inclusion and exclusion criteria	Number of neonates (% female)	Gestation age (weeks) Birth weight (grams)	Number of drugs prescribed per neonate
Europe- Spain (one study)					
Casan 2017 **(139)**	Nov 2015-Feb 2016	Inclusion: All admitted neonates Exclusion: Crystalloid fluids, plasma-expanding serums (except for albumin), TPN, antiseptics, and heparins for catheter obstruction	N=41 (32%)	GA (mean (SD)): 35.9 (4.22) BW (mean (SD)): 3280 (860)	Mean (SD): 6.65 (3.28)
North America-Canada (one study)					
Doherty 2010 **(434)**	May 2009 (one month)	Inclusion: All admitted neonates Exclusion: Not stated	N=38 (53%)	Not stated	Not stated
Asia-India (one study)					
Jain 2014 **(435)**	Jun-Aug 2009	Inclusion: All neonates in NICU for >6 hours and had any drug Exclusion: Nutritional supplements, IV fluids, inotropes, vaccines, vitamin K, topical anaesthetic cream, fluid or heparin for flushing lines, oxygen and blood products	N=156 (not stated)	GA (median, IQR): 32 (30-35) BW (median, IQR): 1348 ,1076 - 1800	Median (IQR): 6 (1-6)
Middle East -Iran (one study)					
Kouti 2019 **(136)**	Jan-Mar 2016 (3 months)	Inclusion: Neonates admitted for at least 24 hours received at least one drug Exclusion: Oxygen therapy, vaccines, blood products (except	N=193 (41%)	GA (mean (SD)): 34 (4.4) BW (mean (SD)): 2463 (955)	Mean (SD): 4.5 (3) Range: 1-17

		immunoglobulin), vitamins, electrolytes, TPN, and IV hydration			
Middle East-Saudi Arabia (one study)					
Mazhar 2018 **(137)**	Jan-Mar 2015 (3 months)	Inclusion: All admitted neonates for minimum of 24 hours and prescribed at least one drug	N=138 (48%)	GA (median, IQR): 35 (35-39) BW: Not stated	Mean (SD): 3.5 (2.3)
Africa-Ethiopia (one study)					
Gidey 2020 **(140)**	Mar–Apr 2019	Inclusion: Admitted for at least 24 hours; prescribed at least one drug Exclusion: Oxygen therapy,PN, blood products, antiseptics, vaccines and IV fluid (normal saline, dextrose); incomplete data	N=122 (41%)	GA: Not stated BW (mean (SD)): 2540 (790)	Mean (SD): 3.02 (1.40)
BW, birthweight; GA, gestation age; IV; intravenous; NICU; neonatal intensive care unit; SD; standard deviation					

9.10 Description of studies on specific pharmacologic groups only (seven studies)

Study ID	Study period	Inclusion and exclusion criteria	Number of neonates (% female)	Gestation age (weeks) Birth weight (grams)	Number of drugs prescribed per neonate
North America -USA (one study)- Antiepileptics					
Ahmad 2017 **(436)**	Jan 2005-Dec 2014	Inclusion: All neonates with data entered with diagnosis of seizure or seizure disorder and received one of following: phenobarbital, phenytoin/ levetiracetam, topiramate, lidocaine or carbamazepine Exclusion: Benzodiazepine as used for sedation	N=9,134 (42%)	GA (mean (SD)): 34.8 (5.8) BW (mean (SD)): 2500 (1200)	Not stated
North America-Canada (one study)-Sedatives and narcotics					
Toye 2018 **(67)**	2004-2009	Inclusion: GA <35 weeks admitted to NICUs contributing data to Canadian Neonatal Network during 2004-2009 Exclusion: Not stated	N=12,415 (not stated)	Not stated	Not stated
Europe-Spain (one study)-Sedatives and analgesics					
Avila-Alvarez 2015 **(141)**	Nov 2012 (one month)	Inclusion: all neonates admitted during study period with corrected age of 44 Exclusion: Not stated	N=468 (45%)	GA (mean (SD)): 34.3 (4.6) BW (mean (SD)): 2182 (9764)	Not stated
Europe-France (one study)-Analgesics					

Benahmed-Canat 2019 **(142)**	Jan 2012-Jun 2013	Inclusion: All neonates undergoing surgery during the study period Exclusion: Not stated	N=168 (40%)	GA (mean (SD)): 35.1 (4.6) BW (mean (SD)): 2337 (1006)	Mean (SD): 2.6 (1.3)
Europe-Estonia (one study)-Cardiovascular drugs					
Hallik 2014 **(144)** (abstract)	Not stated	Not stated	N=726 (not stated)	GA (median, range): 34 (23-42) BW (median, range): 1993 (400-4720)	Not stated
North America-USA (one study)-Drugs used in bronchopulmonary dysplasia (BPD)					
Bamat 2019 **(145)**	Jan 2007– Aug 2016	Inclusion: Symptomatic BPD Exclusion: GA ≥32 weeks, admitted after 36 weeks postmenstrual age; admitted for <1 week	N=3252 (40%)	GA (median, (IQR)): 26 (24–28) BW (median, (IQR)): 790 (640–1040)	Range: 22-50
Europe-Spain (one study)-Intravenous drugs					
De Basagoiti 2019 **(146)**	Jan–Feb 2018	Not stated	Not stated	Not stated	Not stated

BW, birthweight; GA, gestation age; NICU; neonatal intensive care unit; SD; standard deviation

9.11 Final ethics approvals for drug utilisation study

NHS
Health Research Authority
Yorkshire & The Humber - Leeds East Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 0207 104 8081

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

21 May 2018

Dr Shalini Ojha
Room 4117
Medical School Building
Derby
DE22 3DT

Dear Dr Ojha

Study title:	**Drug utilization patterns in neonatal units in the UK: a retrospective pharmacoepidemiological study.**
REC reference:	**18/YH/0209**
Protocol number:	**18023**
IRAS project ID:	**248088**

The Proportionate Review Sub-committee of the Yorkshire & The Humber - Leeds East Research Ethics Committee reviewed the above application on 25 May 2018.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will

be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

- **Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity**

The information given inA6-2 made it clear that data was de-identified to the applicant and that the environment was secure. The Sub-Committee noted that peer review comments were provided in the application. One of the peer reviewers (Law) had expressed concern over anonymity. Members asked that the applicant's response to this query was provided.

Chief Investigator Dr Shalini Ojha explained that the protocol had been amended in response to Dr Law's comment. The table on Page 14 of the Study Protocol included the day, month and year of birth. The "day of birth" data item was removed from the data set that was accessed to ensure that the data set was adequately de-identified.

The researchers had confirmed with the NNRD that the data files were suitably de-identified before transfer to the research team.

The Sub-Committee was satisfied with the response given.

- **Suitability of research summary**

The Sub-Committee recommended that the study summary in A6-1 was revised into lay language.

A revised summary was submitted, which was reviewed and approved by the Sub-Committee.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering letter on headed paper [Response Cover letter]	1.0	16 May 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance certificate]	1.0	26 July 2017
IRAS Application Form [IRAS_Form_08052018]		08 May 2018
Letter from sponsor [Letter of sponsorship]	1.0	03 May 2018

With the Committee's best wishes for the success of this project.

18/YH/0209	Please quote this number on all correspondence

Yours sincerely

pp

Dr Rhona Bratt
Chair

Email: nrescommittee.yorkandhumber-leedseast@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers" [SL-AR2]

Copy to: *Ms Angela Shone, University of Nottingham*
Mr Damon Foster, Research Delivery Operations Manager- Chelsea and Westminster Hospital NHS Foundation Trust

Yorkshire & The Humber - Leeds East Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 25 May 2018

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Rhona Bratt	Retired Multimedia Project Manager	Yes	
Professor Kenneth Brodlie	Retired Professor of Visualization	Yes	
Dr Nicky Kime	Senior Research Fellow	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Katy Cassidy	REC Manager

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Shalini Ojha
Room 4117
Medical School Building
Derby
DE22 3DT
shalini.ojha@nottingham.ac.uk

Email: hra.approval@nhs.net

21 May 2018

Dear Dr Ojha

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Drug utilization patterns in neonatal units in the UK: a retrospective pharmacoepidemiological study.**
IRAS project ID:	**248088**
REC reference:	**18/YH/0209**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales*, as well as any documentation that has been updated as a result of the assessment.

*'In flight studies' which have already started an SSI (Site Specific Information) application for NHS organisations in Wales will continue to use this route. Until 10 June 2018, applications on either documentation will be accepted in Wales, but after this date all local information packs should be shared with NHS organisations in Wales using the Statement of Activities/Schedule of Events for non-commercial studies and template agreement/ Industry costing template for commercial studies.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site

initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Ms Angela Shone
Tel: 0115 951 5670
Email: sponsor@nottingham.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

IRAS project ID	248088

Your IRAS project ID is **248088**. Please quote this on all correspondence.

Yours sincerely

Gemma Oakes
Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Angela Shone, University of Nottingham [Sponsor Contact]*
sponsor@nottingham.ac.uk
Mr Damon Foster, Research Delivery Operations Manager- Chelsea and Westminster Hospital NHS Foundation Trust [Lead NHS R&D Contact]
damon.foster@chelwest.nhs.uk

9.12 Drugs coding and categorisation

Broad group: Agents for metabolic disorders			
Drug ID (as appeared in database)	**Individual drug**	**Drug ID (as appeared in database)**	**Individual drug**
allopurinol	allopurinol	imiglucerase	enzyme (imiglucerase)
carnitine	amino acid derivative (carnitine)	rasburicase	rasburicase
cysteamine (mercaptamine)	amino acid derivative (mercaptamine)	sodium benzoate	sodium benzoate
ubidecarenone	co-enzyme Q10	sodium benzoate infusion	sodium benzoate
cyclic pyranopterin monophosphate (1)	cyclic pyranopterin monophosphate	sodium dichloroacetate	sodium dichloroacetate
agalsidase beta (galactosidase)	enzyme (agalsidase beta)	sodium phenylbutyrate	sodium phenylbutyrate
		sodium phenylbutyrate infusion	sodium phenylbutyrate
(1) https://www.sps.nhs.uk/medicines/cyclic-pyranopterin-monophosphate/:)			
Broad group: Agents for pulmonary hypertension			
bosentan	bosentan	sildenafil	sildenafil
nitric oxide	nitric oxide	silfanadil	sildenafil
Broad group: Agents used in anaesthesia			
atracurium	atracurium	Orabase (1)	benzocaine (topical)
Orobase (1)	benzocaine (topical)	bupivicaine	bupivacaine
Dantrolene (2)	dantrolene	ketamine	ketamine
lidocaine hydrochloride	lidocaine hydrochloride	lignocaine hydrochloride (lidocaine hydrochloride) injection	lidocaine hydrochloride
oxybuprocaine 0.4%	oxybuprocaine 0.4% (ocular)	pancuronium	pancuronium

propofol	propofol	proxymetacaine hydrochloride	proxymetacaine hydrochloride (ocular)
proxymetocaine	proxymetacaine hydrochloride (ocular)	rocuronium	rocuronium
sevoflurane	sevoflurane	suxamethonium	suxamethonium
ametop	tetracaine	vecuronium	vecuronium
vecuronium infusion	vecuronium		

(1) https://www.drugs.com/mtm/orabase.html
(2) https://medlineplus.gov/druginfo/meds/a682576.html

Broad group: Agents used in PDA			
ibuprofen	ibuprofen	indometacin (indomethacin)	indomethacin
indometacin	indomethacin	indomethacin	indomethacin
Broad group: alkalising agents			
sodium bicarbonate	sodium bicarbonate	Tricitrate (1)	tricitrates oral solution
tham (trometamol)	trometamol		
(1): https://www.medicinesforchildren.org.uk/sites/default/files/content-type/leaflet/pdf/20141107132738_0.pdf			
Broad group: Analgesics			
alfentanil	alfentanil	alfentanyl	alfentanil
benzydamine	benzydamine	buprenorphine	buprenorphine
codeine	codeine	diclofenac	diclofenac
diamorphine	diamorphine	morphine	morphine (iv)
methadone	methadone	morphine sulphate	morphine (iv)
iv morphine	morphine (iv)	morphine - iv	morphine (iv)
morphine infusion	morphine (iv)	morphine - oral	morphine (oral)
oral morphine	morphine (oral)	oral morphine - level 1	morphine (oral)
oral morphine - level 3	morphine (oral)	oral morphine - level 4	morphine (oral)

oramorph	morphine (oral)	oromorph	morphine (oral)
oxycodone	oxycodone	remifentanil	remifentanil
sucrose (1)	sucrose (oral)	sucrose (oral) (1)	sucrose (oral)
sweetease (1)	sucrose (oral)	calpol	paracetamol
paracetamol	paracetamol		
(1)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590075/			
Broad group: Antibiotics			
amikacin	amikacin	amoxicillin	amoxicillin
amoxycillin	amoxicillin	ampicillin	ampicillin
azithromycin	azithromycin	azithromycin oral	azithromycin
aztreonam	aztreonam	benzyl penicillin	benzylpenicillin
cefaclor	cefaclor	cefalexin	cefalexin
cefotaxime	cefotaxime	cefradine	cefradine
ceftazidime	ceftazidime	ceftriaxone	ceftriaxone
cefuroxime	cefuroxime	chloramphenicol	chloramphenicol (ocular)
chloramphenical eyedrops	chloramphenicol (ocular)	chloramphenicol eye ointment	chloramphenicol (ocular)
ciprofloxacin	ciprofloxacin	clarithromycin	clarithromycin (iv/oral)
clarithromycin iv	clarithromycin (iv/oral)	clarithromycin oral	clarithromycin (iv/oral)
clindamycin	clindamycin	augmentin	co-amoxiclav
co-amoxiclav	co-amoxiclav	co-amoxiclav (augmentin)	co-amoxiclav
colistimethate sodium	colistimethate sodium	colistin	colistimethate sodium
colomycin	colistimethate sodium	cotramoxizole	co-trimoxazole
co-trimoxazole	co-trimoxazole	daptomycin	daptomycin
erthromycin	erthromycin	erthromycin	erythromycin
flucloxacillin	flucloxacillin	fosfomycin	fosfomycin

fusidic acid	fusidic acid	sodium fusidate	fusidic acid
sodium fusidate / fusidic acid	fusidic acid	fucidin ointment	fusidic acid (topical)
fusidic acid eye drops	fusidic acid (ocular)	fucidine cream	fusidic acid (topical)
gentamicin	gentamicin	gentamicyn eye drops	gentamicin (topical)
gentamicin - topical	gentamicin (topical)	imipenem (primaxin)	imipenem + cilastatin
levoflaxacin	levofloxacin	levofloxacin	levofloxacin
linezolid	linezolid	meropenem	meropenem
metronidazole	metronidazole	bactraban	mupirocin
bactroban	mupirocin	bactroban ointment	mupirocin
bactroban ointment (mupirocin)	mupirocin	mupirocin	mupirocin
neomycin	neomycin	neomycin 0.5% eye drops	neomycin 0.5% (ocular)
netilmicin	netilmicin	nitrofurantoin	nitrofurantoin
ofloxacillin	ofloxacin	ofloxacin eye drops	ofloxacin (ocular)
phenoxymethylpenicillin	phenoxymethylpenicillin	piperacillin	piperacillin + tazobactam
piptazocin	piperacillin + tazobactam	rifampicin	rifampicin
flamazine cream	silver sulfadiazine cream	spiramycin	spiramycin
sulphadiazine	sulfadiazine	teicoplanin	teicoplanin
tetracycline hydrochloride	tetracycline hydrochloride	trimethoprim	trimethoprim
tobramycin	tobramycin	vancomycin	vancomycin
Broad group: Antidotes and chelators			
calcium resonium	calcium polystyrene sulfonate	flumazenil	flumazenil
methylene blue	methylthioninium chloride	naloxone	naloxone
Broad group: Antiemetics			
ondansetron	ondansetron	ondansetrone	ondansetron
Broad group: Anti-fungals			

amphotericin	amphotericin (liposomal)	ambisome (liposomal amphoteracin)	amphotericin (liposomal)
ambisone	amphotericin (liposomal)	amphotericin - liposomal	amphotericin (liposomal)
amphotericin liposomal	amphotericin (liposomal)	liposomal amphoteracin	amphotericin (liposomal)
caspofungin	caspofungin	clotrimazole	clotrimazole (topical)
canestan cream (clotrimazole)	clotrimazole (topical)	clotrimazole cream	clotrimazole (topical)
fluconazole	fluconazole	flucytosine	flucytosine
itraconazole	itraconazole	micafungin	micafungin
daktarin (see miconazole)	miconazole (topical)	miconazole	miconazole (topical)
miconazole gel / cream	miconazole (topical)	nystatin	nystatin (topical)
nystatin suspension	nystatin (topical)	nystatin cream	nystatin (topical)
nystatin ointment	nystatin (topical)	voriconazole	voriconazole
Broad group: Antihistamines			
alimemazine tartrate	alimemazine tartrate	vallergan	alimemazine tartrate
chlorphenamine	chlorphenamine	chlorpheniramine	chlorphenamine
hydroxyzine	hydroxyzine	promethazine	promethazine
Broad group: Antimalarials			
pyrimethamine	pyrimethamine		
Broad groups: Antimuscarinics			
atropine	atropine	cyclopentolate eye drops 0.5%	cyclopentolate 0.5% (ocular)
glycopyrrolate	glycopyrronium bromide	glycopyrronium	glycopyrronium bromide
glycopyrronium bromide	glycopyrronium bromide	hyoscine patch	hyoscine (patch)
ipratropium	ipratropium	ipratropium (atrovent)	ipratropium
oxybutin	oxybutynin	trihexyphenidyl	trihexyphenidyl
tropicamide 0.5%	tropicamide (ocular)	tropicamide eye drops	tropicamide (ocular)

Broad group: Anti-mycobacterials			
isoniazid	isoniazid	pyrozinamide	pyrazinamide
Broad group: Antineoplastic agents			
cytarabine	cytarabine	etoposide	etoposide
chemotherapy agents	chemotherapy agents		
Broad group: Agents for fluids and electrolyte imbalances			
dextrogel	glucose (oral)	glucose gel 40% (oral)	glucose (oral)
glycogel	glucose (oral)	hypostop	glucose (oral)
Broad group: Antivirals			
abacavir	abacavir	aciclovir	aciclovir
acyclovir	aciclovir	adefovir	adefovir
enfuvirtide	enfuvirtide	ganciclovir	ganciclovir
gancyclovir	ganciclovir	lamivudine	lamivudine
kaletra	lopinavir with ritonavir	nevirapine	nevirapine
oseltamivin	oseltamivir	oseltamivir	oseltamivir
tamiflu / oseltamivir	oseltamivir	ribavirin	ribavirin
valganciclovir	valganciclovir	zidovudin	zidovudine
zidovudine (azt)	zidovudine		
Broad group: Blood and related products			
human albumin solution 20%	albumin (human albumin solution 20%)	human albumin solution 4.5%	albumin (human albumin solution 4.5%)
albumin	albumin (unclassified)	cryoprecipitate	cryoprecipitate
gelofusin	gelatin		
Broad group: Blood and blood forming organs			
darbopoetin alfa	epoetins	epoetin alfa and beta	epoetins

erythropoeitin	epoetins		
Broad group: Cardiovascular agents			
aprotinin	aprotinin	tranexamic acid	tranexamic acid
adenosine	adenosine	alteplase	alteplase
amiloride	amiloride	amiodarone	amiodarone
amlodipine	amlodipine	aspirin	aspirin
atenelol	atenolol	atenolol	atenolol
bendrofluazide	bendroflumethiazide	captopril	captopril
catopril	captopril	chlorothiazide	chlorothiazide
chrlorthiazide	chlorothiazide	clonidine	clonidine
clopidogrel	clopidogrel	defibrotide	defibrotide
digoxin	digoxin	dipyridamole	dipyridamole
disopyramide	disopyramide	enalapril	enalapril
enoximone	enoximone	esmolol	esmolol
factor 8	factor VIII	factor vlla (novo 7)	factor Vlla
flecainide	flecainide	frusemide	furosemide
glyceryl trinitrate	glyceryl trinitrate	dalteparin	heparin
clexane	heparin	enoxaparin	heparin
tinzaparin	heparin	hydralazine	hydralazine
hydralazine infusion	hydralazine	hydrochlorthiazide	hydrochlorothiazide
isoprenaline	isoprenaline	labetalol	labetalol
lisinopril	lisinopril	metolazone	metolazone
nifedipine	nifedipine	phentolamine	phentolamine
potassium canrenoate	potassium canrenoate	potassium conreonate	potassium canrenoate
prozocin	prazocin	propranolol	propranolol

recombinant activated protein c	protein C concentrate	sodium nitroprusside	sodium nitroprusside
sotalol	sotalol	aldactone	spironolactone
spironolactone	spironolactone	tenecteplase	tenecteplase
tolazoline	tolazoline	warfarin	warfarin
adrenaline	adrenaline	dopamine	dopamine
adrenaline (epinephrine)	adrenaline	dopamine 2 double	dopamine
adrenaline infusion	adrenaline	dopamine infusion	dopamine
dobutamine	dobutamine	milrinone	milrinone
dobutamine 2 double	dobutamine	noradrenaline	noradrenaline
dobutamine infusion	dobutamine	noradrenaline infusion	noradrenaline
alprostadil (prostaglandin e1)	prostaglandins	prostin e2	prostaglandins
alprostadil (prostaglandin e2)	prostaglandins	epoprostenol	prostaglandins
dinoprosone prostaglandin e2	prostaglandins	epoprostenol (prostacyclin)	prostaglandins
dinoprostine (prostaglandin e2)	prostaglandins	iloprost	prostaglandins
dinoprostone (prostaglandin e2)	prostaglandins	latanoprost	prostaglandins
prostin	prostaglandins	dinoprostone prostaglandin e2 (see alprostadil)	prostaglandins
Broad group: Corticosteroids			
beclomethasone	beclomethasone	beclomethasone (inhaler)	beclomethasone (inhaler)
beclomethasone (nasal spray)	beclomethasone (nasal)	beconase nasal drops	beclomethasone (nasal)
betamethasone	betamethasone	betnesol	betamethasone
betamethasone eye drops	betamethasone (ocular)	budesonide	budesonide
budesonide inhaler	budesonide (inhaler)	dexamethasone	dexamethasone
dexamethasone eye drops	dexamethasone (ocular)	fludrocortisone	fludrocortisone
fluocinolone	fluocinolone	flixotide	fluticasone (inhaler)
hydrocortisone	hydrocortisone	methylprednisolone	methylprednisolone

prednisolone	prednisolone	prednisolone acetate 1% eye drops	prednisolone acetate 1% (ocular)
Broad group: Corticosteroids with combination			
maxitrol	dexamethasone+neomycin (ocular)	tobradex	dexamethasone+neomycin (ocular)
Broad group: Electrolyte replacement agents			
dioralyte	oral rehydration solution		
Broad group: Electrolytes and minerals			
calcium sandoz	calcium supplements	calcium	calcium supplements
calcium gluconate 10%	calcium supplements	magnesium	magenesium supplements
magnesium glycerophosphate	magenesium supplements	magnesium sulphate	magenesium supplements
buffered phosphate	phosphate supplements	buffered po4	phosphate supplements
phosphate - buffered	phosphate supplements	phosphate	phosphate supplements
joules phosphate	phosphate supplements	phosphate - potassium acid phosphate	phosphate supplements
phosphate - sodium acid phosphate	phosphate supplements	polyfusor phosphates	phosphate supplements
potassium acid phosphate	phosphate supplements	potassium phosphate	phosphate supplements
sodium acid phosphate	phosphate supplements	sodium dihydrogen phosphate	phosphate supplements
sodium glycerophosphate	phosphate supplements	sodium phosphate	phosphate supplements
potassium	potassium supplements	potassium bicarbonate	potassium supplements
potassium chloride	potassium supplements	sodium	sodium
sodium + potassium	sodium and potassium	sodium chloride	sodium
zinc sulphate	zinc sulfate		
Broad group: Endocrine agents			
carbimazole	carbimazole	somatropin	growth hormone (somatropin)

growth hormone	growth hormone (unclassified)	acth	hormone (adrenocorticotrophic hormone)
desmopressin (ddavp oral)	hormone (desmopressin)	desmopressin acetate intranasal solution	hormone (desmopressin)
diazoxide	hormone (diazoxide)	glucagon	hormone (glucagon)
glucagon infusion	hormone (glucagon)	gonadorelin	hormone (gonadorelin)
beta hch (pregnyl)	hormone (human chorionic gonadotrophin)	insulin - actrapid	hormone (insulin)
human chorionic gonadotrophin	hormone (human chorionic gonadotrophin)	insulin 1 single	hormone (insulin)
humulin i	hormone (insulin)	insulin actrapid	hormone (insulin)
insulatard	hormone (insulin)	insulin infusion	hormone (insulin)
insulin	hormone (insulin)	novorapid	hormone (insulin)
lanreotide	hormone (lanreotide)	tetracosactrin (tetracosactide)	hormone (tetracosactide)
levothyroxine sodium (thyroxine)	hormone (levothyroxine sodium)	vasopressin	hormone (vasopressin)
liothyronine sodium	hormone (liothyronine sodium)	metformin	metformin
octreotide	hormone (octreotide)	disodium pamidronate	pamidronate disodium
teriparatide	hormone (teriparatide)	lugols iodine	potassium iodide with iodine
propylthiouracil	propylthiouracil		
Broad group: Feed supplements			
maxijul	high energey supplement (carbohydrates)	duocal	high energy supplement (fat and carbohydrate)
polycal	high energey supplement (carbohydrates)	calogen	high energy supplement (fat)
protifar	high energy supplement (protein)		

Broad group: Gastro-intestinal agents			
chenodeoxycholic acid	chenodeoxycholic acid	carobal	feed thickener
domperidone	domperidone	carobel	feed thickener
creon	enzyme (pancreatin)	nutilis	feed thickener
pancrex v capsules	enzyme (pancreatin)	thixo-d	feed thickener
vitaquick	feed thickener	lanzoprazole	lansoprazole
glycerin (glycerol) suppository	glycerol suppository	lonsorprazole	lansoprazole
glycerine chip	glycerol suppository	loperamide	loperamide
lactulose	lactulose	movicol	macrogol 3350 with potassium and sodium salts
lansoprazole	lansoprazole	metoclopramide	metoclopramide
omeprazole	omeprazole	infracol	simeticone
ranitidine	ranitidine	gaviscon	feed thickener
senokot	senna	sucralfate	sucralfate
infacol	simeticone	ursodeoxycholic acid	ursodeoxycholic acid
Broad group: Immunoglobulins			
hepatitis b immunoglobulin	immunoglobulin (hepatitis b)	vigam	immunoglobulin (normal)
flebogamma	immunoglobulin (normal)	immunoglobulin - human normal immunoglobulin	immunoglobulin (normal)
human normal immunoglobulin	immunoglobulin (normal)	immunoglobulin	immunoglobulin (unclassified)
octagam	immunoglobulin (normal)	herpes zoster immunoglobulin (zig)	immunoglobulin (varicella-zoster)
sandoglobulin	immunoglobulin (normal)	zoster immunoglobulin	immunoglobulin (varicella-zoster)
Broad group: Immunostimulants			

filgrastim	G-CSF (filgrastim)	glatiramer	glatiramer
lenograstim	G-CSF (lenograstim)	interferon alfa	interferon alfa
granulocyte colony stimuating factor	G-CSF (unclassified)	beta interferon	interferon beta
peginterferon alpha	peginterferon alfa		
Broad group: Immunosuppressants			
adalimumab	adalimumab	palivizumab	palivizumab
alemtuzumab	alemtuzumab	rituximab	rituximab
avastin	bevacizumab	tacrolimus	tacrolimus
Broad group: Minerals and trace elements			
ferrous fumarate	iron supplements	sodium feredate (sytron)	iron supplements
fersamal	iron supplements	sodium fererate	iron supplements
fersamal (ferrous fumarate)	iron supplements	sytron	iron supplements
fersamal (ferrous fumurate)	iron supplements	sytron - sodium ironedetate (sodium feredate)	iron supplements
ferrous sulphate	iron supplements	iron	iron supplements
iron (sytron)	iron supplements		
Broad group: Miscellaneous			
saliva replacement gel	artificial saliva products	emulsifying ointment	emollients
chlorhexidine	chlorhexidine	hydomol ointment	emollients
chlorhexidine powder	chlorhexidine	ilex skin protection	emollients
chlorohexidine powder	chlorhexidine	hyaluronidase (hyalase)	enzyme (hyaluronidase)
dextrometaphan	dextromethorphan	carmellose	ocular lubricants
aquamax cream	emollients	celluvisc	ocular lubricants
aqueous cream	emollients	gel tears	ocular lubricants
cavalon spray (1)	emollients	hylo-forte	ocular lubricants
cavilon cream (1)	emollients	hypromellose eye drops	ocular lubricants

cavilon stick (1)	emollients	lacri-lube (eye ointment)	ocular lubricants
Cetraban (2)	emollients	lacrilube ointment / drops	ocular lubricants
derma (3)s	emollients	viscotears	ocular lubricants
diprobase cream	emollients	timolol 0.1% gel	timolol 0.1% (ocular)
e45 cream	emollients	Aquacel (4)	wound dressing
emollin spray	emollients	flaminal hydro gel	wound dressing
jelonet dressing (7)	wound dressing	Hydrosorb(5)	wound dressing
leptospermum honey	wound dressing	elfin-imp	research drug (ELFIN)
trial medication	research drug (unclassified)	i2s2	research drug (I2S2)

(1)https://www.drugs.com/sfx/cavilon-durable-barrier-side-effects.html
(2) http://cetraben.co.uk/what-cetraben/
(3) http://medicareplus.co.uk/product/medi-derma-s-barrier-film/
(4) https://www.convatec.co.uk/wound-skin/aquacel-dressings/aquacel-extra/
(5) https://www.wound-care.co.uk/dressings/hydrosorb/
(6) https://www.medisave.co.uk/jelonet-paraffin-gauze

Broad group: Musculoskeletal agents			
baclofen	baclofen	hydroxycholoroquin	hydroxycholoroquin
edrophonium chloride (1)	edrophonium chloride	neostigmine	neostigmine
edrophonium chloride (tensilion)	edrophonium chloride	pyridostigmine	pyridostigmine

(1) https://www.medicinescomplete.com/#/content/martindale/4516-v?hspl=edrophonium

Broad group: Neurological agents			
acetazolamide	acetazolamide	midazolam	midazolam
carbamazepine	carbamazepine	midazolam 2 double	midazolam
chloral hydrate	chloral hydrate	midazolam infusion	midazolam
chlorpromazine	chlorpromazine	nitrazepam	nitrazepam
clobazam	clobazam	paraldehyde	paraldehyde

clonazepam	clonazepam	phenobarbital	phenobarbital
co-careldopa	co-careldopa	phenobarbital (phenobarbitone)	phenobarbital
diazepam	diazepam	phenobarbitone	phenobarbital
dorzolamide	dorzolamide	phenobarbitone - loading dose	phenobarbital
gabapentin	gabapentin	phenobarbitone - maintenance	phenobarbital
haloperidol	haloperidol	phenytoin	phenytoin
lamotrigine	lamotrigine	risperidone	risperidone
levatiracetam (keppra)	levatiracetam	sodium valporate	sodium valproate
levetiracetam	levatiracetam	sodium valproate	sodium valproate
lorazepam	lorazepam	temazepam	temazepam
melatonin	melatonin	thiopentone	thiopental sodium
metaclopramide	metaclopramide	topiramate	topiramate
triclofos	triclofos	vigabatrin	vigabatrin
Broad group: Nutritional supplement			
anamix infant	amino acid (amino acid mix)	glutamine	amino acid (glutamine)
arginine	amino acid (arginine)	isoleucine powder	amino acid (isoleucine)
carglumic acid (carbaglu)	amino acid (carglumic acid)	valine powder	amino acid (valine)
human milk fortifier	breast milk fortifier	docosohexanoic acid	docosohexanoic acid
Broad group: probiotics			
acidophillus	probiotics	infloran	probiotics
bifidobacterium	probiotics	labinic (probiotic)	probiotics
bio-kult	probiotics	lb2 (probiotic)	probiotics
Broad group: Prostaglandins and oxytocics			
oxytocin/ergometrine	ergometrine with oxytocin		
Broad group: Respiratory agents			

acetylcystene	acetylcysteine	survanta	pulmonary surfactants
aminophylline	aminophylline	curosurf	pulmonary surfactants
caffeine	caffeine	curosurf - poractant	pulmonary surfactants
caffeine base	caffeine	poractant alfa - curosurf	pulmonary surfactants
caffeine citrate	caffeine	surfactant	pulmonary surfactants
dnase	dornase alfa	salbutamol	salbutamol
dornase alfa	dornase alfa	salbutamol (ventolin)	salbutamol
doxapram	doxapram	salbutamol iv	salbutamol (iv)
montelukast	montelukast	salmeterol	salmeterol
beractant - survanta	pulmonary surfactants	theophylline	theophylline
Broad group: Retinoid and related drugs			
acitretin	acitretin		
Broad group: Vaccines			
bcg vaccine	vaccine (BCG)	meningococcal c vaccine	vaccine (meningococcal c)
diptheria	vaccine (diphtheria)	mmr	vaccine (MMR)
infanrix	vaccine (DPT)	polio - oral	vaccine (oral polio)
pediacel	vaccine (DTTPH)	prevenar	vaccine (pneumococcal conjugate)
hepatitis b vaccine	vaccine (hepatitis b)	prevenar (pneumococcal conjugate vaccination)	vaccine (pneumococcal conjugate)
influenza immunisation	vaccine (influenza)	pneumococcal vaccine	vaccine (pneumococcal)
rotarix	vaccine (live attenuated rotavirus)	polio vaccine	vaccine (polio)
meningococcal b vaccine	vaccine (meningococcal b)	tetanus toxoid	vaccine (tetanus toxoid)
pertussis (whooping cough)	vaccine (whooping cough)		
Broad group: Vasoconstrictors			

ephedrine	ephedrine	xylometazoline-paediatric	xylometazoline (paediatric)
phenylephrine hydrochloride 2.5%	phenylephrine hydrochloride 2.5% (ocular)		

All drugs' classification are based on BNF for children (online version), unless otherwise indicated

9.13 Calculated Z scores bounds for boys and girls

Z scores bounds for boys			
Gestation age	**Z scores (minus 4SD) for birth weight (grams)**	**Mean birth weight (grams)**	**Z scores (plus 4 SD) for birth weight (grams)**
22 weeks	198	614	990
23 weeks	198	614	990
24 weeks	222	714	1163
25 weeks	246	817	1344
26 weeks	270	924	1538
27 weeks	295	1036	1743
28 weeks	324	1158	1966
29 weeks	358	1290	2208
30 weeks	401	1436	2474
31 weeks	458	1605	2775
32 weeks	535	1799	3111
33 weeks	634	2016	3471
34 weeks	757	2247	3839
35 weeks	906	2486	4196
36 weeks	1077	2726	4527
37 weeks	1503	3500	5497
38 weeks	1503	3500	5497
39 weeks	1503	3500	5497
40 weeks	1503	3500	5497
41 weeks	1503	3500	5497
42 weeks	1503	3500	5497
43 weeks	1503	3500	5497
44 weeks	1503	3500	5497

Z scores bounds for girls			
Gestation age	**Z scores (minus 4SD) for birth weight (grams)**	**Mean birth weight (grams)**	**Z scores (plus 4 SD) for birth weight(grams)**
22 weeks	82	559	914
23 weeks	82	559	914
24 weeks	104	658	1090
25 weeks	129	761	1276
26 weeks	154	867	1473
27 weeks	183	978	1683
28 weeks	218	1093	1905
29 weeks	263	1217	2141
30 weeks	323	1359	2408
31 weeks	401	1525	2710
32 weeks	498	1712	3039
33 weeks	618	1916	3386
34 weeks	758	2134	3739
35 weeks	920	2361	4086
36 weeks	1103	2590	4411
37 weeks	1468	3360	5252
38 weeks	1468	3360	5252
39 weeks	1468	3360	5252
40 weeks	1468	3360	5252
41 weeks	1468	3360	5252
42 weeks	1468	3360	5252
43 weeks	1468	3360	5252
44 weeks	1468	3360	5252

9.14 List of excluded drugs from the analysis

Drug ID	Reason for exclusion	Drug ID	Reason for exclusion
hepsal heparin heparinized saline	heparin sodium (used to open lines)	metanium cream/ dermol/ miconazole cream hc nystaform hc ointment/ octenisan polyfax/ prontoderm/ timodine /tri-adortyl trimovate cream /naseptin cream	topical agents with combination
sodium chloride for flush	used to flush lines	dextrose (see glucose 10% or glucose any conc) dextrose 10% /dextrose 5% / glucose 10% glucose 50%	glucose infusion
cling film eye wrap	used to flush lines	Abidec /dalavit /dalivit healthy start – vitamins /ketovite /multivitamins vitamins (abidec) /folic acid folinic acid (calcium folinate) /arovit vitamin a / thiamine riboflavin /pyridoxal /pyridoxal phosphate pyridoxine /biotin /vitamin d / alfacaladol alfacalcidol / alphacalcidol / calciferol cholecalciferol vitamin e / vitamin e (alphatocopheryl acetate) vitamin k / vitamin k (phyomenadione) vitamin k (phytomenadione) vitamin k - 2nd dose / vitamin vitamins /vitamins (other)	vitamins
eye drops	unspecified name of the drops	Neocate/ thick and easy/ enfamil ar	milk formula
smof/smof lipid total parenteral nutrition	TPN	perfluorocarbon	used for liquid ventilation

none	unrecognised drugs	hartmann's solution	fluids and electrolytes replacement infusions
10% special k		plasmalyte	
5% special k		ringers lactate	
bunesconide puffer k		saline 0.45%	
liquid paraffin 50% in soft white paraffin			
supplements			
ticarcillin			
unlisted drug			

9.15 Full list of range values of the drugs selected to describe their change in use over time (all GA)

Prescribed drugs	2010	2011	2012	2013	2014	2015	2016	2017	Biggest % value	Smallest % value	Range
Sodium	16.6	20.4	22.8	24.7	25.8	26.5	27.3	27.3	27.3	16.6	10.7
Benzylpenicillin	51.0	51.1	50.6	53.7	56.9	58.6	59.9	59.4	59.9	50.6	9.3
Gentamicin	51.9	50.8	50.8	52.7	54.7	56.3	58.1	57.1	58.1	50.8	7.3
Cefotaxime	15.6	15.4	14.4	13.2	11.9	11.4	11.9	12.1	15.6	11.4	4.2
Iron supplements	11.8	10.9	10.2	9.9	9.3	9.2	8.3	7.7	11.8	7.7	4.1
Pulmonary surfactants	3.9	2.6	3.9	5.8	6.4	6.5	6.4	6.0	6.5	2.6	3.9
Domperidone	4.0	3.7	3.4	3.2	1.8	0.7	0.5	0.4	4.0	0.4	3.6
Amoxicillin	6.4	7.0	7.0	6.1	4.7	4.2	4.5	3.8	7.0	3.8	3.2
Flucloxacillin	7.6	7.2	6.5	6.4	6.0	5.7	5.3	4.9	7.6	4.9	2.7
Ranitidine	5.1	4.9	4.2	4.1	3.1	2.7	2.6	2.5	5.1	2.5	2.6
Feed thickeners	5.1	4.7	4.4	4.1	3.9	3.7	3.3	3.0	5.1	3.0	2.1
Caffeine	11.8	11.5	11.1	11.1	10.6	10.7	10.2	10.0	11.8	10.0	1.8
Phosphate supplements	6.6	6.3	6.0	6.0	5.8	5.6	5.0	4.8	6.6	4.8	1.8
Probiotics	0.2	0.2	0.3	0.8	1.1	1.6	0.9	1.3	1.6	0.2	1.4
Nystatin (topical)	5.2	5.1	5.2	5.3	5.1	4.7	4.5	3.9	5.3	3.9	1.4
Vancomycin	4.5	4.3	3.9	3.8	3.8	3.6	3.4	3.1	4.5	3.1	1.4
Metronidazole	3.9	3.8	3.4	3.3	2.8	2.7	2.6	2.5	3.9	2.5	1.4
Amikacin	1.4	1.9	2.0	2.1	2.5	2.7	2.6	2.5	2.7	1.4	1.3

Chlorhexidine	1.1	1.2	1.2	1.2	1.9	1.9	2.2	1.0	2.2	1.0	1.2
Chloramphenicol (ocular)	2.6	2.4	2.1	2.0	1.9	1.7	1.6	1.5	2.6	1.5	1.1
Furosemide	3.4	3.3	3.1	3.0	2.9	2.8	2.8	2.5	3.4	2.5	0.9

9.16 Full list of range values of the drugs selected to describe their change in use over time (very preterm)

Prescribed drugs	2010	2011	2012	2013	2014	2015	2016	2017	Biggest % value	Smallest % value	Range
Pulmonary surfactants	17.4	19.5	19.7	30.5	34.2	34.9	35.1	34.7	35.1	17.4	17.7
Sodium*	51.0	57.4	61.0	65.2	66.3	65.3	66.8	67.8	67.8	51.0	16.9
Domperidone	17.8	17.3	17.5	17.0	10.4	3.8	3.0	2.6	17.8	2.6	15.2
Caffeine*	76.5	79.8	81.1	84.4	84.6	87.0	88.9	91.0	91.0	76.5	14.5
Probiotics	0.7	1.1	2.0	5.8	9.5	13.8	8.6	13.7	13.8	0.7	13.2
Benzylpenicillin	76.4	76.7	76.6	81.4	86.7	86.4	88.9	88.3	88.9	76.4	12.5
Gentamicin	79.1	78.2	79.8	81.9	85.0	84.1	88.1	86.4	88.1	78.2	9.8
Cefotaxime	30.5	32.0	29.3	26.9	24.4	24.2	24.3	24.9	32.0	24.2	7.8
Ranitidine	19.6	19.6	17.9	19.3	14.6	12.7	13.4	13.9	19.6	12.7	6.9
Nystatin (topical)	13.0	14.6	15.8	17.9	18.0	17.7	19.1	18.3	19.1	13.0	6.1
Paracetamol	6.1	6.5	6.5	6.8	6.7	7.8	11.0	11.6	11.6	6.1	5.5
Amoxicillin	10.7	12.9	13.6	11.7	9.6	8.8	9.5	8.1	13.6	8.1	5.5
Vaccine (meningococcal b)	0.0	0.0	0.0	0.0	0.0	0.0	3.6	5.3	5.3	0.0	5.3
Vaccine (live attenuated rotavirus)	0.0	0.0	0.0	0.0	2.9	3.1	4.0	4.9	4.9	0.0	4.9
Morphine (iv)	21.1	22.2	22.8	24.5	25.9	25.5	25.3	24.9	25.9	21.1	4.7
Fuconazole	4.6	6.1	6.0	6.7	8.1	7.4	8.3	8.7	8.7	4.6	4.1
Chlorhexidine	1.9	2.1	2.2	2.5	4.2	4.5	6.0	3.1	6.0	1.9	4.0

Fentanyl	1.7	2.2	2.4	2.6	2.7	3.6	4.4	5.7	5.7	1.7	4.0
Atropine	3.6	4.8	5.2	6.5	5.8	6.2	6.4	7.6	7.6	3.6	4.0
Suxamethonium	4.9	5.6	6.2	7.7	7.6	7.8	8.3	8.7	8.7	4.9	3.8
Cyclopentolate 0.5% (ocular)	6.2	6.9	7.2	8.1	9.2	8.9	8.7	9.8	9.8	6.2	3.5
Iron supplements	65.1	65.3	66.6	67.6	67.8	68.5	68.6	67.4	68.6	65.1	3.5
Phosphate supplements	37.2	36.3	36.6	37.6	39.1	38.4	38.3	39.8	39.8	36.3	3.5
Metronidazole	12.5	14.5	13.8	13.4	12.9	11.2	11.8	11.9	14.5	11.2	3.2
Glycerol suppository	6.5	7.1	8.1	8.4	8.6	8.2	9.4	9.7	9.7	6.5	3.2
Phenylephrine hydrochloride 2.5% (ocular)	7.0	7.8	8.3	9.2	9.6	9.3	9.5	10.2	10.2	7.0	3.2

9.17 Full list of range values of the drugs selected to describe their change in use over time (extremely preterm)

Prescribed drugs	2010	2011	2012	2013	2014	2015	2016	2017	Biggest % value	Smallest % value	Range
Pulmonary surfactants	33.6	35.0	34.2	52.5	61.4	63.1	61.9	59.4	63.1	33.6	29.6
Domperidone	31.2	30.8	29.8	30.9	16.7	9.1	7.4	5.8	31.2	5.8	25.4
Paracetamol	18.8	19.3	20.1	20.9	20.7	27.0	36.5	37.8	37.8	18.8	19.0
Fluconazole	34.0	36.9	41.5	46.9	45.8	49.1	48.6	51.8	51.8	34.0	17.8
Benzylpenicillin	75.4	76.2	77.7	82.7	90.2	88.7	92.1	91.8	92.1	75.4	16.7
Probiotics	3.1	2.2	2.6	9.1	10.8	18.0	9.6	17.7	18.0	2.2	15.7
Vaccine (live attenuated rotavirus)	0.0	0.0	0.0	0.2	8.9	12.4	14.4	14.7	14.7	0.0	14.7
Caffeine	79.5	80.9	84.1	86.2	86.9	89.4	92.8	93.6	93.6	79.5	14.1
Insulin	29.7	32.3	32.2	35.7	37.4	40.3	42.4	43.6	43.6	29.7	14.0
Vaccine (meningococcal b)	0.0	0.0	0.0	0.0	0.0	0.3	13.0	13.9	13.9	0.0	13.9
Indomethacin	14.7	6.6	13.0	2.2	1.5	1.7	1.6	1.1	14.7	1.1	13.6
Phosphate supplements	57.0	59.0	60.9	64.0	64.9	67.6	68.2	69.4	69.4	57.0	12.5
Ranitidine	39.7	39.2	36.9	37.4	28.8	28.3	27.4	30.1	39.7	27.4	12.4
Sodium*	78.9	84.1	84.1	85.6	86.2	88.5	89.8	90.2	90.2	78.9	11.3
Chlorothiazide	25.4	28.1	29.6	33.3	33.8	36.6	34.8	35.3	36.6	25.4	11.2
Gentamicin	81.6	80.3	82.4	84.7	89.1	88.7	91.4	90.7	91.4	80.3	11.1

Nystatin (topical)	28.2	29.7	31.8	35.2	34.7	33.6	39.1	36.7	39.1	28.2	10.9
Ibuprofen	14.3	21.0	17.8	22.5	23.3	22.5	24.6	22.2	24.6	14.3	10.3
Vaccine (DPT)	0.0	0.0	0.0	0.0	2.7	5.4	5.1	9.0	9.0	0.0	9.0
Iron supplements	70.4	71.2	74.6	76.2	77.2	78.9	78.6	79.2	79.2	70.4	8.9
Cefotaxime	47.6	47.5	43.9	43.2	40.0	39.9	38.8	43.9	47.6	38.8	8.9
Spironolactone	36.0	36.5	39.5	41.8	43.3	44.8	43.1	44.1	44.8	36.0	8.8
Cyclopentolate 0.5% (ocular)	12.9	14.7	13.8	17.7	19.0	19.6	20.0	21.7	21.7	12.9	8.8
Morphine (oral)	7.2	8.1	10.5	11.6	11.7	13.3	13.2	15.8	15.8	7.2	8.6
Morphine (iv)	62.1	63.7	61.5	65.4	68.5	69.7	69.9	70.0	70.0	61.5	8.5
Nitric oxide	5.8	5.3	7.5	9.4	11.8	12.9	13.2	13.7	13.7	5.3	8.4
Fentanyl	6.1	8.2	8.2	8.3	8.5	10.5	11.6	14.0	14.0	6.1	7.9
Dobutamine	23.2	24.5	22.0	24.1	29.9	27.7	29.7	29.2	29.9	22.0	7.8
Dopamine	35.5	37.8	35.8	37.4	42.0	42.4	42.7	43.1	43.1	35.5	7.7
Adrenaline	9.9	9.8	9.1	6.5	12.3	14.1	13.9	13.3	14.1	6.5	7.6
Phenylephrine hydrochloride 2.5% (ocular)	13.6	15.1	14.9	18.5	18.9	19.1	20.0	21.0	21.0	13.6	7.4
Furosemide	44.9	45.4	49.0	48.8	50.3	50.2	51.9	50.6	51.9	44.9	7.0
Dexamethasone	13.3	13.5	16.8	18.3	18.6	18.7	18.8	20.2	20.2	13.3	6.9
Suxamethonium	12.1	13.2	13.7	16.0	15.8	17.0	16.1	18.6	18.6	12.1	6.6
Omeprazole	7.1	8.5	9.2	8.0	9.8	10.1	10.9	13.6	13.6	7.1	6.4
Vecuronium	6.8	7.1	3.9	4.0	7.2	9.6	9.4	9.1	9.6	3.9	5.7
Atropine	9.9	11.2	12.2	13.5	12.9	14.3	13.3	15.4	15.4	9.9	5.5
Vaccine (pneumococcal conjugate)	6.4	8.1	7.4	8.1	8.7	10.2	11.8	11.7	11.8	6.4	5.4

Atracurium	7.4	9.7	11.9	11.8	12.0	12.7	11.8	11.7	12.7	7.4	5.4
Chlorhexidine	2.0	2.2	1.8	3.7	4.1	5.0	7.1	3.7	7.1	1.8	5.3
Sodium bicarbonate	26.3	29.8	29.0	29.7	30.8	30.2	31.2	31.6	31.6	26.3	5.3
Flucloxacillin	51.2	49.6	49.3	54.5	50.9	53.5	52.3	51.8	54.5	49.3	5.2
Metronidazole	33.8	31.6	32.1	33.3	28.6	28.6	28.7	30.8	33.8	28.6	5.2

9.18 Neonatal demographics according to different birth weight categories

Demographic comparison		All birth weight categories	ELBW < 1000 g	VLBW 1000 to 1499 g	LBW 1500 to 2499 g	Normal birth weight ≥2500 g
Number of neonates n (%)		638,843 (99.3)	20,339 (3)	35,639 (6)	177,023 (28)	405,842 (63)
Female n (%)		283,553 (44)	10,165 (50)	17,513 (49)	85,956 (49)	169,919 (42)
Length of hospital stay in days median (IQR)		5 (3-13)	82 (54-108)	44 (31-60)	12 (5-20)	3 (2-6)
Discharge destination n (%)	Home	419,671 (66)	14,467 (71)	33,185 (93)	141,430 (80)	230,589 (56.5)
	Died	8,666 (1)	4,311 (21)	1,131 (3.2)	1,335 (1)	1,889 (0.5)
	Ward	192,766 (30)	415 (2)	457(1.3)	30,838 (17)	161,056 (39.7)
	Transfer	16,022 (3)	1,049 (5)	797 (2.3)	3,130 (1.8)	11,049 (3)
	Missing	1,715 (0.0)	97 (1)	69 (0.2)	290 (0.2)	1,259 (0.3)

ELBW, extremely low birth weight; VLBW, very low birth weight; LBW, low birth weight

9.19 Most frequently prescribed drugs overall and in each GA in England and Wales (Top 50)

	Drug	n (%)	Drug	n (%)
All gestational ages	Benzylpenicillin	355,679 (56%)	Domperidone	12,850 (2%)
	Gentamicin	347,713 (54%)	Fluconazole	12,740 (2%)
	Sodium	156,109 (24%)	Chloramphenicol (ocular)	12,416 (2%)
	Cefotaxime	83,281 (13%)	Dobutamine	12,224 (2%)
	Caffeine	69,060 (11%)	Chlorothiazide	10,365 (2%)
	Iron supplements	60,488 (9%)	Atropine	10,228 (2%)
	Morphine (iv)	53,147 (8%)	Insulin	10,220 (2%)
	Flucloxacillin	38,716 (6%)	Chlorhexidine	9,392 (1%)
	Phosphate supplements	36,258 (6%)	Teicoplanin	9,327 (1%)
	Pulmonary surfactants	35,118 (5%)	Co-amoxiclav	9,041 (1%)
	Amoxicillin	33,838 (5%)	Meropenem	8,879 (1%)
	Nystatin (topical)	30,841 (5%)	Glycerol suppository	8,779 (1%)
	Feed thickeners	25,044 (4%)	Phenobarbital	8,269 (1%)
	Paracetamol	24,704 (4%)	Phenylephrine hydrochloride 2.5% (ocular)	8,005 (1%)
	Vancomycin	23,706 (4%)	Cyclopentolate 0.5% (ocular)	7,627 (1%)
	Ranitidine	22,339 (3%)	Atracurium	7,550 (1%)
	Metronidazole	19,566 (3%)	Nitric oxide	7,442 (1%)
	Dopamine	19,227 (3%)	Aciclovir	7,278 (1%)
	Furosemide	18,729 (3%)	Morphine (oral)	6,979 (1%)
	Miconazole (topical)	18,665 (3%)	Pancuronium	6,825 (1%)
	Potassium supplements	17,343 (3%)	Adrenaline	6,766 (1%)

	Amikacin	14,520 (2%)	Hydrocortisone	6,631 (1%)
	Spironolacton	13,593 (2%)	Ceftazidime	6,625 (1%)
	Suxamethonium	13,130 (2%)	Fentanyl	6,451 (1%)
	Sodium bicarbonate	12,995 (25%)	Sucrose (oral)	6,427 (1%)
	Drug	**n (%)**	**Drug**	**n (%)**
Term neonates	Benzylpenicillin	189,413 (50%)	Sodium bicarbonate	3,211 (1%)
	Gentamicin	183,602 (48%)	Feed thickeners	3,159 (1%)
	Sodium	66,144 (17%)	Potassium supplements	2,980 (1%)
	Cefotaxime	41,605 (11%)	Atracurium	2,819 (1%)
	Morphine (iv)	19,399 (5%)	Adrenaline	2,718 (1%)
	Amoxicillin	16,485 (4%)	Atropine	2,675 (1%)
	Paracetamol	11,624 (3%)	Pancuronium	2,656 (1%)
	Nystatin (topical)	9,347 (2%)	Trimethoprim	2,571 (1%)
	Flucloxacillin	8,454 (2%)	Sucrose (oral)	2,544 (1%)
	Amikacin	7,526 (2%)	Furosemide	2,368 (1%)
	Miconazole (topical)	6,457 (2%)	Vecuronium	2,217 (1%)
	Phenobarbital	6,097 (2%)	Midazolam	2,182 (1%)
	Dopamine	6,045 (2%)	Chloramphenicol (ocular)	2,165 (1%)
	Aciclovir	5,254 (1%)	Hydrocortisone	1,956 (1%)
	Pulmonary surfactants	4,989 (1%)	Domperidone	1,796 (0%)
	Ranitidine	4,476 (1%)	Chloral hydrate	1,782 (0%)
	Co-amoxiclav	4,411 (1%)	Calcium supplements	1,756 (0%)
	Prostaglandins	4,250 (1%)	Fentanyl	1,725 (0%)
	Metronidazole	4,035 (1%)	Iron supplements	1,583 (0%)
	Dobutamine	3,842 (1%)	Magnesium supplements	1,420 (0%)

	Chlorhexidine	3,823 (1%)	Phenytoin	1,388 (0%)
	Suxamethonium	3,666 (1%)	Teicoplanin	1,337 (0%)
	Vancomycin	3,606 (1%)	Meropenem	1,217 (0%)
	Morphine (oral)	3,460 (1%)	Ocular lubricants	1,169 (0%)
	Nitric oxide	3,425 (1%)	Noradrenaline	1,135 (0%)
	Drug	**n (%)**	**Drug**	**n (%)**
Moderate to late preterm neonates	Benzylpenicillin	115,236 (58%)	Sucrose (oral)	2,629 (1%)
	Gentamicin	112,699 (57%)	Emollients	2,599 (1%)
	Sodium	47,087 (24%)	Domperidone	2,558 (1%)
	Cefotaxime	22,059 (11%)	Dopamine	2,302 (1%)
	Caffeine	16,341 (8%)	Furosemide	1,993 (1%)
	Iron supplements	16,095 (8%)	Clotrimazole (topical)	1,925 (1%)
	Morphine (iv)	10,892 (5%)	Glycerol suppository	1,846 (1%)
	Amoxicillin	9,979 (5%)	Co-amoxiclav	1,729 (1%)
	Flucloxacillin	8,696 (4%)	Calcium supplements	1,610 (1%)
	Pulmonary surfactants	8,551 (4%)	Sodium bicarbonate	1,581 (1%)
	Nystatin (topical)	7,950 (4%)	Fentanyl	1,566 (1%)
	Phosphate supplements	7,289 (4%)	Teicoplanin	1,458 (1%)
	Feed thickeners	6,311 (3%)	Trimethoprim	1,432 (1%)
	Miconazole (topical)	5,924 (3%)	Dobutamine	1,417 (1%)
	Paracetamol	4,911 (2%)	Atracurium	1,372 (1%)
	Chloramphenicol (ocular)	4,597 (2%)	Aciclovir	1,211 (1%)
	Ranitidine	4,590 (2%)	Prostaglandins	1,061 (1%)
	Metronidazole	4,250 (2%)	Spironolactone	1,026 (1%)
	Amikacin	3,930 (2%)	Nitric oxide	1,022 (1%)

	Suxamethonium	3,521 (2%)	Phenobarbital	1,015 (1%)
	Chlorhexidine	3,453 (2%)	Meropenem	1,009 (1%)
	Vancomycin	3,448 (2%)	Pancuronium	965 (0%)
	Potassium supplements	3,184 (2%)	Erythromycin	951 (0%)
	Benzocaine (topical)	3,105 (2%)	Ceftazidime	942 (0%)
	Atropine	2,645 (1%)	Simeticone	938 (0%)
	Drug	**n (%)**	**Drug**	**n (%)**
Ver preterm neonates	Caffeine	35,482 (84%)	Paracetamol	3,332 (8%)
	Gentamicin	34,905 (83%)	Dopamine	3,290 (8%)
	Benzylpenicillin	34,857 (83%)	Teicoplanin	3,145 (7%)
	Iron supplements	28,280 (67%)	Suxamethonium	3,003 (7%)
	Sodium	26,404 (63%)	Fluconazole	2,957 (7%)
	Phosphate supplements	15,970 (38%)	Probiotics	2,946 (7%)
	Pulmonary surfactants	11,952 (28%)	Chlorothiazide	2,812 (7%)
	Flucloxacillin	11,673 (28%)	Sodium bicarbonate	2,484 (6%)
	Cefotaxime	11,366 (27%)	Atropine	2,443 (6%)
	Morphine (iv)	10,137 (24%)	Insulin	2,343 (6%)
	Feed thickeners	9,619 (23%)	Dobutamine	1,926 (5%)
	Nystatin (topical)	7,091 (17%)	Meropenem	1,886 (4%)
	Ranitidine	6,870 (16%)	Ceftazidime	1,847 (4%)
	Vancomycin	6,763 (16%)	Omeprazole	1,693 (4%)
	Metronidazole	5,360 (13%)	Amikacin	1,635 (4%)
	Furosemide	4,991 (12%)	Erythromycin	1,583 (4%)
	Domperidone	4,644 (11%)	Clotrimazole (topical)	1,453 (3%)
	Amoxicillin	4,453 (11%)	Chlorhexidine	1,404 (3%)

	Potassium supplements	4,395 (10%)	Fentanyl	1,343 (3%)
	Phenylephrine hydrochloride 2.5% (ocular)	3,743 (9%)	Piperacillin + tazobactam	1,250 (3%)
	Spironolactone	3,716 (9%)	Atracurium	1,220 (3%)
	Miconazole (topical)	3,534 (8%)	Co-amoxiclav	1,195 (3%)
	Glycerol suppository	3,480 (8%)	Research drug (ELFIN)	1,145 (3%)
	Chloramphenicol (ocular)	3,450 (8%)	Nitric oxide	1,082 (3%)
	Cyclopentolate 0.5% (ocular)	3,431 (8%)	Vaccine (pneumococcal conjugate)	1,082 (3%)
	Drug	n (%)	Drug	n (%)
Extremely preterm neonates	Caffeine	16,622 (87%)	Meropenem	4,767 (25%)
	Gentamicin	16,507 (86%)	Ibuprofen	4,037 (21%)
	Sodium	16,474 (86%)	Domperidone	3,852 (20%)
	Benzylpenicillin	16,173 (84%)	Teicoplanin	3,387 (18%)
	Iron supplements	14,530 (76%)	Phenylephrine hydrochloride 2.5% (ocular)	3,382 (18%)
	Morphine (iv)	12,719 (66%)	Cyclopentolate 0.5% (ocular)	3,343 (17%)
	Phosphate supplements	12,250 (64%)	Dexamethasone	3,320 (17%)
	Flucloxacillin	9,893 (52%)	Hydrocortisone	3,015 (16%)
	Vancomycin	9,889 (52%)	Suxamethonium	2,940 (15%)
	Pulmonary surfactants	9,626 (50%)	Amoxicillin	2,921 (15%)
	Furosemide	9,377 (49%)	Gycerol suppository	2,833 (15%)
	Fluconazole	8,509 (44%)	Ceftazidime	2,783 (15%)
	Cefotaxime	8,251 (43%)	Miconazole (topical)	2,750 (14%)
	Spironolactone	7,890 (41%)	Piperacillin + tazobactam	2,664 (14%)
	Dopamine	7,590 (40%)	Atropine	2,465 (13%)
	Insulin	7,041 (37%)	Pancuronium	2,209 (12%)

Potassium supplements	6,784 (35%)	Chloramphenicol (ocular)	2,204 (12%)
Nystatin (topical)	6,453 (34%)	Morphine (oral)	2,195 (11%)
Ranitidine	6,403 (33%)	Atracurium	2,139 (11%)
Chlorothiazide	6,163 (32%)	Adrenaline	2,133 (11%)
Feed thickeners	5,955 (31%)	Nitric oxide	1,193 (10%)
Metronidazole	5,921 (31%)	Omeprazole	1,855 (10%)
Sodium bicarbonate	5,719 (30%)	Fentanyl	1,817 (9%)
Dobutamine	5,039 (26%)	Vaccine (DTTPH)	1,806 (9%)
Paracetamol	4,837 (25%)	Probiotics	1,758 (9%)

9.20 Number of unique drugs per patient in median (range, IQR) by year of admission

Year of admission	Total	Extremely preterm	Very preterm	Moderate to late preterm	Term
2010	2 (0-55, 0-3)	15 (0-55, 10-22)	7 (0-50, 4-10)	2 (0-36, 0-3)	2 (0-37, 0-2)
2011	2 (0-69, 0-3)	16 (0-69, 10-23)	7 (0-46, 5-11)	2 (0-32, 0-3)	2 (0-34, 0-2)
2012	2 (0-54, 0-3)	16 (0-54, 11-24)	7 (0-45, 5-11)	2 (0-39, 0-3)	2 (0-40, 0-3)
2013	2 (0-54, 0-3)	17 (0-54, 12-24)	8 (0-40, 5-12)	2 (0-41, 0-3)	2 (0-40, 0-3)
2014	2 (0-47, 0-3)	18 (0-57, 12-25)	8 (0-50, 5-12)	2 (0-41, 0-3)	2 (0-42, 0-3)
2015	2 (0-57, 0-3)	18 (0-57, 13-26)	8 (0-47, 5-11)	2 (0-41, 0-3)	2 (0-46, 0-3)
2016	2 (0-63, 0-3)	19 (0-61, 13-26)	8 (0-63, 5-12)	2 (0-57, 1-3)	2 (0-47, 2-3)
2017	2 (0-66, 0-3)	19 (0-56, 13-27)	8 (0-66, 6-12)	2 (0-45, 1-3)	2 (0-37, 0-3)

9.21 The top 50 drugs in terms of their calculated total number of days of use

Drugs	Number of neonates prescribed the drug at least once	Average number of days of exposure in median	Total number of days of use
Caffeine*	69060	20	1381200
Benzylpenicillin	355679	3	1067037
Gentamicin	347713	3	1043139
Iron supplements	60488	15	907320
Phosphate supplements	36258	19	688902
Sodium*	156109	4	624436
Cefotaxime	83281	4	333124
Spironolactone	13593	24	326232
Feed thickeners	25044	12	300528
Ranitidine	22339	10	223390
Domperidone	12850	17	218450
Chlorothiazide	10365	21	217665
Morphine (iv)	53147	3	159441
Flucloxacillin	38716	4	154864
Nystatin (topical)	30841	5	154205
Vancomycin	23706	6	142236
Probiotics	5490	19	104310
Fluconazole	12740	8	101920
Amoxicillin	33838	3	101514

Omeprazole	5318	17	90406
Potassium supplements	17343	5	86715
Metronidazole	19566	4	78264
Ursodeoxycholic acid	3522	22	77484
Morphine (oral)	6979	11	76769
Furosemide	18729	4	74916
Miconazole (topical)	18665	4	74660
Paracetamol	24704	3	74112
Meropenem	8879	7	62153
Chloramphenicol (ocular)	12416	5	62080
Dopamine	19227	3	57681
Teicoplanin	9327	5	46635
Erythromycin	4490	10	44900
Dexamethasone	4848	9	43632
Amikacin	14520	3	43560
Insulin	10,220	4	40880
Research drug (ELFIN)	1778	22	39116
Chlorhexidine	9392	4	37568
Co-amoxiclav	9041	4	36164
Pulmonary surfactants	35118	1	35118
Ceftazidime	6625	5	33125
Piperacillin + tazobactam	5515	6	33090
Trimethoprim	4858	6	29148
Aciclovir	7278	4	29112

Clotrimazole (topical)	5790	5	28950
Sodium bicarbonate	12995	2	25990
Dobutamine	12224	2	24448
Benzocaine (topical)	5798	4	23192
Nitric oxide	7442	3	22326
Loperamide	866	25	21650
Emollients	5244	4	20976

9.22 Percentage of very preterm neonates prescribed a particular drug each year (drugs with fluctuating trends)

Drugs with fluctuating trends	2010	2011	2012	2013	2014	2015	2016	2017
Probiotics	0.7	1.1	2.0	5.8	9.5	13.8	8.6	13.7
Gentamicin	79.1	78.2	79.8	81.9	85.0	84.1	88.1	86.4
Cefotaxime	30.5	32.0	29.3	26.9	24.4	24.2	24.3	24.9
Ranitidine	19.6	19.6	17.9	19.3	14.6	12.7	13.4	13.9
Nystatin (topical)	13.0	14.6	15.8	17.9	18.0	17.7	19.1	18.3
Amoxicillin	10.7	12.9	13.6	11.7	9.6	8.8	9.5	8.1
Morphine (iv)	21.1	22.2	22.8	24.5	25.9	25.5	25.3	24.9
Fluconazole	4.6	6.1	6.0	6.7	8.1	7.4	8.3	8.7
Chlorhexidine	1.9	2.1	2.2	2.5	4.2	4.5	6.0	3.1
Atropine	3.6	4.8	5.2	6.5	5.8	6.2	6.4	7.6
Cyclopentolate 0.5% (ocular)	6.2	6.9	7.2	8.1	9.2	8.9	8.7	9.8
Iron supplements	65.1	65.3	66.6	67.6	67.8	68.5	68.6	67.4
Phosphate supplements	37.2	36.3	36.6	37.6	39.1	38.4	38.3	39.8
Metronidazole	12.5	14.5	13.8	13.4	12.9	11.2	11.8	11.9
Glycerol suppository	6.5	7.1	8.1	8.4	8.6	8.2	9.4	9.7

9.23 Percentage of extremely preterm neonates prescribed a particular drug each year (drugs with fluctuating trends)

Drugs with fluctuating trends	2010	2011	2012	2013	2014	2015	2016	2017
Fluconazole	34.0	36.9	41.5	46.9	45.8	49.1	48.6	51.8
Benzylpenicillin	75.4	76.2	77.7	82.7	90.2	88.7	92.1	91.8
Probiotics	3.1	2.2	2.6	9.1	10.8	18.0	9.6	17.7
Vaccine (meningococcal b)	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.2
Indomethacin	14.7	6.6	13.0	2.2	1.5	1.7	1.6	1.1
Ranitidine	39.7	39.2	36.9	37.4	28.8	28.3	27.4	30.1
Sodium*	78.9	84.1	84.1	85.6	86.2	88.5	89.8	90.2
Chlorothiazide	25.4	28.1	29.6	33.3	33.8	36.6	34.8	35.3
Gentamicin	81.6	80.3	82.4	84.7	89.1	88.7	91.4	90.7
Nystatin (topical)	28.2	29.7	31.8	35.2	34.7	33.6	39.1	36.7
Ibuprofen	14.3	21.0	17.8	22.5	23.3	22.5	24.6	22.2
Cefotaxime	47.6	47.5	43.9	43.2	40.0	39.9	38.8	43.9
Spironolactone	36.0	36.5	39.5	41.8	43.3	44.8	43.1	44.1
Cyclopentolate 0.5% (ocular)	12.9	14.7	13.8	17.7	19.0	19.6	20.0	21.7
Morphine (iv)	62.1	63.7	61.5	65.4	68.5	69.7	69.9	70.0
Nitric oxide	5.8	5.3	7.5	9.4	11.8	12.9	13.2	13.7
Dobutamine	23.2	24.5	22.0	24.1	29.9	27.7	29.7	29.2
Dopamine	35.5	37.8	35.8	37.4	42.0	42.4	42.7	43.1
Adrenaline	9.9	9.8	9.1	6.5	12.3	14.1	13.9	13.3

Phenylephrine hydrochloride 2.5% (ocular)	13.6	15.1	14.9	18.5	18.9	19.1	20.0	21.0
Furosemide	44.9	45.4	49.0	48.8	50.3	50.2	51.9	50.6
Suxamethonium	12.1	13.2	13.7	16.0	15.8	17.0	16.1	18.6
Omeprazole	7.1	8.5	9.2	8.0	9.8	10.1	10.9	13.6
Vecuronium	6.8	7.1	3.9	4.0	7.2	9.6	9.4	9.1
Atropine	9.9	11.2	12.2	13.5	12.9	14.3	13.3	15.4
Vaccine (pneumococcal conjugate)	6.4	8.1	7.4	8.1	8.7	10.2	11.8	11.7
Atracurium	7.4	9.7	11.9	11.8	12.0	12.7	11.8	11.7
Chlorhexidine	2.0	2.2	1.8	3.7	4.1	5.0	7.1	3.7
Sodium bicarbonate	26.3	29.8	29.0	29.7	30.8	30.2	31.2	31.6
Flucloxacillin	51.2	49.6	49.3	54.5	50.9	53.5	52.3	51.8
Metronidazole	33.8	31.6	32.1	33.3	28.6	28.6	28.7	30.8

9.24 Average duration of drug exposure in days for the 10 most frequently prescribed drugs according to gestational age group

Most frequently prescribed drugs across all gestation age	Average duration of drug exposure in days reported in median (IQR)			
	Term	**Moderate to late preterm**	**Very preterm**	**Extremely preterm**
Benzylpenicillin	3 (2-4)	3 (2-4)	4 (3-5)	4 (3-6)
Gentamicin	3 (2-4)	3 (2-4)	4 (3-6)	8 (4-14)
Sodium	3 (2-4)	3 (2-5)	13 (5-27)	39 (7-22)
Cefotaxime	3 (2-5)	3 (2-5)	5 (3-8)	7 (4-12)
Caffeine*	1 (1-3)	7 (4-10)	22 (14-31)	48 (37-60)
Iron supplements	6 (2-14)	5 (2-11)	16 (8-28)	47 (29-67)
Morphine (IV)	3 (2-5)	2 (1-4)	3 (1-5)	8 (3-19)
Flucloxacillin	3 (2-5)	4 (2-6)	5 (3-7)	7 (4-12)
Phosphate supplements	5 (2-11)	8 (5-14)	19 (10-31)	40 (20-61)
Pulmonary surfactants	Not included as they are given in one dose			

*caffeine results reported by merging caffeine, caffeine citrate and caffeine base data

9.25 Average duration of drug exposure in days for the 10 most frequently prescribed drugs according to birth weight group

Most frequently prescribed drugs across all gestation age	Average duration of drug exposure in days reported in median (IQR)			
	Normal birth weight	Low birth weight	Very low birth weight	Extremely low birth weight
Benzylpenicillin	3 (2-4)	3 (2-4)	4 (3-5)	4 (3-6)
Gentamicin	3 (2-4)	3 (2-4)	4 (3-7)	7 (4-14)
Sodium	3 (2-5)	3 (2-6)	14 (6-28)	37(15-62)
Cefotaxime	3 (2-5)	3 (3-5)	5 (3-8)	7 (4-12)
Caffeine*	2 (1-5)	10 (5-16)	25 (15-35)	45 (30-59)
Iron supplements	5 (2-12)	6 (3-13)	17 (9-30)	44 (26-66)
Morphine (IV)	3 (2-5)	2 (1-5)	3 (2-6)	8 (3-9)
Flucloxacillin	3 (2-5)	4 (3-6)	5 (3-7)	7 (4-12)
Phosphate supplements	4 (2-10)	9 (5-15)	18 (10-30)	38 (19-60)
Pulmonary surfactants	Not included as they are given in one dose			

*caffeine results reported by merging caffeine, caffeine citrate and caffeine base data

9.26 Variables used to calculate the number of neonates with PDA

Neonates (GA< 32 weeks) with PDA records in the NNRD	n	(%)
1. PDA diagnosis variables		
1.1 Neonates with records of PDA in 'diagnosis day' variable	14,455	24
1.2 Neonates with records of PDA in 'diagnosis at admission' variable	3,968	6
1.3 Neonates with records of PDA in 'diagnosis at discharge' variable	15,714	26
A) All neonates with records of PDA diagnosis in any of the fields '1.1' or '1.2' or '1.3'	17,703	29
2. Neonates without records of PDA diagnosis but had pharmacological treatment or surgical		
2.1 Neonates without records of PDA diagnosis but had indomethacin	189	0.4
2.2 Neonates without records of PDA diagnosis but had ibuprofen	280	0.6
2.3 Neonates without records of PDA diagnosis but had PDA surgery	27	0.1
B) All neonates without records of PDA diagnosis but had pharmacological or surgical treatment in any of the fields '2.1' or '2.2' or '2.3'	478	1
Total number of neonates who had PDA in the NNRD are those with records in A) and B)	18,181	30

9.27 Variables used to calculate the number of neonates who had a treatment for PDA

Neonates with various treatment strategies	n	(%)
1. Neonates with indomethacin records		
1.1 Neonates with records of indomethacin from ‘drugs day’ or ‘treatment for pda’ variables	1,417	8
1.2 Neonates with records of indomethacin and ibuprofen	324	2
1.3 Neonates with records of indomethacin and surgery	137	1
1.4 Neonates with records of indomethacin and ibuprofen and surgery	61	0.3
All neonates with any records of indomethacin from 1.1 or 1.2 or 1.3 or 1.4	1,417	8
2. Neonates with ibuprofen records		
2.1 Neonates with records of ibuprofen from ‘drugs day’ or ‘treatment for pda’ variables	4,926	27
2.2 Neonates with records of indomethacin and ibuprofen	324	2
2.3 Neonates with records of ibuprofen and surgery	596	3
2.4 Neonates with records of indomethacin and ibuprofen and surgery	61	0.3
All neonates with any records of ibuprofen from 2.1 or 2.2 or 2.3 or 2.4	4,926	27
3.Neonates with surgery records		
3.1 Neonates with records of surgery from ‘treatment for pda’ variable	1,037	6
3.2 Neonates with records of surgery and indomethacin and ibuprofen	61	0.3
All neonates with records of surgery from 3.1 or 3.2	1,037	6

9.28 Variables used to extract records of paracetamol across the entire cohort

Neonates with paracetamol records	n	(%)
1. Neonates with any record of paracetamol from ‘drugs day’ variable	8,169	13
2. Neonates with a record of paracetamol only	5,877	10
3. Neonates with any records of paracetamol and ibuprofen	1,733	3
4. Neonates with any records of paracetamol and indomethacin	545	1
5. Neonates with any records of paracetamol and surgery	558	1
6. Neonates with any records of paracetamol and indomethacin and ibuprofen	176	0.3

9.29 Prevalence of PDA in neonates admitted each month from January 2010 to December 2017

Admission month	Neonates with PDA records	Number of neonates admitted each month	Prevalence (%) of PDA in each month*	Admission month	Neonates with PDA records	Number of neonates admitted each month	Prevalence (%) of PDA in each month*
Jan-10	160	595	27	Jan-14	189	651	29
Feb-10	149	523	28	Feb-14	179	561	32
Mar-10	148	563	26	Mar-14	177	601	29
Apr-10	169	603	28	Apr-14	198	630	31
May-10	186	606	31	May-14	211	654	32
Jun-10	164	581	28	Jun-14	188	619	30
Jul-10	189	663	29	Jul-14	236	698	34
Aug-10	149	614	24	Aug-14	190	647	29
Sep-10	167	572	29	Sep-14	170	586	29
Oct-10	163	694	23	Oct-14	216	655	33
Nov-10	143	625	23	Nov-14	204	626	33
Dec-10	175	658	27	Dec-14	176	597	29
Jan-11	179	624	29	Jan-15	194	642	30
Feb-11	183	574	32	Feb-15	173	597	29
Mar-11	148	591	25	Mar-15	209	640	33
Apr-11	197	683	29	Apr-15	209	658	32
May-11	188	693	27	May-15	210	714	29
Jun-11	171	646	26	Jun-15	192	610	31
Jul-11	174	600	29	Jul-15	200	651	31
Aug-11	167	635	26	Aug-15	188	654	29

Sep-11	182	607	30	Sep-15	201	652	31
Oct-11	187	662	28	Oct-15	200	687	29
Nov-11	203	633	32	Nov-15	203	608	33
Dec-11	165	620	27	Dec-15	192	632	30
Jan-12	182	621	29	Jan-16	198	659	30
Feb-12	200	615	33	Feb-16	217	652	33
Mar-12	179	635	28	Mar-16	202	717	28
Apr-12	202	638	32	Apr-16	196	642	31
May-12	183	615	30	May-16	209	722	29
Jun-12	193	600	32	Jun-16	180	622	29
Jul-12	191	670	29	Jul-16	179	623	29
Aug-12	225	698	32	Aug-16	205	688	30
Sep-12	185	601	31	Sep-16	204	634	32
Oct-12	206	681	30	Oct-16	192	659	29
Nov-12	186	623	30	Nov-16	191	675	28
Dec-12	164	666	25	Dec-16	197	661	30
Jan-13	183	628	29	Jan-17	197	638	31
Feb-13	161	564	29	Feb-17	171	614	28
Mar-13	197	655	30	Mar-17	211	635	33
Apr-13	214	672	32	Apr-17	220	707	31
May-13	207	705	29	May-17	213	673	32
Jun-13	180	600	30	Jun-17	212	674	31
Jul-13	194	640	30	Jul-17	181	656	28
Aug-13	210	672	31	Aug-17	214	706	30
Sep-13	195	635	31	Sep-17	195	630	31

Oct-13	209	666	31	Oct-17	193	645	30
Nov-13	212	629	34	Nov-17	170	661	26
Dec-13	188	609	31	Dec-17	177	599	30

*prevalence of PDA calculated by dividing number of records of neonates who have PDA by the number of neonates admitted each month and multiplied by 100

9.30 Combination of PDA treatment by gestation age groups

Gestation age (weeks)	Total number of neonates	Received Ibuprofen+ indomethacin n (%)		Received Ibuprofen + indomethacin + paracetamol n (%)		Received Ibuprofen+ Paracetamol n (%)		Received Indomethacin+ Paracetamol n (%)		Received Ibuprofen+ indomethacin+ surgery n (%)	
22	27	0	0	0	0.0	8	30	1	3.7	0	0.0
23	997	37	3.7	23	2.3	170	17	63	6.3	10	1.0
24	2,339	77	3.3	49	2.1	429	18	130	5.6	12	0.5
25	2,636	82	3.1	38	1.4	396	15	132	5.0	18	0.7
26	2,900	49	1.7	28	1.0	312	11	98	3.4	10	0.3
27	2,807	40	1.4	20	0.7	221	8	60	2.1	6	0.2
28	2,479	29	1.2	13	0.5	120	5	37	1.5	3	0.1
29	1,772	7	0.4	4	0.2	51	3	18	1.0	1	0.1
30	1,276	2	0.2	1	0.1	18	1	5	0.4	1	0.1
31	948	1	0.1	0	0.0	8	1	1	0.1	0	0.0
22-27 weeks	11,706	39	0.3	18	0.2	197	2	61	0.5	5	0.0
28-31 weeks	6,475	285	4.4	158	2.4	1536	24	484	7.5	56	0.9
22-31 weeks	18,181	324	1.8	176	1.0	1733	10	545	3.0	61	0.3

PDA, patent ductus arteriosus

N.B: treatment combination is not exclusively limited to those as a neonate might be receiving any additional treatment strategy in addition to each combination

9.31 Use of ibuprofen, indomethacin in neonates with PDA

Admission month	Neonates with PDA records	Percentage of neonates with indomethacin records	Percentage of neonates with ibuprofen records	Admission month	Neonates with PDA records	Percentage of neonates with indomethacin records	Percentage of neonates with indomethacin records
Jan-10	160	33	13	Jan-14	189	1	29
Feb-10	149	32	13	Feb-14	179	1	28
Mar-10	148	39	18	Mar-14	177	3	31
Apr-10	169	28	15	Apr-14	198	1	19
May-10	186	27	16	May-14	211	2	29
Jun-10	164	23	16	Jun-14	188	1	27
Jul-10	189	18	21	Jul-14	236	3	27
Aug-10	149	13	23	Aug-14	190	2	28
Sep-10	167	11	29	Sep-14	170	2	28
Oct-10	163	7	26	Oct-14	216	3	30
Nov-10	143	4	27	Nov-14	204	1	27
Dec-10	175	6	31	Dec-14	176	1	28
Jan-11	179	4	30	Jan-15	194	2	24
Feb-11	183	6	32	Feb-15	173	0	27
Mar-11	148	3	36	Mar-15	209	4	27
Apr-11	197	2	40	Apr-15	209	4	26
May-11	188	6	29	May-15	210	1	25
Jun-11	171	7	30	Jun-15	192	2	30
Jul-11	174	10	36	Jul-15	200	1	28

Aug-11	167	10	28	Aug-15	188	4	29
Sep-11	182	14	25	Sep-15	201	2	22
Oct-11	187	17	23	Oct-15	200	3	27
Nov-11	203	16	29	Nov-15	203	0	29
Dec-11	165	19	25	Dec-15	192	2	28
Jan-12	182	24	25	Jan-16	198	1	27
Feb-12	200	21	25	Feb-16	217	3	28
Mar-12	179	18	16	Mar-16	202	1	35
Apr-12	202	21	21	Apr-16	196	3	34
May-12	183	17	23	May-16	209	2	31
Jun-12	193	13	24	Jun-16	180	4	31
Jul-12	191	17	21	Jul-16	179	1	31
Aug-12	225	21	24	Aug-16	205	1	30
Sep-12	185	11	27	Sep-16	204	1	31
Oct-12	206	13	26	Oct-16	192	2	29
Nov-12	186	8	25	Nov-16	191	7	31
Dec-12	164	6	34	Dec-16	197	13	34
Jan-13	183	4	26	Jan-17	197	6	32
Feb-13	161	3	27	Feb-17	171	9	25
Mar-13	197	3	37	Mar-17	211	10	30
Apr-13	214	4	23	Apr-17	220	8	27
May-13	207	1	26	May-17	213	8	27
Jun-13	180	4	24	Jun-17	212	8	25
Jul-13	194	4	31	Jul-17	181	14	30
Aug-13	210	4	29	Aug-17	214	7	22

Sep-13	195	3	26	Sep-17	195	10	29
Oct-13	209	2	26	Oct-17	193	10	30
Nov-13	212	0	29	Nov-17	170	14	31
Dec-13	188	2	28	Dec-17	177	8	26

9.32 Detailed search strategy used in the systematic review

Database (Total hits 2458)	Search terms	Combination of the search terms (A combination of title abstract key words, and Mesh terms (1964 – end January 2019)
Medline Provided By ProQuest (1946 to present) **Number of hits** **836**	Population Search Terms (Defined as infants <37 weeks gestational age): prematurity – preterm – premature*- premmie*- preemie* Mesh Terms (INFANT, PREMATURE- INFANT, EXTREMELY PREMATURE- PREMATURE BIRTH) Intervention Search Terms (Ibuprofen and most commonly used brands) ibumetin – motrin – nuprin – advil – nurofen – brufen Mesh Terms (IBUPROFEN – ANTI-INFLAMMATORY AGENTS, NON-STERIODAL) Comparison Search Terms (not applicable, as no specific comparator according to the objective of this systematic review) Outcome Search Terms (Toxicity related terms) Adverse effect*- side effect*- adverse drug reaction*- tolerabil* - complication* - harm* Mesh Terms (ABNORMALITIES,DRUG-INDUCED, DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS-LONG TERM ADVERSE EFFECTS - IBUPROFEN/-ae - IBUPROFEN/-tu - IBUPROFEN/-to)	(((exp IBUPROFEN/ OR exp "ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL"/ OR (ibumetin).ti,ab OR (motrin).ti,ab OR (nuprin).ti,ab OR (advil).ti,ab OR (nurofen).ti,ab OR (brufen).ti,ab) AND (exp "DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS"/ OR exp "LONG TERM ADVERSE EFFECTS"/ OR IBUPROFEN/-ae OR IBUPROFEN/-tu OR IBUPROFEN/-to OR (adverse effect*).ti,ab OR (side effect*).ti,ab OR (adverse drug reaction*).ti,ab OR (tolerabil*).ti,ab OR exp "ABNORMALITIES, DRUG-INDUCED"/ OR (complication*).ti,ab OR (harm*).ti,ab)) AND ((prematurity).ti,ab OR (preterm).ti,ab OR (premature*).ti,ab OR (premmie*).ti,ab OR (preemie*).ti,ab OR exp

		"INFANT, PREMATURE"/ OR exp "INFANT, EXTREMELY PREMATURE"/ OR exp "PREMATURE BIRTH"/)) [DT 1964-2017]
Embase Provided by Ovid (1974 to present) **Number of hits** **747**	Population Search Terms (Defined as infants less than 37 weeks gestational age) Prematurity – preterm – premature* - premmie* – preemie* Mesh terms(PREMATURITY) Intervention Search Terms (Ibuprofen and most commonly used brands) Mesh terms (IBUPROFEN) N.B: The other brands were included in embase as subheadings of Ibuprofen; therefore, they were not searched individually. Outcome Search Terms (Toxicity related terms) Side effect* - Tolerabil* - complication* - harm* Mesh terms (IBUPROFEN/ae -IBUPROFEN/to - IBUPROFEN/dt - ADVERSE DRUG REACTION - DRUG INDUCED MALFORMATION N.B: Adverse effect in Embase thesaurus is subheading of adverse drug reaction	((exp IBUPROFEN/ AND (exp IBUPROFEN/ae OR exp IBUPROFEN/to OR exp IBUPROFEN/dt OR exp "ADVERSE DRUG REACTION"/ OR (side effect*).ti,ab OR (tolerabil*).ti,ab OR exp "DRUG INDUCED MALFORMATION"/ OR (complication*).ti,ab OR (harm*).ti,ab)) AND ((prematurity).ti,ab OR (preterm).ti,ab OR (premature*).ti,ab OR (premmie*).ti,ab OR (preemie*).ti,ab OR exp PREMATURITY/)) [DT 1964-2017]
CINAHL Provided by EBSCO (1981 to present) **Number of hits** **163**	Population Search Terms (Defined as infants less than 37 weeks gestational age) Prematurity – preterm – premature* - premmie* - preemie* Mesh terms (INFANT, PREMATURE - CHILDBIRTH, PREMATURE) N.B: INFANT, PREMATURE from CINAHL thesaurus of infant. CHILDBIRTH, PREMATURE from CINAHL thesaurus of premature. Intervention Search Terms (Ibuprofen and most commonly used brands) Ibumetin – motrin – advil – nuprin – nurofen – brufen Mesh terms (IBUPROFEN- ANTIINFLAMMATORY AGENTS, NON-STEROIDAL) Outcome Search Terms (Toxicity related terms)	(((exp IBUPROFEN/ OR exp "ANTIINFLAMMATORY AGENTS, NON-STEROIDAL"/ OR (ibumetin).ti,ab OR (motrin).ti,ab OR (advil).ti,ab OR (nuprin).ti,ab OR (nurofen).ti,ab OR (brufen).ti,ab) AND (exp "ADVERSE DRUG EVENT"/ OR exp "DRUG TOXICITY"/ OR IBUPROFEN/ae OR IBUPROFEN/tu OR IBUPROFEN/de OR (adverse effect*).ti,ab OR (side effect*).ti,ab OR (adverse drug reaction*).ti,ab OR

	Adverse effect* - side effect* - adverse drug reaction* - complication* - harm* - tolerabil* Mesh terms (ADVERSE DRUG EVENT- DRUG TOXICITY- IBUPROFEN/ae - IBUPROFEN/tu - IBUPROFEN/de)	(tolerabil*).ti,ab OR (complication*).ti,ab OR (harm*).ti,ab)) AND ((prematurity).ti,ab OR (preterm).ti,ab OR (premature*).ti,ab OR (premmie*).ti,ab OR (preemie*).ti,ab OR exp "INFANT, PREMATURE"/ OR exp "CHILDBIRTH, PREMATURE"/)) [DT 1981-2017]"
BNI Provided by ProQuest (1992 to present) **Number of hits** **11**	Population Search Terms (Defined as infants less than 37 weeks gestational age) Prematurity – preterm – premature* - premmie* - preemie* Mesh terms (NEONATES:BIRTHWEIGHT) N.B: NEONATES: BIRTHWEIGHT from BNI thesaurus of preterm-preterm babies Intervention Search Terms (Ibuprofen and most commonly used brands) Ibuprofen – Non-steroidal anti-inflammatory –" Non-steroidal anti-inflammatory" - motrin – advil – nuprin – nurofen – brufen – ibumetin N.B: no Mesh terms for any of the intervention terms in this database Outcome Search Terms (Toxicity related terms) Adverse effect* - side effect* - adverse drug reaction* - tolerabil* -complication* -harm* Mesh terms (DRUGS: ADVERSE REACTIONS)	~"((((ibuprofen).ti,ab OR (Non-steroidal anti-inflammatory).ti,ab OR ("Non-steroidal anti-inflammatory").ti,ab OR (ibumetin).ti,ab OR (motrin).ti,ab OR (nuprin).ti,ab OR (advil).ti,ab OR (nurofen).ti,ab OR (brufen).ti,ab) AND (exp "DRUGS : ADVERSE REACTIONS"/ OR (adverse effect*).ti,ab OR (side effect*).ti,ab OR (adverse drug reaction*).ti,ab OR (tolerabil*).ti,ab OR (complication*).ti,ab OR (harm*).ti,ab)) AND ((prematurity).ti,ab OR (preterm).ti,ab OR (premature*).ti,ab OR (premmie*).ti,ab OR (preemie*).ti,ab OR exp "NEONATES : BIRTHWEIGHT"/)) [DT 1992-2017]"

PubMed Provided by US national library of medicine **Number of hits** **473**	N.B: PubMed uses same Mesh as Medline <u>Population Search Terms</u> (Defined as infants less than 37 weeks gestational age): prematurity – preterm – premature* premmie*- preemie** Mesh Terms (INFANT, PREMATURE- INFANT, EXTREMELY PREMATURE- PREMATURE BIRTH) <u>Intervention Search Terms</u> (Ibuprofen and most commonly used brands) ibumetin – motrin – nuprin – advil – nurofen – brufen Mesh Terms (IBUPROFEN – ANTI-INFLAMMATORY AGENTS, NON-STERIODAL) <u>Outcome Search Terms</u> (Toxicity related terms) Adverse effect*- side effect*- adverse drug reaction*- tolerabil* - complication* -harm* Mesh Terms (ABNORMALITIES,DRUG-INDUCED, DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS-LONG TERM ADVERSE EFFECTS - IBUPROFEN/-ae - IBUPROFEN/-tu - IBUPROFEN/-to)	(((((ibuprofen[MeSH Terms]) OR anti-inflammatory agents, non-steroidal[MeSH Terms]) OR ((((((ibumetin[Title/Abstract]) OR motrin[Title/Abstract]) OR nuprin[Title/Abstract]) OR advil[Title/Abstract]) OR nurofen[Title/Abstract]) OR brufen[Title/Abstract]))) AND ((((((((drug-related side effects and adverse reactions[MeSH Terms]))) OR long term adverse effects[MeSH Terms]) OR (((("ibuprofen/adverse effects"[MeSH Terms]) OR "ibuprofen/therapeutic use"[MeSH Terms]) OR "ibuprofen/toxicity"[MeSH Terms])) OR ((((adverse effect*[Title/Abstract]) OR side effect*[Title/Abstract]) OR adverse drug reaction*[Title/Abstract]) OR tolerabil*[Title/Abstract])) OR abnormalities, drug-induced[MeSH Terms]) OR ((complication*[Title/Abstract]) OR harm*[Title/Abstract]))) AND (((((((prematurity[Title/Abstract]) OR preterm[Title/Abstract]) OR premature*[Title/Abstract]) OR premmie*[Title/Abstract]) OR preemie*[Title/Abstract])) OR (((infant, premature[MeSH Terms]) OR infant, extremely premature[MeSH Terms]) OR premature birth[MeSH Terms]))

		AND (("1964/01/01"[PDat] : "2017/12/31"[PDat]))
IPA Provided by Ovid (1970 to 31 January 2019) **Number of hits** **7**	N.B: There is no Mesh terms in this database so the search run in all fields as key words and use same terms as Embase because it is a drug database Population Search Terms (Defined as infants less than 37 weeks gestational age) prematurity – preterm – premature* premmie*- preemie* af Intervention Search Terms (Ibuprofen and most commonly used brands) Ibuprofen.af Outcome Search Terms (Toxicity related terms) "Adverse drug reaction" – side effect* - tolerabil* -" drug induced malformation"- complication* - harm*	1 (adverse drug reaction xy or side effect* or tolarabil* or drug induced malformation xy or complication* or harm*).af. 2. (prematurity or preterm or premature* or premmie* or preemie*).af. 3. 1 and 2 and 3 limit 4 to yr="1967 - 2017"
Cochrane library **Number of hits** **179** **(Reviews:66** **Trials:107** **DARE:6)**	N.B: uses same Mesh as Medline Population Search Terms (Defined as infants less than 37 weeks gestational age): prematurity – preterm – premature* premmie*- preemie* Mesh Terms (INFANT, PREMATURE- INFANT, EXTREMELY PREMATURE- PREMATURE BIRTH) Intervention Search Terms (Ibuprofen and most commonly used brands) ibumetin – motrin – nuprin – advil – nurofen – brufen Mesh Terms (IBUPROFEN – ANTI-INFLAMMATORY AGENTS, NON-STERIODAL) Outcome Search Terms (Toxicity related terms) Adverse effect*- side effect*- adverse drug reaction*- tolerabil* - complication* - harm* Mesh Terms (ABNORMALITIES,DRUG-INDUCED, DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS-LONG TERM ADVERSE EFFECTS - IBUPROFEN/-ae - IBUPROFEN/-tu - IBUPROFEN/-to)	(((exp IBUPROFEN/ OR exp "ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL"/ OR (ibumetin).ti,ab OR (motrin).ti,ab OR (nuprin).ti,ab OR (advil).ti,ab OR (nurofen).ti,ab OR (brufen).ti,ab) AND (exp "DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS"/ OR exp "LONG TERM ADVERSE EFFECTS"/ OR IBUPROFEN/-ae OR IBUPROFEN/-tu OR IBUPROFEN/-to OR (adverse effect*).ti,ab OR (side effect*).ti,ab OR (adverse drug reaction*).ti,ab OR (tolerabil*).ti,ab OR exp "ABNORMALITIES, DRUG-INDUCED"/ OR (complication*).ti,ab OR

		(harm*).ti,ab)) AND ((prematurity).ti,ab OR (preterm).ti,ab OR (premature*).ti,ab OR (premmie*).ti,ab OR (preemie*).ti,ab OR exp "INFANT, PREMATURE"/ OR exp "INFANT, EXTREMELY PREMATURE"/ OR exp "PREMATURE BIRTH"/)) [DT 1964-2017]
Clinical trials.gov **Number of hits** **42**	Keyword search by typing in the advanced search bar : Ibuprofen and premature infants	
Grey literature **Number of hits** **0**	Using keywords: Ibuprofen, PDA and premature infants www.greylit.org	

9.33 Studies excluded after full text review with reasons (n=64)

Study ID	Reason(s) for exclusion
Adamska (2005)	Polish; could not be translated
Adamska(2000)	Polish; could not be translated
Akisu (2001)	Turkish; could not be translated
Alba (2015)	Conference abstract -treatment not clear
Antonucci (2009)	PKPD study
Arslan (2010)	Turkish; could not be translated
Babayigit (2018)	No adverse effects
Bagnoli (2013)	Unable to extract adverse effects data)
Bagheri (2016)	not measure adverse effects
Bhatt (2012)	Evaluated regional tissue oxygenation only
Bixler (2017)	No adverse effects
Boghossian (2017)	No adverse effects
Brunner (2013)	Unclear which Cox inhibitor was associated with IVH
Calkavur(2010)	Conference abstract - insufficient data
Chinta(2015)	Conference abstract - insufficient data
Concheiro-Guisan(2014)	Conference abstract - insufficient data
Constance (2017)	No adverse effects mentioned
Cooper-Peel(1996)	PKPD study
Dani (2018)	No adverse effects mentioned
De Carolis (2000)*	Evaluated effect on cerebral and renal hemodynamic
De Albuquerque Botura (2017)	No study group received ibuprofen only
Demirel (2012)	PKPD study
Ding (2018)	No adverse effects mentioned
Ethington (2011)	Unclear if the adverse effects were related to ibuprofen or indomethacin

Fesharaki (2012)	Iranian; could not be translated
Fonseca (2014)	Unclear reporting of adverse effects
Gimeno (2007)	Spanish - translation showed to be a review article
Gorman(2015)	Evaluated effect on cerebral and somatic regional tissue oxygenation
Gournay (2002)	Case report included in Gournay 2004
Goudjil(2012)	Conference abstract - insufficient reported data on ibuprofen adverse effects
Guimaraes (2009)	No adverse effects mentioned
Härkin (2018)	No adverse effects mentioned
Hochwald et al., 2018	No study group received ibuprofen only
Hariprasad (2002)	Letter to editor – no adverse effect reported
Hoxha (2012)	Conference abstract - insufficient data. Primary publication included (Hoxha 2013)
Jansen (2017)	No adverse effects mentioned
Kang (2017)	No adverse effects mentioned
Kaur (2018)	Not included ibuprofen as intervention
Kim(2015)	Conference abstract. Primary publication (Kim 2016) included
Letshwiti (2017)	No adverse effects mentioned
Lin (2012)	Chinese; could not be translated
Mehralizadeh (2011)	Conference abstract - insufficient data
Mian(2016)	Unclear if the adverse effects were related to ibuprofen or indomethacin
Mitra (2016)	Systematic review protocol
Morley (2003)	Letter to editor-no adverse effects reported
Mosca(1997)	Evaluated effect on cerebral perfusion and oxygenation
Naulaers (2005)	Evaluated effect on cerebral perfusion and oxygenation
Nimiri(2010)	No adverse effects mentioned
Olgun (2014)	Conference abstract - insufficient data

Pacifici (2014)	Review article
Patel (2000)	Evaluated effect on cerebral hemodynamic
Raaijmakers (2018)	Measure long term renal adverse effects
Rheinlaender(2010)	No adverse effects mentioned
Richards (2009)	No adverse effects mentioned
Romagnoli (2018)	No adverse effects mentioned
Sari (2013)	Letter to editor – no adverse effects reported
Sedsikaite(2014)	Conference abstract - insufficient data
Shin(2017)	Letter to editor. Primary publication (Kim-2016) included
Terek (2014)	No adverse effects mentioned
Thibaut (2011)	Review article
Vanhaesebrouck(2007)	No adverse effects mentioned
Woodhead(2015)	Conference abstract - insufficient data
Zanardo (2005)	PKPD study
Zecca (2009)	PKPD study

*This study ‘Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates ‘published in Clinical Pharmacology and Therapeutics 67(6): 676-683 differs to another study included in this review published by same author and year

9.34 Trials excluded as no results posted (n=2)

1.NCT02602054	
Trial name	The Best Treatment Strategy: Surgical Versus Pharmacological, to Close the Ductus Arteriosus Persistent in Preterm Infants. A Randomized Controlled Trial
Methods	RCT, setting: NICU, Mexico
Participants	40 premature neonates with PDA
Interventions	Experimental group: Surgical treatment Control group: one of the following drugs to be administered -Indomethacin: 3 doses (1 dose every 12 hours) for 2 days. Dose: 0.1 - 0.25 mg / kg -Ibuprofen: 3 doses (1 dose every 24 hours) for 2 days. Dose 05 - 10 mg / kg -Acetaminophen: 12 doses (1 dose every 6 hours) for 3 days Dose 15 mg / kg
Outcomes	Success rate of closure patent ductus arteriosus Adverse effects and complications of treatment Death before discharge
Starting date	October 2015
Contact information	Esaú Luis Nieto, Pediatrician 5564787736 dresauln@gmail.com
Notes	Primary estimated completion date: October 2017 Contacted on: 09 Feb 2018
2.NCT01149564	
Trial name	Comparison of Oral and Intravenous Ibuprofen for Treatment of Patent Ductus Arteriosus in Extremely Premature Infants: A Randomized Controlled Trial
Methods	RCT Setting: NICU, Taiwan
Participants	70 neonate< 28 weeks, RDS requiring assisted ventilation, a PDA without other cardiac anomalies
Interventions	Intervention group: Oral ibuprofen Placebo group: IV ibuprofen Dose (both): initial 10 mg/kg then 5 mg/kg at 24-hour intervals as indicated by PDA flow pattern.
Outcomes	Number with PDA closed or adverse effects as a measure of efficiency and safety.
Starting date	December 2009
Contact information	Bai-Horng Su, MD, PhD 886-4-22052121 ext 2061 bais@ms49.hinet.net
Notes	Primary estimated completion date: June 2012 Contacted on: 09 Feb 2018

9.35 Ongoing trials awaiting results (n=10)

1.NCT 02422966	
Trial name	Efficacy and safety of intravenous paracetamol in comparison to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: study protocol for a randomized control trial
Methods	Multicentre RCT Settings: NICUs (Italy)
Participants	110 neonates (GA 24 - 31 weeks) with PDA (ECHO)
Interventions	Group I: IV paracetamol,15mg/kg/dose every 6 hours for a total of 12 doses Group II: IV ibuprofen, initial dose of 10mg/kg followed by 5mg/kg after 24 and 48 hours
Outcomes	PDA closure rate, need for surgical ligation, reopening of the duct, renal failure, NEC, liver failure
Starting date	Dec 2015
Contact information	Angelini S.p.A. - Piazzale della Stazione, 00071S. Palomba - Pomezia (Roma) Italy. Tel. +3906910451.Website: http://www.angelini.it/wps/wcm/connect/it/home
Notes	Estimated completion: Dec 2017
2.NCT 02056223	
Trial name	Paracetamol versus Ibuprofen for Patent Ductus Arteriosus Closure in Preterm Infants. A Prospective, Randomized, Controlled, Double Blind, Multicenter Clinical Trial
Methods	Multicentre RCT, Double Blind, Settings: NICUs (Italy)
Participants	120 neonates ≤ 31+ 6 days weeks with Hs PDA
Interventions	Group A: Boluses of paracetamol 15 mg/kg four time a day for three consecutive days Group B: Boluses of ibuprofen 10-5-5-mg/kg/dose once daily for three consecutive days
Outcomes	PDA closure, oliguria (first 14 days of life), NEC (first 14 days of life), IVH (within 28 days of life)
Starting date	Feb 2014
Contact information	Paola Lago, MD 0039 049 821 ext 3545 paola.lago@aopd.veneto.it Sabrina Salvadori, MD 0039 049 821 ext 3546 sabrina.salvadori@aopd.veneto.it
Notes	Estimated completion: Jul 2019
3. NCT 01630278	
Trial name	Impact of Early Targeted Ibuprofen Treatment of Patent Ductus Arteriosus (PDA) on Long Term Neurodevelopmental Outcome in Very Premature Infants (TRIOCAPI)

Methods	RCT Setting: France
Participants	363 neonates with GA< 28 weeks and postnatal age < 12 hours
Interventions	Ibuprofen group: Ibuprofen before 12 hours of life Placebo group: Placebo before 12 hours of life
Outcomes	2-year survival without cerebral palsy, other prematurity-related morbidities (pulmonary, digestive, neurological, renal)
Starting date	Mar 2012
Contact information	Not mentioned
Notes	Estimated completion: Feb 2019
4. NCT02884219	
Trial name	Multi-centre, Randomized Non-inferiority Trial of Early Treatment Versus Expectative Management of Patent Ductus Arteriosus in Preterm Infants (BeNeDuctus Trial Belgium Netherlands Ductus Trial
Methods	RCT Setting: Belgium
Participants	564 neonates GA <28 weeks with PDA
Interventions	Active Comparator: Early Treatment with ibuprofen or indomethacin within the first 3 days of life Expectative Treatment: No intervention
Outcomes	Mortality, and/or NEC, and/or BPD (day 1 to 3 months) Short term adverse effects (day 1 to 3 months) Long-term neurodevelopmental consequences (at corrected age of 2 years)
Starting date	Dec 2016
Contact information	Willem P de Boode, MD PhD +31 24 361 44 30 willem.deboode@radboudumc.nl
Notes	Estimated completion: December 2019
5. NCT02128191	
Trial name	Efficacy and Safety of No Treatment Compared With Oral Ibuprofen Treatment for Patent Ductus Arteriosus in Preterm Infants: a Randomized, Double-blind, Placebo-controlled, Non-inferiority Clinical Trial
Methods	RCT, non-inferiority trial Setting: Samsung Medical Centre, Seoul
Participants	142 neonates with GA ≤ 30 weeks or BW ≤ 1250 g with PDA during 5 to 14 days of life
Interventions	Ibuprofen group: Initial dose of 10 mg/kg, then two doses of 5 mg/kg at 24 and 48 hours (oral) Placebo group: Initial dose of normal saline, then second and third dose at 24 and 48 hours
Outcomes	Moderate to severe BPD or mortality at 36 weeks postmenstrual age, IVH (grade 3 or greater), retinopathy

	of prematurity, NEC (stage 2b or greater), duration of PDA and intubation, adverse effects, growth velocity
Starting date	Jul 2014
Contact information	Se In Sung, M.D. 82-2-3410-1775 sein.sung@samsung.com
Notes	Estimated completion: Apr 2019
6. NCT 02884219	
Trial name/title	Early Treatment Versus Expectative Management of PDA in Preterm Infants (BeNeDuctus)
Methods	Multi-centre, RCT
Participants	564 neonates with GA < 28 weeks or BW ≤1000g
Interventions	Ibuprofen vs. Indomethacin (dosage not mentioned)
Outcomes	Primary outcome: composite of mortality, and/or NEC (Stage > IIa), and/or BPD (all at a postmenstrual age of 36 completed weeks) Secondary outcome: cardiovascular failure, adverse effects and long-term neurodevelopmental consequences
Starting date	Dec 2016
Contact information	Willem Boode, MD, PhD, Netherland Phone: +31243614430 Email: willem.deboode@radboudumc.nl
Note	ClinicalTrials.gov identifier: NCT 02884219 As of Jan 2019, this trial was still ongoing
7. NCT 03103022	
Trial name/title	Combination of Acetaminophen and Ibuprofen in the Management of Patent Ductus Arteriosus
Methods	Prospective cohort studies
Participants	30 neonates with GA <30 weeks
Interventions	Oral ibuprofen:10mg/kg/dose for the first dose, then 5mg/kg/dose at 24 and 48 hours Oral acetaminophen:15mg/kg/dose every 6 hours for 3 days
Outcomes	Primary outcome: Efficacy of ductal closure and safety Secondary outcome: Ductal reopening, sepsis, NEC, BPD, IVH, periventricular leukomalacia, retinopathy of prematurity and ventilator days and developmental status
Starting date	Jun 2017
Contact information	Sanket D Shah, MD, University of Florida, United States Phone: 904-244-3508 Email: sanket.shah@jax.ufl.edu
Note	ClinicalTrials.gov identifier: NCT 03103022 As of January 2019, this trial was still ongoing
8. NCT 03648437	

Trial name/title	Paracetamol and Ibuprofen in Closing Patent Ductus Arteriosus (PDI)
Methods	RCT
Participants	20 neonates with GA <37 weeks
Interventions	Ibuprofen: IV every 24h for 3 days, dosages: 10-5-5 mg/kg Paracetamol: IV for 3 days: loading dose 20mg/kg, then 7.5mg/kg every 6h (up to12 doses)
Outcomes	Primary outcome: Efficacy of the ductal closure and safety Secondary outcome: Complications (not mentioned), need for ductal therapies, cardiac ultrasound findings, duration of ventilation assist, long-term complications of prematurity
Starting date	Sept 2018
Contact information	Outi Aikio, MD, PhD, Finland Phone: +35883155810 Email: outi.aikio@ppshp.fi
Note	ClinicalTrials.gov identifier: NCT 03648437 As of January 2019, this trial was still ongoing
9. NCT 03701074	
Trial name/title	Randomized Controlled Trial to Evaluate the Safety and Efficacy of Acetaminophen in Preterm Infants Used in Combination with Ibuprofen for Closure of the Ductus Arteriosus
Methods	RCT
Participants	80 neonates with GA ≤27 6/7 weeks
Interventions	Ibuprofen and placebo: Ibuprofen18 mg/kg/dose then 2 doses (9 mg/kg/dose) at 24 hours. Placebo sterile water, with similar volume and colour as ibuprofen for 3 days at 6 hours intervals Ibuprofen and acetaminophen: Ibuprofen 18 mg/kg/dose then 2 doses (9 mg/kg/dose) at 24 hours. Oral Acetaminophen at 15 mg/Kg/dose every 6 hours for 3 days
Outcomes	Primary outcome: Efficacy for the ductal closure and safety Secondary outcome: Liver injury, renal injury, haematological adverse effects, BPD, retinopathy of prematurity, intestinal perforation, NEC, GI haemorrhage, late onset sepsis, periventricular leukomalacia
Starting date	Dec 2018
Contact information	Fabien Eval, MD, University of South Alabama, United State Phone: 2514151055 Email: feyal@health.southalabama.edu
Note	ClinicalTrials.gov identifier: NCT 03701074 As of January 2019, this trial was still ongoing

10. CTRI/2014/08/004805	
Trial name/title	Oral Paracetamol vs. Oral Ibuprofen for closure of Hemodynamically significant Patent Ductus Arteriosus in Preterm Neonates (32 weeks): A Blinded Randomized Controlled Non-Inferiority Trial
Methods	RCT
Participants	196 neonates with GA ≤32 weeks
Interventions	Ibuprofen: 10mg/kg followed by 5mg/kg at 24 and 48 hours Paracetamol:15mg/kg every 6 hours for 3 days in first course and same dose in second course until PDA is patent
Outcomes	Primary outcome: Efficacy of the ductal closure and safety Secondary outcome: azotaemia, oliguria, hepatitis, deranged coagulogram, IVH, periventricular leukomalacia, NEC, BPD and retinopathy of prematurity, reopening of PDA, need for surgical ligation and mortality rate
Starting date	Apr 2014
Contact information	Dr Ashutosh Kumar, Senior Resident, Newborn unit (Dept. of Pediatrics), Nehru Hospital PGIMER Chandigarh 160012, India Phone: 08194951444 Email: ashuarnav@gmail.com
Note	Clinical Trials Registry – India CTRI number: CTRI/2014/08/004805 As of January 2019, this trial was still ongoing

9.36 Risk of bias of the included randomised controlled trials (n=42)

Study ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Al-lawama 2018 **(179)**	Low Performed by computer	Low Randomisation to each group via opaque envelopes	High Not blinded, ibuprofen and paracetamol were given at different times	High Not blinded	Low Outcomes reported for all randomised neonates	Low Registered: ISRCTN (12302923) and no conflicts	Low Funding source and sponsor mentioned; no COI
Aly 2007 **(289)**	Low Sealed envelopes	Low Via opaque envelopes	High Not blinded	Unclear ECHO cardiographers were blinded but assessors of adverse effects were not blinded	Low All neonates are accounted for	Unclear Study protocol not available	Unclear Funding source and sponsor not mentioned
Aranda 2009 **(286)**	Low Central randomisation using a dynamic allocation method of coin randomisation	Low As previous column	Low Drugs were contained in indistinguishable colourless solution by researcher pharmacist	Low Cardiologists (performing ECHO) were blinded. Adverse effects data were evaluated via committee who received blinded summary data	Low All neonates are accounted for	Low Registered: (NCT0044-0804) and no conflicts	High Commercial sponsor and funder: possible COI
Asadpour 2018 **(311)**	Unclear	Low Via opaque envelopes	High Not blinded, ibuprofen and	Unclear Outcome assessor	Unclear No loss of follow up but the number of the	Unclear	Low Funding source and

	Method not clearly mentioned		acetaminophen given at different times	blinding not mentioned	randomised neonates not clearly reported	No study protocol available	sponsor mentioned
Balachander 2018 **(312)**	Low Block randomisation using 'www.sealedenvelopes.com'	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but information not clearly given	Low No loss to follow up	Unclear Registered: CTRI/2016/09/007261) Protocol provided but no specified the adverse effects	Low Funding source and sponsor mentioned
Bravo 2013 **(315)**	Unclear Mentioned randomising but not specified the method	Unclear Same	High Blinding not possible	Unclear ECHO and ultrasound performers blinded	Low No loss to follow up	Low Registered at clinical trials.gov (NCT01593163) with no conflicts	Low Funding source and sponsor mentioned
Cherif 2008 **(305)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Different routes of administration	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low No loss to follow up	Low Registered: (NCT0064-2330) and no conflicts	Unclear Funding source and sponsor not mentioned
Chotigeat 2003 **(290)**	Unclear Method not clearly mentioned	Unclear Same	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear No study protocol available	High Baseline difference in age when they received first dose
Dang 2013	Low	Low	High	High	Low	Low	Unclear

(303)	Performed by computer-study protocol	Via sealed envelopes	Not blinded	Not blinded	All neonates are accounted for	Trial registered: Chinese Clinical Trials (ChinCTR-TRC-12002177) and no conflicts	Funding source and sponsor not mentioned
Dani 2000 (44)	Unclear Method not clearly mentioned	Low Via sealed envelopes	High Not blinded	Unclear Not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Dani 2012 **(363)**	Unclear Method not clearly mentioned	Low Via sealed envelopes	High Blinding not possible (different doses)	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	High 11 neonates in low dose group and 9 in high dose group died after randomisation and were not considered in outcome assessment	Low Registered: (NCT-01243996) and no conflicts	Unclear No Funding source and sponsor not mentioned
De Carolis 2000 **(354)**	Unclear Method not clearly mentioned	Low Via permuted blocks	Unclear Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned

Demir 2017 **(313)**	Unclear Method not clearly mentioned	High Via sealed envelopes not opaque	High Not blinded	Unclear Not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Low Funding source and sponsor mentioned with no COI
El-Mashad 2017 **(307)**	Low Performed by software	Low Via opaque envelopes	High Not blinded	Low All treating staff and outcome assessors blinded	Low All neonates are accounted for	Unclear No study protocol available	Low No COI
Erdeve 2012 **(306)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Low Registered: (NCT-01261117) and no conflicts	Unclear Funding source and sponsor not mentioned
Fakhraee 2007 **(291)**	Unclear Method not clearly mentioned	Unclear Not mentioned	Unclear Not mentioned	Unclear Not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Ghanem 2010 **(287)**	Unclear Method not clearly mentioned	Unclear Not mentioned	Unclear Not mentioned	Unclear Not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned

Gokmen-Eras (2011-2013) **(281,284)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low risk All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Gournay 2004 **(355)**	Unclear Mentioned randomising but not specified the method	Low Via blocks of four	Low Drugs supplied in similar vials	Low All accessors blinded	Low All neonates are accounted for	Unclear No study protocol available	High Analysis was per-protocol and COI
Hammerman 2008 **(292)**	Low Performed by computer	Unclear Not mentioned	High Not blinded-different routes	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Low Funding source and sponsor mentioned with no COI
Hoxha-Pistulli (2013-2014) **(280,283)**	Unclear Method not clearly mentioned	Unclear Not mentioned	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Kanmaz 2013 **(359)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned

Lago 2002 **(293)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Lago 2014 **(310)**	Low Performed by computer generated	Unclear Not mentioned	Low Infusions similar in appearance	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Lin 2017 **(294)**	Low Performed by computer generated	Low Via permuted blocks	Low Clear and indistinguishable drugs	Low All involved staff blinded	Low All neonates are accounted for	Low Trial registered: (NCT01758 91) and no conflicts	Low Funding source and sponsor mentioned with no COI
Navarro 2005 **(437)**	Low Performed by computer	Low Via opaque envelopes	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Oncel (2014-2017) **(282,285)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Low Trial registered: (NCT-01536158) and no conflicts	Unclear risk Funding source and sponsor not mentioned

Overmeire 1997 **(296)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Overmeire 2000 **(297)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Overmeire 2004 **(356)**	Unclear Method not clearly mentioned	Low Via blocks of ten	Low Both infusions had similar packs. And all staff blinded	Low All involved staff blinded	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Pezzati 2014 **(262)**	Unclear Method not clearly mentioned	Unclear Not mentioned	Unclear Not mentioned	Unclear Not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Pourarian 2015 **(309)**	Unclear Method not clearly mentioned	Low Via opaque envelopes	High Not blinded	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Low All neonates are accounted for	Unclear No study protocol available	Low Funding source and sponsor mentioned and no COI

Salama 2008 **(298)**	Low Simple block randomisation	Low As previous column	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Sangtawesin 2006 **(357)**	Unclear Method not clearly mentioned	Low Block randomisation	Low Similar appearance volumes and schedule	Low As previous column	Low All neonates are accounted for	Unclear No study protocol available	Low Funding source and sponsor mentioned and no COI
Sangtawesin 2008 **(365)**	Unclear Method not clearly mentioned	Low Block randomisation	Low Similar appearance volumes and schedule	Low All involved staff blinded	Low All neonates are accounted for	Unclear No study protocol available	Low Funding source and sponsor mentioned and no COI
Sadeghi-Moghaddam 2017 **(314)**	Low Block randomisation	Unclear Not mentioned	High Not blinded-different regimen	Unclear ECHO performer blinded but outcome assessor blinding not mentioned	Unclear Not mentioned	Unclear No study protocol available	High Convenience sampling was used
Sosenko 2012 **(288)**	Low Using random number table	Low Via opaque sealed envelopes	Low All involved staff blinded	Low As previous column	Low All neonates are accounted for	Low Trial registered: (NCT00802685) and no conflicts	Unclear Funding source and sponsor not mentioned
Su 2003 **(299)**	Unclear	Unclear Not mentioned	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear	Unclear Funding source and

	Method not clearly mentioned					No study protocol available	sponsor not mentioned
Su 2008 **(300)**	Low Using random number table	Unclear Not mentioned	Low All involved staff blinded	Low As previous column	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Supapa-nnachart 2002 **(301)**	Unclear Method not clearly mentioned	Low Via opaque sealed envelopes	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Yadav 2014 **(302)**	Low Performed by computer	Low Via opaque sealed envelopes	High Not blinded	High Not blinded	Low All neonates are accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned
Yang 2016 **(304)**	Low Using random number table	Unclear Not mentioned	High Not blinded	High Not blinded	Low All neonates accounted for	Unclear No study protocol available	Unclear Funding source and sponsor not mentioned

ECH, echocardiography; ISRCTN, International standard randomised controlled trial number

9.37 Characteristics of the included RCTs (n=42)

Characteristics of the included RCTs: ibuprofen vs. placebo for PDA prophylaxis (six studies)

Study ID	Setting	Participants	Intervention	Comparator	Number of adverse effects	Notes
De Carolis (2000) **(354)**	Single centre Italy Apr 1996 - July 1997	N=50 <u>Inclusion criteria</u> • GA < 31 weeks <u>Exclusion criteria</u> • BW < 500 g • Antenatal indomethacin • Persistent PHT • Platelet count <50X109/l • Congenital malformations/heart defects	IV ibuprofen: 10-5-5 mg/kg every 24 hours within 2 hours of birth N=23; mean (SD) 28.1 (1.1) weeks and 934 (288) g	No treatment N=23; mean (SD): 28.0 (1.9) weeks and 993 (308) g	Ibuprofen = 27 Placebo =19	
Gournay (2004) **(355)**	Multi-centre (11 centres) France Mar 2001-Dec 2001	N=131 <u>Inclusion criteria</u> • GA < 28 weeks <u>Exclusion criteria</u> • Maternal use of nephrotoxic medication within 3 days before delivery • Congenital malformations • Shock or life-threatening infection • Hydrops fetalis • IVH (3-4)	IV ibuprofen: 10-5-5 mg/kg every 24 hours within 6 hours of birth N= 65; mean (SD) 26 (0.9) weeks and 844 (181) g	IV placebo: Saline in volumes and schedule same as ibuprofen within 6 hours of birth N= 66; mean (SD): 26 (0.9) weeks and 851 (164) g	Ibuprofen =136 Placebo =107	Study terminated (three cases of severe PHT in placebo group). ECHO (day 3) in both groups, ibuprofen if significant PDA. If no closure by day 7, indomethacin

		• Neurological dysfunction • Substantial right-to-left shunt • Clinical bleeding				followed by surgical ligation.
Kanmaz (2013) **(359)**	Single centre-Turkey Jul 2011-Nov 2011	N=46 <u>Inclusion criteria</u> • GA of < 28 weeks and/or BW of <1000 g enrolled 12 to 24 hours after birth <u>Exclusion criteria</u> • Major congenital abnormalities • Life threatening infection • IVH (3-4) • Urine output <1 mL/kg/h during the preceding 8 h • Serum creatinine level of >1.6 mg/dL • Platelet count of <60000 mm3 • Tendency to bleed • Hyperbilirubinemia requiring exchange transfusion • Persistent PHT	Oral ibuprofen: 10-5-5 mg/kg every 24 hours within 12–24 hours of birth N=23; mean (SD): 25.6 (1.6) weeks and 775 (131) g	No treatment N=23; mean (SD): 26.4 (1.7) weeks and 749 (225) g	Ibuprofen group=21 Control group=22	Study terminated (high incidence of adverse effects)
Overmeire (2004) **(356)**	Multi-centre Belgium Feb 1999 - Sept 2001	N=415 <u>Inclusion criteria</u> • GA 24-30 weeks within 6 hours of birth <u>Exclusion criteria</u> • Major congenital malformation	IV ibuprofen:10-5-5 mg/kg within first 6 hours of life N=205; mean (SD): 28.1 (1.7) weeks and 1048 (315 g)	IV saline in similar volume and regimen N=210; mean (SD) 28.1 (1.6) weeks and 1065 (324) g	Ibuprofen = 262 Placebo = 235	Eight neonates had incomplete course [5 rise in creatinine/oliguria, 2 died,

		• IVH > grade 1 • Congenital infection or septicaemia • Uncontrolled hypotension • Serum creatinine >115µmol/l • Bilirubin >85 µmol/l • Tendency to bleed				1 severe IVH]
Sangtawesin (2006) **(357)**	Single centre Thailand Jul 2003 - Apr 2004	N=42 <u>Inclusion criteria</u> • GA 28-32 weeks • BW ≤1500g <u>Exclusion criteria</u> • Maternal prenatal infection • Maternal drug abuse • Maternal NSAIDs use • Hydrops fetalis • Unstable clinical conditions • Congenital heart disease • Persistent PHT • Serum creatinine <u>≥</u> 1.5 mg/dL • Platelet count <u>≤</u>75,000 cells/L • Abnormal coagulogram	Oral ibuprofen:10-5-5 every 24 hours N= 22; mean (SD): 30.6 (1.8) weeks and 1280 (80) g	Placebo (orange starch): three doses with the same method and time schedule of ibuprofen N=20; mean (SD): 30.2 (2.1) weeks and 1214 (218) g	Ibuprofen =46 Placebo =29	High prevalence of GI bleeding
Sangtawesin (2008) **(365)**	Single centre Thailand	N=62 <u>Inclusion criteria</u> • BW <1500g • PDA (ECHO)	Oral ibuprofen:10-5-5 mg/kg every 24 hours N=31; mean (SD):	Placebo (orange starch): same method and time schedule as ibuprofen	Ibuprofen = 33 Placebo = 33	-

	Oct 2005-Oct 2006	Exclusion criteria • Congenital heart disease • Symptomatic PDA • Maternal prenatal infection • Maternal drug abuse • Maternal NSAIDs • Hydrops fetalis • Other major congenital anomalies • Persistent PHT • Serum creatinine > 1.5 mg/dL and or BUN> 30 mg/dL • Platelet count < 75,000 cells/mm3 • Abnormal coagulogram	29.3 (1.9) weeks and 1157 (264) g	N= 31; mean (SD): 29.3 (2.2) weeks and 1163 (261 g)		
Characteristics of the included RCTs: Ibuprofen for PDA prophylaxis vs. Ibuprofen for PDA treatment (one study)						
Dani (2000) (44)	Single centre Italy Time frame - not given	N=80 Inclusion criteria • GA < 34 weeks • Nasal CPAP with >30% oxygen • Platelet count ≥75000/mL • Serum creatinine≤ 1.5 mg/dL • Absence of IVH (3-4) before randomisation Exclusion criteria • Congenital malformations • Persistent PHT	IV prophylactic ibuprofen: 10-5-5 mg/kg every 24 hours within 24 hours of life N=40; mean (SD): 29.2 (2.4) weeks and 1231(445) g	Ibuprofen for treatment (rescue group): Same treatment but after PDA (ECHO) N=40; mean (SD): 29.6 (5.6) weeks and 1226 (505) g	Ibuprofen treatment =6 Ibuprofen prophylaxis =9	-
Characteristics of the included RCTs: Ibuprofen vs. placebo for PDA treatment (three studies)						

Aranda (2009) **(286)**	Multi-centre (11 centres) USA Mar 2002 - Mar 2005	N=136 Inclusion criteria: • GA ≤ 30 weeks, BW: 500-1000g, <72 hours old • Non symptomatic PDA (ECHO) Exclusive criteria: • Congenital bacterial infection • Maternal antenatal NSAIDs exposure <72 hours before delivery • Treatment with a steroid at any time since birth • Unremitting shock • Renal failure or oliguria • Platelet count <75,000/mm3 • Bleeding tendency • Expected survival <48 hours	IV Ibuprofen: 10-5-5 mg/kg every 24 hours N= 68; mean (SD): 26.1 (1.3) weeks and 798.5 (128.7) g	Placebo: indistinguishable solution at same volumes N=68; mean (SD): 26.2 (1.4) weeks and 797.3 (132.8) g	Ibuprofen =145 Placebo =155	
Ghanem (2010) **(287)**	Single centre Saudi Arabia Nov 2006 - Apr 2008	N=66 Inclusion criteria: • GA <32 weeks and BW <1500 g • Postnatal age (48-96 hours) • RDS necessitating treatment • Hs-PDA (ECHO) Exclusion criteria: • Congenital anomalies • IVH (grade 3) • Serum creatinine ≥ 1.5 mg% • Platelet count 660,000/mL3 • Tendency to bleed • Hyperbilirubinemia	Oral ibuprofen: 10mg/kg ECHO performed at 24 hours, 48 hours- if PDA present, 2nd dose and 3rd dose (5mg/kg) given. N=33; mean (SD): 28.8 (2.8) weeks and 1035 (353) g	Placebo and two imaging procedure similar to ibuprofen group N=33; mean: (SD) 28.9 (2.7) weeks and 1047 (403) g	Ibuprofen =9 Placebo =13	-

Sosenko (2012) **(288)**	Single centre USA Jan 2008 - Aug 2010	N=105 Inclusion criteria • BW: 500 - 1250 g • GA: 23 - 32 weeks • >24 hours old but ≤14 days old Exclusion criteria • Severely small for GA • Congenital malformations • Proven sepsis • Serum creatinine >1.7 • Oliguria (urine output <1 cc/kg/hr) • Pulmonary hypertension • Abdominal pathology • Bleeding diathesis	Early treatment: IV ibuprofen 10-5-5 mg/kg N=54; median (10-90th centile) 26 (23-28) weeks and mean (SD) 854 (204) g [If Hs-PDA developed in either group before 28 days, neonates received un-blinded, open label ibuprofen and when contraindicated or unsuccessful, PDA ligation]	Expectant treatment: Placebo at similar volume and regimen N=51; median (10-90th centile): 25 (24-2) weeks and mean (SD) 842 (203) g	Ibuprofen = 38 Placebo =35	Study stopped as ibuprofen recalled by manufacturer
Characteristics of the included RCTs: ibuprofen vs. indomethacin for PDA treatment (16 studies)						
Aly (2007) **(289)**	Single centre Egypt Time frame – not given	N=21 Inclusion criteria: • GA: 27-35 weeks • Postnatal age (2-7) days with PDA (ECHO) • Moderate to severe RDS Exclusion criteria: • Congenital anomalies • Hydrops fetalis • Hyperbilirubinemia • Life threatening infections • Platelet count < 60.000/ml • Bleeding tendency	Oral ibuprofen: (10-5-5 mg/kg) every 24 hours N=12; mean (SD): 31.2 (2.5) weeks and 1884 (485) g	IV indomethacin: three doses 0.2mg/kg at 12-hours intervals N=9; mean (SD): 32.9 (1.6) weeks and 1884 (485) g	Ibuprofen =None Indomethacin =2	-

Chotigeat (2003) **(290)**	Single centre Thailand Jan 2001-May 2002	N=30 <u>Inclusion criteria:</u> • GA<34 weeks • RDS • Age <10 days • PDA (ECHO) <u>Exclusion criteria:</u> • Congenital anomaly • IVH (within 24 hours) • Urine output <1ml/kg/hour • Serum creatinine ≥1.6mg/dl • Tendency to bleed • NEC • Hyperbilirubinemia	Oral ibuprofen: three doses at 24 hours N=15; mean (SD): 30.8 (2.3) weeks and 1412 (354) g	Indomethacin: three doses at 12 hours N=15; mean (SD): 29.86 (2.92) weeks and 1434 (421) g	Ibuprofen =15 Indomethacin =19	Rescue with IV indomethacin (0.2mg/kg 3 doses 12hrly) mechanical ventilation (5 neonates in indomethacin group and 6 in ibuprofen group)
Fakhraee (2007) **(291)**	Single centre Iran Jun 2003 - Jun 2004	N=36 <u>Inclusion criteria:</u> • GA <34 weeks • Age ≤ 14 days • Platelet count ≥ 100,000/µmol • Serum creatinine ≤ 1.6 mg/dL • Absence of clinical abnormal clotting • IVH • PDA (ECHO) <u>Exclusion criteria:</u> • Congenital anomalies • Hydrops fetalis	Oral ibuprofen: (10-5-5) at 24 hours N=18; mean (SD): 31.5 (1.4) weeks and 1658 (386.6) g	Oral indomethacin: 0.2mg/kg, three doses at 24 hours N=18; mean (SD): 30.9 (2.0) weeks and 1522 (357.7) g	Ibuprofen =1 Indomethacin =4	-

		• Urine output < 1ml/kg/hr in the preceding 12 hours • Bleeding tendency • Hyperbilirubinemia				
Hammerman (2008) **(292)**	Single centre Israel Feb 2002 - Dec 2006	N=63 <u>Inclusion criteria</u> • GA ≤ 33 weeks • BW ≤ 1750 g <u>Exclusion criteria</u> • Congenital heart lesions • Documented infection • Thrombocytopenia • IVH (grade 4)	IV ibuprofen:10-5-5 every 24 hours N=32; mean (SD): 27.8 (2.6) weeks and 1060 (350) g	Continuous indomethacin: infused for 36 hours N= 31; mean (SD): 27.8 (2.8) weeks and 1100 (450) g	Ibuprofen =46 Indomethacin =41	-
Lago (2002) **(293)**	Two centres Italy Jan 1998-Dec 2000	N= 175 <u>Inclusion criteria</u> • GA ≤ 34 weeks • Postnatal age 48–72 hour • RDS with mechanical ventilation • PDA (ECHO) <u>Exclusion criteria</u> • Congenital anomalies • Persistent PHT • Recent bleeding (< 48 hours) • Platelet count of <u><</u>50,000/mm3 • Urine output <1 ml/kg/hour during the previous 12 • Serum creatinine > 140 mmol/l and BUN >14 mmol/l	IV Ibuprofen:10-5-5 mg/kg every 24 hours, repeated if PDA present and neonate was mechanically ventilated N=94; mean (SD): 28 (2) weeks and 1126 (412) g	IV indomethacin: 0.2-0.2-0.2 mg/kg at 12 hours N=81; mean (SD) 29 (3) weeks and 1214 (427) g	Ibuprofen =60 Indomethacin =49	-

Lin (2017) **(294)**	Two centres – USA and China Time frame – not given	N=150 <u>Inclusion criteria</u> • BW <1000g • RDS on X-ray • PDA (ECHO) <u>Exclusion criteria</u> • Evidence of infection or sepsis • Congenital anomaly • Oliguria (urine output <1ml/kg/h) or serum creatinine > 2 mg/dl • Low platelet count (<50,000/mm cube) or bleeding tendency	IV Ibuprofen: 10-5-5 mg/kg every 24 hours N=71; mean (SD): 26.2 (1.7) weeks and 801 (156) g	Indomethacin: 0.2-0.1-0.1 mg/kg every 24 hours N=73; mean (SD): 26.3 (1.6) weeks and 812 (160) g	Ibuprofen =96 Indomethacin =114	-
Navarro (2005) **(437)** Translated form Spanish using google translate	Single centre Spain Jan 2003 - Jul 2004	N=47 <u>Inclusion criteria:</u> • GA <34 weeks • First week of life • Hs-PDA (ECHO) <u>Exclusion criteria</u> • Urine output <1ml/kg/h in last 8 hours • Creatinine > 1.8mg/dl • Platelet count < 60,000/µmol • Active bleeding • IVH (3-4) • Severe hyperbilirubinemia	IV Ibuprofen: 10-5-5 every 24 hours N=23; mean (range): 28.5 (27 to 30) weeks and 1169 (489) g	Indomethacin: 0.2mg/kg every 12 hours(three doses) N= 24; mean (range or SD): 28 (26 to 31) weeks and 1205 (512) g	Ibuprofen =17 Indomethacin =23	-

Overmeire (1997) **(296)**	Single centre Belgium Time frame-not given	N=40 <u>Inclusion criteria</u> • GA < 33 weeks • RDS • Postnatal age 48 - 72 hours <u>Exclusion criteria</u> • Congenital malformations • Persistent PHT • Hydrops fetalis • IVH (<48 h) • Clinical bleeding • Thrombocyte count < 60 000/mm^3 • Oliguria of <1 ml/kg/hour in preceding 8 hours • BUN > 14 mmol/l, serum creatinine > 140 mmol/l • Hyperbilirubinemia needing transfusion	IV ibuprofen:10-5-5 mg/kg every 24 hours N=20; mean (SD): 29.0 (2.4) weeks and 1270 (450) g	Indomethacin: 0.2 mg/kg at 12 hours (three doses) N=20; mean (SD): 28.7 (1.9) weeks and 1210 (360) g	Ibuprofen =17 Indomethacin =22	-
Overmeire (2000) **(297)**	Multi-centre Belgium Time frame-not given	N=148 <u>Inclusion criteria</u> • GA ≤ 32 weeks • Age of 2 to 4 days • PDA (ECHO) • RDS necessitating respiratory support <u>Exclusion criteria</u> • Major congenital anomalies • Life-threatening infection • Hydrops fetalis	IV ibuprofen: 10-5-5 mg/kg every 24 hours N=74; mean (SD): 29.0 (2.3) weeks and 1230 (390) g	IV indomethacin: 0.2mg/kg every 12 hours (three doses) N=74; mean (SD): 29.0 (2.1) weeks and 1230 (380) g	Ibuprofen =60 Indomethacin =68	-

		• IVH (in 24 hours) • Urine output < 1 ml/kg/hr • Serum creatinine ≥ 1.6 mg/dl or BUN > 40 mg/dl • Platelet count ≤ 60,000mm^3 • Tendency to bleed • Hyperbilirubinemia requiring transfusion				
Pezzati (1999) **(262)**	Single centre-Italy Time frame-not given	N=17 Inclusion criteria • GA <33 weeks • RDS • Hs-PDA (second day of life)	IV ibuprofen: 10-5-5 mg/kg every 24 hours N=9; mean (SD): 29.1 (2.2) weeks and 1151 (426) g	IV indomethacin: 0.2-0.1-0.1 mg/kg every 24 hours N=8; mean (SD): 29.5 (2.6) weeks and 1277 (440) g	Ibuprofen =None Indomethacin =None	-
Salama (2008) **(298)**	Single centre Qatar Jan 2005 – Mar 2007	N=41 Inclusion criteria • GA < 34 weeks • BW < 2500 g • Hs-PDA (ECHO) with a diameter > 1.5 mm Exclusion criteria • Congenital anomalies • Serum creatinine ≥140 umol/l, BUN > 14 mmol/l • Platelet count <50,000/mm3 • NEC, abdominal distention, feeding intolerance • Tendency to bleed • Hyperbilirubinemia requiring transfusion • Anuria < 0.5 ml/kg/hour in preceding 8 hours	Oral ibuprofen:10-5-5 mg/kg every 24 hours. If PDA persist, a second course of ibuprofen given. If PDA persist, a course of indomethacin given N=21; mean (SD): 27.7 (2.5) weeks and 1094 (480) g	IV Indomethacin: 0.2 mg/kg/dose every 24 hours. If PDA persist, a second course given N= 20; mean (SD): 27.7 (2.5) weeks and 1094 (480) g	Ibuprofen =10 Indomethacin =17	-

		• Active infection				
Sadeghi-Moghaddam (2017) **(314)**	Single centre Iran Time frame-not given	N=80 <u>Inclusion criteria:</u> • GA <32 weeks • BW <1500g with hs-PDA • RDS requiring respiratory support <u>Exclusion criteria</u> • Congenital heart defect • Life-threatening infection • NEC • Bleed, or platelet counts <60,000/mL • Liver failure • Severe intracerebral haemorrhage • Severe hyperbilirubinemia • Creatinine >1.5 • Obvious bleeding • Mother/infant treated with NSAIDs or drugs contradicted to ibuprofen	Oral ibuprofen: Doses according to age and weight of neonates at 24 hours intervals for three doses N=40; mean (SD): 29.2 (1.8) weeks and 1182.37 (197.25) g	Indomethacin: Doses according to age and weight of neonates N=40; mean (SD): 28.9 (1.93) weeks and 1166.25 (175.12) g	Ibuprofen =9 Indomethacin =10	--
Su (2003) **(299)**	Single centre Taiwan Jan 2001 - Dec 2002	N=63 <u>Inclusion criteria</u> • GA<u><</u> 32 weeks • BW<u>≤</u>1500g • On CPAP • Platelet count ≥100, 000/μL • Serum creatinine ≤1.5 mg/dL	IV ibuprofen: 10-5-5 mg/kg every 24 hours N=32; mean (SD): 28.7 (2.2) weeks and 1134 (200 g)	Indomethacin: 0.2-0.2-0.2 mg/kg every 12 hours N=31; mean (SD): 28.2 (2.4) weeks and 1110 (244 g)	Ibuprofen =14 Indomethacin =22	-

		• Absence of abnormal clotting function • IVH (3-4) • PDA (ECHO) <u>Exclusion criteria</u> • Congenital anomalies • Life threatening infection • Hydrops fetalis • Recent IVH (within 24 hours) • Urine output < 1 mL/kg/h during the preceding 8 h • Bleeding tendency				
Su (2008) **(300)**	Single centre Taiwan Feb 2004 – Oct 2006	N=119 <u>Inclusion criteria</u> • GA ≤28 weeks • RDS • PDA (ECHO) <u>Exclusion criteria</u> • Severe congenital anomalies • Lethal cardiopulmonary conditions	IV Ibuprofen:10-5-5 mg/kg every 24 hours N=60; median (range) 25 (23-28) weeks and 825 (550-990) g	Indomethacin: initial dose and then 0.1 mg/kg in neonates < 48h old, 0.2 mg/kg in neonates > 48h every 24 hours N=59; median (range): 25 (23-28) weeks 762 (540-980) g	Ibuprofen =94 Indomethacin =103	If PDA present within 48 hours, same drug regimen given. If PDA persisted after two courses, ligation considered
Supapannachart (2002) **(301)**	Single centre Thailand Apr 2000 – Aug 2001	N=18 <u>Inclusion criteria</u> • GA <34 weeks • Symptomatic PDA <u>Exclusion criteria</u> • Congenital anomalies • CHD or PHT	Oral ibuprofen: 10mg/kg daily for three days N=9; mean (SD): 30.1 (2.7) weeks and 1447 (38) g	Indomethacin (oral/IV):0.2mg/kg every 12 hours (three doses) N=9; mean (SD): 30.4 (2.6) weeks and 1432 (530) g	Ibuprofen =12 Indomethacin =13	Indomethacin given in ibuprofen if PDA persist. If no response, Ligation considered in both groups

		• Congenital infection • IVH • Bleeding • Thrombocytopenia • Oliguria (urine output <1ml/kg/h				
Yadav (2014) **(302)**	Two centre India Mar 2010 - May 2012	N=83 <u>Inclusion criteria</u> • GA<37 weeks • BW< 2500g up to 28 days of age • PDA (ECHO) <u>Exclusion criteria</u> • Congenital heart disease • Severe PHT • Hydrops fetalis • Multiple congenital anomalies • Maternal prenatal infection • Critical illness • IVH (3-4) • Platelet count <50,000/cu mm • Abnormal coagulogram • Serum creatinine ≥ 1.5 mg/dl	Oral ibuprofen: 10-5-5 mg/kg every 24 hours N=48; mean (SD): 29.6 (3.1) weeks and 1140 (450) g	Oral Indomethacin: 0.20–0.25 mg/kg every 24 hours for three doses-based on GA N=35; mean (SD): 30.3 (3.1) weeks and 1380 (450) g	Ibuprofen =4 Indomethacin =13	If PDA persisted, second course of same treatment repeated. If PDA persist, ligation considered
Characteristics of the included RCTs: Ibuprofen vs. paracetamol for PDA treatment (six studies)						
Al-Lawama (2018) **(179)**	Single centre Jordan	N=22 <u>Inclusion criteria:</u> • GA ≤32 weeks	Oral ibuprofen: 10mg/kg/dose once daily for three days	Oral paracetamol: 10mg/kg/dose every 6 hours for three days	Ibuprofen =7	--

	Mar 2015 – Oct 2016	• BW ≤1500g Exclusion criteria: • Congenital heart diseases • Major congenital malformation • IVH (3-4) • Renal impairment • Pulmonary haemorrhage • Thrombocytopaenia • Elevated alanine transaminase	N=9; mean (range): 28 (25-35) weeks; mean (SD) 1192 (269) g	N=13; mean (range): 28 (23-32) weeks; mean (SD) 1059 (386) g	Paracetamol =15	
Asadpour (2018) **(311)**	Single centre Iran 2016 to 2017	N=50 Inclusion criteria: • PDA • GA < 37 weeks Exclusion criteria: Not stated	Oral ibuprofen: 10-5-5 mg/kg every 24 hours N=25; mean (SD): not stated	Oral paracetamol: 10mg/kg every 6 hours for three days N=9; mean (SD) not stated	Ibuprofen =5 Paracetamol =None	-
Balachander (2018) **(312)**	Single centre India Oct 2014 – Jan 2016	N=110 Inclusion criteria: • GA ≤ 37 weeks • BW ≤ 2500g • Symptomatic hs-PDA Exclusion criteria: • Other cardiac anomalies or duct dependent lesions • Major congenital malformations • Oliguria (urine output <1ml/kg/hour in preceding 24 hours) • Serum creatinine >1.6mg/dl	Oral ibuprofen: (10-5-5 mg/kg every 24 hours) N=75; mean (SD): 31.54 (2.9) weeks and 1513.4 (414.9) g	Oral paracetamol: 15mg/kg/dose every 6 hours N=75; mean (SD): 31.58 (2.9) weeks and 1534.8 (408.2) g	Ibuprofen =112 Paracetamol =109	-

		• IVH (within 24 hours) • NEC • Jaundice requiring transfusion • Platelet counts <50,000/mm^3 • Overt bleeding				
Dang (2013) **(303)**	China Time frame-not given	N=160 Inclusion criteria • GA ≤ 34 weeks • Postnatal age ≤ to 14 days • Hs-PDA (ECHO) Exclusion criteria: • CHD • Life-threatening infection • IVH (3–4) • Urine output < 1 ml/kg/hour in preceding 8 hours • Serum creatinine > 88.4 µmol/L • Platelet count of <50x109 /L • Hyperbilirubinemia • NEC and/or intestinal perforation • Liver dysfunction	Oral ibuprofen: 10-5-5 mg/kg every 24 hours N=80; mean (SD): 30.9(2.2) weeks and 1531(453.5) g	Oral paracetamol: 15mg/kg every 6h for three days N=80; mean (SD): 31.2(1.8) weeks and 1591(384.6) g	Ibuprofen =96 Paracetamol =59	Rescue treatment if PDA present after two courses.
Oncel (2014-2017)* **(282,285)**	Single centre Turkey Feb- Dec 2012	N=90 Inclusion criteria • GA≤ 30 weeks • BW ≤ 1250 g • Postnatal age 48-96 hours	Oral Ibuprofen: 10-5-5 every 24 hours N=40; mean (SD): 27.3 (2.1) weeks and 973 (224) g	Oral paracetamol: 15mg/kg every 6 hours for three days	Ibuprofen =34 Paracetamol =35	*Oncel 2017 is a follow up trial of Oncel 2014. Both included as one RCT.

		• PDA (ECHO) Exclusion criteria • Congenital abnormalities • Right-to-left ductal shunting • Life-threatening infection • IVH (3-4) • Urine output < 1 mL/kg/h in last 8h • Serum creatinine >1.6 mg/dL • Platelet count <60 000/mm3 • Liver failure • Hyperbilirubinemia • Persistent PHT		N=40; mean (SD): 27.3 (1.7) weeks and 931 (217) g		
Yang (2016) **(349)**	Single centre China Oct 2012 - Jun 2015	N=87 Inclusion criteria: • GA <3 7 weeks admitted within 24 hour of birth • PDA (ECHO 15 hours-10 days after birth) Exclusion criteria • Thrombocytopenia • Haemorrhagic disease • Oliguria • NEC • Intestinal perforation • Serum creatinine >159.1 µmol/l • Alanine amino transferase >40 U/l • CHD	Oral Ibuprofen:10-5-5 mg/kg every 24 hours N= 43; mean (SD): 33.4 (2.1) weeks and 2091 (657) g	Oral paracetamol: 15 mg/kg every 6 hours for three days N=44; mean (SD): 33.6 (2.1) weeks and 2219 (606) g	Ibuprofen =21 Paracetamol =15	-

Characteristics of the included RCTs: oral vs. IV ibuprofen for PDA treatment (four studies)						
Cherif (2008) **(305)**	Single centre RCT Tunisia Jan 2007 – Dec 2007	N=64 <u>Inclusion criteria</u> • GA < 32 weeks • BW <1500 g • Respiratory distress • PDA (ECHO) <u>Exclusion criteria:</u> • Right-to-left shunting • Major congenital anomalies • IVH (3–4) • Tendency to bleed • Serum creatinine level >16 mg/dL; serum BUN >9 mg/Dl	Oral ibuprofen:10-5-5 mg/kg every 24 hours N = 32; mean (SD): 29.3 (1.2) weeks and 1227.2 (188) g	IV ibuprofen: 10-5-5 mg/kg every 24 hours N=32; mean (SD): 28.3 (1.1) weeks and 1197.72 (158) g	Oral ibuprofen =27 IV ibuprofen =31 Total: 58	-
Erdeve (2012) **(306)**	Single centre Turkey Jan 2010 - Feb 2011	N=80 <u>Inclusion criteria</u> • GA ≤28 weeks • BW <1000 g • Postnatal age 48–96 hours • PDA (ECHO) <u>Exclusion criteria</u> • Congenital abnormalities • Life-threatening infection • IVH (3-4) • Urine output < 1 ml/kg/h in last 8 hours, serum creatinine level >1.6 mg/dl • Platelet count <60 000/mm3,	IV ibuprofen: 10-5-5mg/kg N=34; mean (SD): 26.3 (1.3) weeks and 872 (123) g	Oral ibuprofen : 10-5-5mg/kg N=36;mean (SD): 26.4 (1.1) weeks and 892 (117) g	Oral ibuprofen =23 IV ibuprofen =27 Total: 50	After ECHO; second course given by same route if PDA persisted. 10 [6 in IV and 4 in oral] excluded as of death

		• Tendency to bleed • Hyperbilirubinemia • Persistent PHT				
Gokmen –Eras (2011-2013)* **(281,284)**	Single centre Turkey Jan 2009 - Feb 2010 Follow up published as Eras 2013	N=108 <u>Inclusion criteria:</u> • GA ≤ 32 weeks • BW ≤1500 g • 48 to 96 hours • PDA (ECHO) <u>Exclusion criteria:</u> • Congenital abnormalities • Life-threatening infection • IVH (3-4) • Urine output <1 mL/kg/h in last 8h • Creatinine level >1.6 mg/dL • Platelet count <60 000/mm3 • Tendency to bleed • Hyperbilirubinemia • Persistent PHT	IV ibuprofen: 10-5-5 mg/kg every 24 hours N=50; mean (SD): 28.7 (2.1) weeks and 1205 (366) g	Oral Ibuprofen: 10-5-5mg/kg every 24 hours N= 52; mean (SD): 28.5 (1.9) weeks and 1170 (297) g	Oral ibuprofen =30 IV ibuprofen =31	*Eras 2013 is follow up trial of Gokmen 2011, adverse effects of both studies were added together. ECHO performed on day three of treatment – second course of same treatment given if PDA still present
Hoxha-Pistulli **(280,283)**	Single centre Albania Jan 2010 – Dec 2012	N=80 [94 neonates assessed. 14 not included (reasons given).80 randomised] <u>Inclusion criteria</u> • GA (28-32 weeks) • BW ≤ 2000g • Age 48 to 96h • PDA (ECHO) • RDS requiring > 25 % oxygen	Oral ibuprofen: (10mg) N=36,19 (53%) 28-30 weeks; 9 (25%) <1000g	IV ibuprofen: (10mg) N=32,18 (56%) 28-30 weeks; 6 (19%) <1000g	Oral ibuprofen = 12 IV ibuprofen =14 Total: 26	*Different publication of the same study reporting different outcomes. After 24 hours, if PDA present (ECHO) 5 mg ibuprofen

		Exclusion criteria • Congenital malformations • IVH (3-4) • Congenital bacterial infection • Renal failure or oliguria • Platelet count < 60,000/mL^3 • Bleeding tendency • Serum creatinine <1.6 mg/l; BUN <60 mg/% • Hyperbilirubinemia				given. Third dose given after 24 hours if PDA still present.
Characteristics of the included RCTs: Oral ibuprofen vs. rectal ibuprofen (one study)						
Demir (2017) **(313)**	Single centre Turkey Jan 2014 - Jul 2015	N=72 Inclusion criteria: • GA ≤ 32 weeks • BW ≤ 1500 g • Hs-PDA Exclusion criteria: • Major congenital anomalies • Right-to-left ductal shunts • Life threatening infections • IVH (3-4) • Urinary output <1mL/kg/hour • Serum creatinine levels >1.6mg/dL • Thrombocyte count <60,000/mm3 • Hyperbilirubinemia • Persistent PH	Oral ibuprofen: 10-5-5 mg/kg every 24 hours N=36; mean (SD): 30.2 (2.04) weeks and 1435 (343) g	Rectal ibuprofen: 10-5-5 mg/kg every 24 hours N=36; mean (SD): 29.7 (2.3) week and BW 1330 (457) g	Oral ibuprofen =19 Rectal ibuprofen =13 Total: 32	--
Characteristics of the included RCTs: Ibuprofen vs. indomethacin vs. paracetamol (3 arm trial); (one study)						

El-Mashed (2017) **(307)**	Single centre- Egypt Jan 2012 - Dec2015	N=300 <u>Inclusion criteria</u> • GA< 28 weeks or • BW< 1500 g • First 2 weeks of life • Hs-PDA (ECHO and clinical examination) <u>Exclusion criteria</u> • Congenital anomalies • Life threatening sepsis • NEC • IVH • Urine output <1ml/kg/h in the last 24 h • Serum creatinine >1.5 mg/dl • Platelet count <100,000/ml • Congenital heart, or duct-dependent lesions	IV Ibuprofen: 10-5-5 mg/kg/day N=100; mean (SD): 25 (2.1) weeks and 1000 (120) g	IV Paracetamol: 15 mg/kg infusion followed by 15 mg/kg/6 hours for three days N=100; mean (SD): 26 (1.9) weeks and 1100 (130) g IV Indomethacin: 0.2 mg/kg infusion (three doses) every 12 hours N=100; mean (SD): 26 (2.1) weeks and 1100 (140) g	Ibuprofen =25 Indomethacin =36 Paracetamol =11	-
Characteristics of the included RCTs: comparison of different doses/regimen of Ibuprofen used for PDA treatment (four studies)						
Bravo (2013) **(315)**	Single centre- Spain 11-month study period	N=49 <u>Inclusion criteria</u> • GA: 24 - 34 weeks • PDA (ECHO) <u>Exclusion criteria:</u> • Life-threatening congenital defects • Congenital heart disease • Contraindication for ibuprofen	Received first dose of ibuprofen (10mg/kg/dose) ECHO guided treatment: additional doses of ibuprofen (5 mg/kg at 24-hours) only if the PDA was still 1.5mm at the time of the corresponding ibuprofen dose	Received first dose of ibuprofen (10mg/kg/dose) Standard ibuprofen treatment: received two additional doses of 5 mg/kg at 24-hours following the first dose	ECHO guided =28 Standard treatment=21	-

		• Severe intracranial haemorrhage • Intestinal ischaemia or severe PH	N=28; mean (SD): 27.2 (2.2)	N=21; mean (SD): 27.3 (2.1)		
Dani (2012) **(363)**	Multi-centre (four) Italy Jul 2007 - Jun2009	N=95 <u>Inclusion criteria</u> • GA <29 weeks • PDA (ECHO) • Age 12–24 h • RDS <u>Exclusion criteria</u> • Congenital anomalies • Life-threatening infection • Pulmonary hypertension (ECHO) • Death before end of first course of ibuprofen • Urine output <1 ml/kg /h last 12 hours • Serum creatinine ≥1.5 mg/dl • Platelet count ≤50,000/mm^3 • Tendency to bleed	Low dose IV ibuprofen:10-5-5 mg/kg every 24 hours N=35; mean (SD): 26(1.7) weeks and 835 (215) g	High dose IV ibuprofen: 20-10-10 mg/kg every 24 hours N=35; mean (SD): 25.6(1.8) weeks and 781(225) g	Low dose ibuprofen= 28 High dose ibuprofen =37 Total:65	-
Pourarian (2015) **(309)**	Two centres Iran Apr 2012 - May 2013	N=65 <u>Inclusion criteria</u> • GA≤ 37 weeks • Postnatal age 3-7 days • PDA (ECHO) <u>Exclusion criteria</u> • Major CHD • Persistent PHT	High dose ibuprofen:20-10-10 mg/kg every 24 hours N= 30 ; mean (SD): 30 (2.6) weeks and 1339 (542) g	Standard dose ibuprofen:10-5-5 mg/kg every 24 hours N= 30; mean (SD): 31.3 (2.1) weeks and 1493 (346) g	Standard dose =7 High dose =9 Total: 16	Three in high and two in standard dose group died before end of the first course of treatment. In both groups, second course (20-10-10) given if PDA persisted

		• Life-threatening infections • Severe bleeding • Death before the first course of ibuprofen • Urine output (<1ml/kg/h); serum creatinine≥1.8mg/dl • Platelet count ≤50,000/mm3 • Tendency to bleed				
Lago (2014) **(310)**	Single centre Italy Feb 2008 – Jun 2010	N=112 <u>Inclusion criteria:</u> • GA< 32 • RDS on ventilation <u>Exclusion criteria:</u> • Renal impairment • Thrombocytopenia • Bleeding disorders • IVH (3-4) • Severe hyperbilirubinemia • Sepsis • Birth asphyxia • Congenital malformation	Standard treatment (bolus): daily Ibuprofen boluses of 10, 5 and 5 mg/kg every 24 hours N= 56; mean (SD): 27.4 (2.7) weeks and 1027 (346) g	Continuous infusion: 10-5-5 mg/kg every 24 hours N=55; mean (SD): 27.3 (2.1) weeks and 1012 (315)g	Bolus dose =40 Continuous dose =28 Total: 68	In both groups, second course was given if PDA persisted.

AE, adverse effects; BW, birth weight; BUN, blood-urea nitrogen; ECHO, echocardiography; CHD, congenital heart disease; CPAP, continuous positive airway pressure; GA, gestational age; GI, gastrointestinal; hsPDA, haemodynamically significant PDA; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NSAIDs, non-steroidal anti-inflammatory drugs; PDA, patent ductus arteriosus; PHT, pulmonary hypertension; RDS, respiratory distress syndrome; SD, standard deviation

9.38 Characteristics of the prospective cohort studies (n=7)

Characteristics of the included prospective cohort studies with comparison group(s) and the reported adverse effects (three studies)						
Study ID	**Setting**	**Inclusion criteria**	**Ibuprofen group**	**Comparator**	**Adverse effects (n)**	**Notes**
Bourgoin 2016 **(321)**	Multi-centre (three NICUs) France Jan 2003-Dec 2011	GA: 24-28 weeks	hs-PDA (ECHO) 10-5-5 mg/kg (route not mentioned) N = 248	No hs-PDA N = 505 hs-PDA (ECHO) treated with surgical ligation N = 104	Ibuprofen= 146 No treatment= 209 Surgical ligation=37	
Pourarian 2008 **(324)**	Single centre Iran 2001 Over six months period	GA: < 37 weeks within ten days of life; hs-PDA (ECHO)	Oral ibuprofen:10-5-5 mg/kg every 24 hours; two further courses if needed N = 10	Oral indomethacin 0.2mg/kg for three doses at 24 hours intervals; two further courses if needed N = 10	Ibuprofen = 1 Indomethacin = 1	
Varvarigou 1996 **(361)**	Single centre Canada Feb 1993 - Aug 1993	BW: < 1500g and GA: < 32 weeks	IV ibuprofen:10-5-5 mg/kg every 24 hours within three hours of birth N= 12 Single dose of IV ibuprofen (10mg/kg) within three hours of birth N=11	IV saline N= 11	Ibuprofen three doses = 5 Ibuprofen one dose =8 Saline = 10	

Characteristics of the included prospective cohort studies without comparison group(s) and the reported adverse effects (four studies)					
Study ID	**Setting**	**Inclusion criteria**	**Ibuprofen protocol**	**Adverse effects (n)**	**Notes**

Bersani 2011 **(360)**	Single centre Italy Jan 2000-Nov 2007	GA: <28 weeks	PDA prophylaxis within two hours of birth: 10-5-5 mg/kg every 24 hours. Second course if PDA persisted after 72 hours; if still persistent: indomethacin	72	Treatment discontinued in 11 neonates (pulmonary hypertension)
Cherif 2007 **(322)**	Single centre Tunisia May 2005-Sept 2006	GA: <32 weeks and BW: <2000g, 48-96 hours old, RDS + PDA (ECHO)	PDA treatment: Oral 10-5-5 mg/kg every 24 hours	56	
Sahin 2016 **(323)**	Single centre Turkey Oct 2011-Apr 2014	GA: < 33 weeks with hs-PDA (ECHO)	PDA treatment: Oral 10-5-5 mg/kg every 24 hours. Three courses given if hs-PDA (ECHO) after each course	4	
Tantawy 2011 **(325)**	Single centre Egypt Jan 2009 – Sept 2009	GA< 34 weeks RDS+PDA (ECHO)	PDA treatment: Oral 10-5-5 mg/kg every 24 hours. Second course of 20-10-10mg/kg every 24 hours if PDA persisted	15	

ECHO, echocardiography; hs, hemodynamically significant; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome

9.39 Characteristics of the retrospective cohort studies (n=26)

Characteristics of the included retrospective cohort studies with comparison group(s) (16 studies)

Study ID	Setting	Inclusion criteria	Ibuprofen group	Comparator	Adverse effects (n)	Notes
Bauer 2011 **(326)**	Single centre USA 2006-2010	PDA and treated with either ibuprofen or indomethacin	N = 99	Indomethacin N = 101	Ibuprofen group = 11 Indomethacin group= 9	Conference abstract Dose regimen not stated
El Hassan 2014 **(327)**	40 centres USA Jan 2007-Dec 2010	BW <1000 g Neonates with clinical symptoms and PDA (ECHO)	N = 306	Indomethacin N = 426	Ibuprofen = 357 Indomethacin = 516	Dose regimen not stated
Fanos 2004 **(328)**	Single centre Italy 1995 - 2001	GA < 30 weeks, BW ≤ 1300 g	IV ibuprofen: 10-5-5 mg/kg every 24 hours N = 20	Indomethacin: three doses 0.2 mg/kg every 12 hours N = 20 No treatment N = 20	Ibuprofen =1 Indomethacin =none No treatment =1	Second course of same treatment if PDA persisted followed by surgical ligation
Gulack 2015 **(329)**	Multi-centre USA 2006-2012	GA < 28 weeks received either drug between days 2 and 14	N = 1177	N = 5172	Ibuprofen = 645 Indomethacin =2415	Dose regimen not stated
Heo 2012 **(330)**	Single centre Korea Jan 2008-Dec 2010	PDA (ECHO)	Oral ibuprofen:10-5-5 mg/kg every 24 hours N = 22	IV Indomethacin: three doses every 12 hours (< 48 hours of life, 0.2 -0.1-0.1mg/kg; 2–7 days of life 0.2 mg/kg; and > 7 days of life, 0.2 -0.25 - 0.25 mg/kg,). N=27	Ibuprofen =12 Indomethacin =21	Study all included “mature infants” defined as ≥37 weeks gestational age. These were excluded from the review

Katakam 2010 **(331)**	Single centre USA Nov 2005-Nov 2007	Symptomatic PDA (ECHO) with at least one dose of ibuprofen or indomethacin	Oral ibuprofen:10-5-5 mg/kg every 24 hours N = 57	Indomethacin: three doses every 12 hours intervals (< 48 hours of life, 0.2 -0.1 -0.1 mg/kg; 2–7 days of life 0.2 mg/kg; and > 7 days of life, 0.2 - 0.25 - and 0.25 mg/kg). N = 65	Ibuprofen = 25 Indomethacin = 34	Prophylactic indomethacin in ibuprofen group
Kushnir 2011 **(333)**	Single centre USA 2005-2008	Any neonate requiring treatment for PDA	Ibuprofen:10-5-5 mg/kg every 24 hours N = 182	Indomethacin: (< 750 g: 0.2-0.1-0.1 mg/kg/dose ; 750 g to 1 kg: 0.2-0.2-0.2 mg/kg/dose ; > 1kg: 0.2 mg/kg/dose). N = 161	Ibuprofen = 195 Indomethacin = 169	No prophylactic indomethacin used
Lee 2011 **(334)**	Single centre Taiwan Jan 2005-Dec 2010	BW <1500g, age 48-96 hr, hs-PDA (ECHO)	Oral ibuprofen:10-5-5 mg/kg every 24 hours N = 52	IV indomethacin:(<48 hours of life, 0.2 -0.1-0.1 mg/kg; 2-7 days of life, 0.2 mg/kg; & > 7 days of life, 0.2 - 0.25 - 0.25 mg/kg) N = 88	Ibuprofen = 20 Indomethacin = 86	
Linder 2010 **(335)**	Single centre Israel Jan 2000 – June 2003	PDA (ECHO)	IV ibuprofen:10-5-5 mg/kg every 24 hours N=73	IV indomethacin: 0.2-0.2-0.2 mg/kg every 12 hours N=46	Ibuprofen = 45 Indomethacin = 62	No prophylactic indomethacin used. Course repeated if no closure
Munoz-Garcia 2015 **(336)**	Single centre Spain Jan 2011-Nov 2012	GA ≤ 32 weeks	Hs-PDA treated with ibuprofen N = 9	PDA (not hs-PDA)- No treatment N = 20	Ibuprofen =7 No treatment=6	

Rheinlaender 2009 **(343)**	Single centre German 1998-2003	Hs-PDA received indomethacin or ibuprofen	Ibuprofen:10-5-5 mg/kg every 24 hours N= 91	Indomethacin: three doses every 12 hours of 0.2 mg/kg, then 0.1 mg/kg daily for six days; N = 87	Ibuprofen = 125 Indomethacin =90	
Salas 2017 **(344)**	Single centre USA Jan 2004-Dec 2013	GA 24 -31 weeks; BW 500 - 1500 g, and survival > 7 days	IV ibuprofen: 10-5-5 mg/kg every 24 hours N=96	IV indomethacin: three doses based on age N=102 No treatment N=401	Ibuprofen= 4 Indomethacin=3 No treatment =21	
Sivanandan 2013 **(345)**	Single centre Canada Mar 2009- Feb 2011	GA < 32 weeks received at least one dose of ibuprofen or indomethacin for symptomatic PDA	IV ibuprofen: 10-5-5 mg/kg every 24 hours N=70	IV indomethacin: three doses 12 hourly based on age N=54	Ibuprofen =68 Indomethacin =52	
Tefft 2010 **(346)**	Single centre USA Jan 2005 – June 2008	BW: < 1500 g	Early treatment: at day one of life: IV ibuprofen 10-5-5 mg/kg every 24 hours N=80 A second course given, if ECHO confirmed PDA at day three	IV indomethacin in neonates with PDA (ECHO): Protocol not given N=105	Ibuprofen= 55 Indomethacin =82	
Vida 2009 **(348)**	Single centre Italy Jan 2001-June 2007	PDA after 48 hours of life (GA<32 weeks) received ibuprofen	IV ibuprofen in three different cycles. Each cycle: 10-5-5 mg/kg every 24 hours N=201 First cycle: N=92 Second cycle:	Surgical ligation N=52	First cycle=55 Second cycle=22 Third cycle=13 Total for ibuprofen =90 Surgical ligation=60	ECHO 24 hours after last dose of first cycle to determine subsequent courses and/ surgical ligation

			N=45 Third cycle: N=12			
Yang 2013 **(349)**	Single centre Korea Jan 2007 – June 2011	BW <1000 g with PDA (ECHO)	Oral ibuprofen: 10-5-5 mg/kg every 24 hours N=22	IV indomethacin: three doses based on age N=26	Ibuprofen =31 Indomethacin =38	ECHO performed after first dose to determine subsequent doses

Characteristics of the included retrospective cohort studies compared different ibuprofen regimen (six studies)

Study ID	Setting	Inclusion criteria	Ibuprofen regimes	Adverse effects (n)	Notes
De Carolis 2011 (41)	Single centre Italy 2000-2008	GA ≤ 28 weeks received course of prophylactic ibuprofen of 10-5-5 mg/kg every 24 hours	Ibuprofen lysine N = 156 Ibuprofen sodium N = 60	Ibuprofen lysine = 41 Ibuprofen sodium = 32 Total = 73	
Dornelles 2016 **(364)**	Single centre Brazil Jan 2010–Dec 2013	All neonates received IV ibuprofen	Low-dose ibuprofen: 10-5-5 mg/kg daily N = 44 High dose ibuprofen: 20-10-10 mg/kg daily N = 33	Low dose= 45 High dose = 32 Total = 77	
Meißner 2012 **(337)**	Single centre Germany	All neonates received ibuprofen for PDA	High dose ibuprofen: 20-10-10 mg/kg daily N = 23 Low-dose ibuprofen: 10-5-5 mg/kg daily N = 19	Low dose= 3 High dose = 3 Total = 6	

Mekkhayai 2015 **(338)**	Single centre Thailand Jan 2010 – Dec 2014	GA <37 weeks with clinical and/or PDA (ECHO) and received three doses of ibuprofen	Standard:10-5-5 mg/kg every 24 hours N = 63 High dose: 10-10-10 mg/kg every 24 hours N = 63	Low dose= 11 High dose = 12 Total = 23	
Olukman 2012 **(341)**	Single centre Turkey Apr 2009 – Jun 2010	hs-PDA (ECHO) at 24-48 hours of age	Oral = 24 IV = 42 10-5-5 mg/kg every 24 hours. Second or third doses given if PDA persisted	Oral = 39 IV= 70 Total = 109	
Van der Lugt 2012 **(347)**	Single centre Netherlands Nov 2005-sept 2011	GA <32 weeks treated with ibuprofen	IV ibuprofen: (10-5-5 mg/kg every 24 hours) N=164 received one course; then 43 received second course and 11 received third course	First course= 14 Second course=1 Unspecified after which course=14 Total=29	ECHO performed 24 hours after third dose to determine subsequent courses / ligation

Characteristics of the included retrospective cohort studies without comparison group(s) (four studies)

Study ID	Setting	Inclusion criteria	Ibuprofen protocol	Adverse effects (n)	Notes
Kim 2016 **(332)**	Single centre South Korea Jan 2010-Dec 2014	BW < 1500 g received ibuprofen for symptomatic PDA	IV or oral: 10-5-5 mg/kg every 24 hours N = 144	30	
Ndour 2016 **(339)**	Single centre France 2009 -2014	All neonates treated with ibuprofen	Dose regimen not stated N = 227	49	Conference abstract

Olgun 2016 **(340)**	Single centre Turkey 2008 – 2010	Neonates with hs-PDA	Oral: 10-5-5 mg/kg every 24 hours ECHO after 3rd dose – if hs-PDA persists second and third course given as needed N= 97	27
Rao 2011 **(438)**	Single centre USA Jan 2007 – Oct 2009	Neonates with PDA treated with ibuprofen	IV ibuprofen: (10-5-5 mg/kg every 24 hours)	136

BW, birth weight; ECHO, Echocardiography; GA, gestational age; hs, hemodynamically significant; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome

9.40 Final ethics approvals for the review of neonatal formularies study

University of Nottingham
UK | CHINA | MALAYSIA

Email: FMHS-ResearchEthics@nottingham.ac.uk

Faculty of Medicine & Health Sciences
Research Ethics Committee
c/o Faculty PVC Office
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham, NG7 2UH

16 April 2018

Dr Shalini Ojha
Clinical Associate Professor of Neonatology
Division of Medical Sciences & Graduate Entry Medicine
School of Medicine
Royal Derby Hospital Centre
Uttoexeter Road
Derby
DE22 3DT

Dear Dr Ojha

Ethics Reference No: 283-1803– **please always quote**	
Study Title: **RE**view of Neonatal Drug **F**ormularies and other Practice Guidelines used **I**n **NE**onatal units across UK.	
Short Title: REFINE study **Acronym:** REFINE	
Chief Investigator/Supervisor: Dr Shalini Ojha, Clinical Associate Professor of Neonatology, Division of Medical Sciences & Graduate Entry Medicine	
Lead Investigators/student: Ms Asma Al-Turkait, PhD	
Other Key Investigators: Sharon Conroy, Associate Professor, Division of Medical Sciences and Graduate Entry Medicine, Lisa Szatkowski, Associate Professor in Medical Statistics, Division of Epidemiology and Public Health.	
Type of Study: Review of existing practice guidelines, PhD	
Proposed Start Date: 01/04/2018	**Proposed End Date:** 01/04/2019 12mths

Thank you for submitting this straightforward application which did not require a full committee meeting review and the following documents were received:

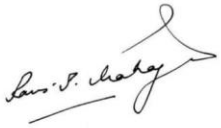
- FMHS REC Application form and supporting documents version 1.0: date 29/03/2018.

These have been reviewed and are satisfactory and the study has been given a favourable opinion.

A favourable opinion has been given on the understanding that:

1. The protocol agreed is followed and the Committee is informed of any changes using a notice of amendment form (please request a form).
2. The Chair is informed of any serious or unexpected event.
3. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely



Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

9.41 A copy of the invite email letter to participate in the study

University of Nottingham
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School of Medicine
Division of Medical Sciences and
Graduate Entry Medicine
University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road
Derby, DE22 3DT

Invitation to contribute to

"**RE**view of Neonatal Drug **F**ormularies and other Practice Guidelines used **I**n **NE**onatal units across UK"

(REFiNE study)

Investigators: Asma Al-Turkait, Sharon Conroy, Shalini Ojha

Paediatric Pharmacology Group, School of Medicine,

University of Nottingham, UK

Dear Colleagues,

We are writing to request your contribution to our study. Thank you very much for taking time to read this.

As you are aware, newborn infants, particularly those born preterm, are vulnerable to inappropriate prescribing due to their small size and immaturity. The problem is further compounded by the lack of research and evidence for rational prescribing in this population. Our literature review revealed that currently, there are no prescribing tools available for use in neonatal practice.

We are collecting information from all neonatal units in the UK to investigate the current guidelines and polices for prescribing and drug use in neonatal units in the UK. We will then put together all this information to describe the current practices including variations and identify the most important drugs used in neonatal medicine as a first step to creating a tool for drug prescribing for newborn infants.

This study has been reviewed and approved by the Faculty of Medicine and Health Sciences (FMHS) Research Ethics Committee **(FMHS Ref no: 283-1803)**.

What do we need form you?

For this study, we would be very grateful if you would share your hospital's neonatal drug formulary, any guidelines that refer to prescribing (such as a guideline for management of Patent Ductus Arteriosus that contains information on how to prescribe ibuprofen), and any other document that contains drug related information. These may include Paediatric or adult guidelines that are used on your neonatal units.

How can you send us this information?

If you have this information in an electronic format, please email them to mzxaa9@nottingham.ac.uk

If the information can be obtained via an accessible website, please send the web link to the above email address.

If you have the information in paper format, please send us an email at the above email address and we will send you a pre-paid envelope for posting the information.

Contact for further information

If you have need any further information about the study or would like to share any other information or idea, we would love to hear from you. Please email or write to us: our addresses are given at the end of this letter.

University of Nottingham
UK | CHINA | MALAYSIA

School of Medicine
Division of Medical Sciences and Graduate Entry Medicine
University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road
Derby, DE22 3DT

Best wishes,

Asma Al-Turkait
PhD Student
School of Medicine
University of Nottingham
Medical School Building
Derby, DE22 3DT
mzxaa@nottingham.ac.uk

Sharon Conroy
Associate Professor
Room 4119
Medical School
Royal Derby Hospital
Uttoxeter Road
Derby DE22 3DT
sharon.conroy@nottingham.ac.uk

Shalini Ojha
Clinical Associate Professor of Neonatology
School of Medicine
University of Nottingham
Room 4117,
Medical School Building
Derby, DE22 3DT
shalini.ojha@nottingham.ac.uk

9.42 Benzylpenicillin in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2 UNIT-3	UNIT-4	UNIT-5A	UNIT-5B	UNIT-6
Indication	Treatment of infections for term and preterm neonates	First line antibiotic if streptococcal infections suspected or proven Initial treatment of suspected sepsis acquired at birth	• Sepsis • Meningitis	Infections	• EOS • GBS meningitis • NEC	• EOS • Meningitis
Dosage regimen	• GA (< 30 week) and postnatal age 0-28 days:50mg/kg 12 hourly • GA (< 30 weeks) and postnatal age > 28 days: 50mg/kg 8 hourly • GA (30-36 weeks) and postnatal age 0-14 days: 50mg/kg 12 hourly • GA (30-36 weeks) and postnatal age > 14 days: 50 mg/kg 8 hourly • GA (37-term) and postnatal age 0-28 days: 50 mg/kg 8	• <7 days: 50mg/kg 12 hourly • 7 to 28 days: 50mg/kg 8 hourly • >28 days: 50mg/kg 6 hourly	• Sepsis: 60 mg/kg • Meningitis (suspected): < 7 days: 100 mg/ kg IV 12 hourly. If > 7 days: 8 hourly. If > 28 days: 6 hourly	• < 7 days: 50mg/kg twice daily • 7-28 days: 50mg/kg three times/day	• EOS: 25mg/kg every 12 hours • GBS meningitis: 50mg/kg 12 hourly for 14 days	• EOS: IV Preterm: 50mg/kg/dose two times daily, Term < 7 days: 50mg/kg/dose 2 times daily. Term 7 to 28 days: 50mg/kg /dose 3 times daily • Meningitis: Preterm neonate: 75 mg/kg/dose 3 times daily

	hourly, GA (37-term) and postnatal age > 28 days: 50mg/kg 6 hourly					
Instruction for administration	IV over 5-30 minutes	IV over 3-5 minutes Doses > 50mg/kg give IV infusion over 15 minutes to avoid CNS toxicity	Over 15 - 30 minutes	Not stated	Not stated	Slow IV Bolus / infusion over 5-30 minutes
Contra-indications	Not stated					
Cautions	Avoid cephalosporins and other beta-lactams in penicillin allergy	For incompatible drugs use separate line. Flush between drugs	Not stated	Not stated	Not stated	Longer administration time in high doses to avoid CNS toxicity and convulsions
Monitoring for adverse effects	CNS toxicity and convulsions	Not stated	Not stated	Adjust in renal impairment	Not stated	Large doses cause hypokalaemia or hypernatremia

Comparison	**UNIT-7**	**UNIT-8**
Indication	• EOS: 1st line • Meningitis	• Sepsis • Meningitis • NEC
Dosage regimen	• EOS: < 7 days: 25 mg/kg every 12 hours; change to 25mg/kg every 8 hours. 7-28 days: 25 mg/kg every 8 hours (50 mg/kg every 8 hours in severe infection)	50mg/kg 12 hourly up to 7 days

	• Meningitis: < 7 days: 50 mg/kg every 12 hours. Neonate 7-28 days: 50 mg/kg every 8 hours	
Instruction for administration	IV bolus over 3 - 5 minutes (peripheral) or IV infusion over 30 minutes	IV
Contraindications	Not stated	
Cautions	high doses/severe renal impairment (CNS toxicity, convulsions)	Not stated
Monitoring for adverse effects	Not stated	

CNS, central nervous system; EOS, early onset sepsis; GBS, group B streptococcal meningitis; NEC, necrotising enterocolitis; IV, intravenous

9.43 Gentamicin in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2	UNIT-3	UNIT-4	UNIT-5A	UNIT-5B	UNIT-6	UNIT-7	UNIT-8
Indication	Infections	Infections of Gram-negative organisms and staphylococci		Infections	Infections	• NEC • EOS • Meningitis	• EOS • LOS	Sepsis	EOS
Dosage regimen	< 32 weeks: 5mg/kg 36 hourly ≥32 weeks: 5mg/kg 24 hourly	<7 days: 5mg/kg 36 hourly ≥ 7days: 5mg/kg 24 hourly		< 32 weeks: 3mg/kg 36 hourly ≥32 weeks: 4mg/kg 36 hourly	< 28 weeks: 4mg/kg 36 hourly ≥28 weeks: 4mg/kg 24 hourly		< 32 weeks: 5mg/kg 48 hourly ≥32 weeks: 5mg/kg 24 hourly	< 7 days: 5mg/kg/dose 36 hourly ≥7 days: 5mg/kg/dose 24 hourly	
Instruction for administration	IV infusion over 30 minutes IV injection over 3-5 minutes	IV bolus over 3-5 minutes		IV	Not stated	Not stated	Slow IV bolus over 3-5 minutes	IV bolus by peripheral cannula or central line over 5 minutes	Slow IV over at least 3 minutes
Contraindications	Not stated							Not stated	
Cautions	Only intrathecal preparations used intrathecally	Not stated		Not stated	Not stated		Not stated	Ototoxicity	Ototoxicity

Monitoring for adverse effects	Trough: 6 hours before 3rd dose (6 hours before 2nd dose if poor renal function, or child is unstable) Therapeutic levels:<2mg/L	Trough: **B**efore 2nd dose. Therapeutic levels: 5-10mg/L	Ototoxicity Trough: Before the 2nd and 3rd doses Therapeutic levels: < 2mg/L	Adjust in renal impairment. Trough at 2nd and 4th dose. Therapeutic levels: < 2mg/L		Not stated	Trough: Before 2nd dose Therapeutic levels: ≤ 2mg/L	Trough: Before 2nd dose
EOS, early onset sepsis; LOS, late onset sepsis								

9.44 Cefotaxime in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2 UNIT-3	UNIT-4	UNIT-5A	UNIT-5B	UNIT-6	UNIT-7	UNIT-8
Indication	Infections	Gram negative and Gram-positive infections Meningitis	LOS (1st line)	Infections	Meningitis	Treatment of severe infection & meningitis	infections	Gram negative or suspected meningitis
Dosage regimen	< 7 days: 50mg/kg 12 hourly ≥ 7days: 50mg/kg 6-8 hourly	< 7 days: 50mg/kg 12 hourly ≥7 days: 50mg/kg 6-8 hourly 21-28 days: 50mg/kg 6 hourly	< 7 days: 50 mg/kg 12 hourly > 7 days: 50mg/kg 8 hourly > 21 days: 50mg/kg 6 hourly	< 7 days: 25-50 mg/kg 12 hourly 7-21 days: 25-50 mg/kg 8 hourly 21-28 days: 25-50 mg/kg 6 hourly			< 7 days: 50 mg/kg 12 hourly 7-20 days: 50mg/kg 8 hourly 21-27 days: 50mg/kg 6 hourly	< 7 days: 50mg/kg 12 hourly 7-20 days: 50mg/kg 8 hourly ≥21 days:50 mg/kg 6 hourly
Instruction for administration	IV injection: Over 3-5 minutes IV infusion: Over 20-60 minutes	IV over 3-5 minutes	Not stated	Not stated			IV bolus over 3-5 minutes or intermittent IV infusion over 30 minutes	Slow IV
Contraindications	Use alternative if cephalosporin allergy	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated

Cautions	Late-onset neutropenia and eosinophilia (reversible)	Not stated	Not stated	Not stated		Not stated	Not stated
Monitoring for adverse effects	Late-onset neutropenia and eosinophilia (reversible)	Not stated	Not stated	Adjust in renal impairment		Not stated	Not stated

LOS, late onset sepsis; IV, intravenous

9.45 Flucloxacillin in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2 UNIT-3	UNIT-4	UNIT-5A	UNIT-5B	UNIT-6	UNIT-7	UNIT-8
Indication	Infections	Infections of Gram positive organisms (staphylococci)	Infections	Infections	Infections and Staphylococcal skin infection	• Suspected staphylococcal infections • Osteomyelitis, cerebral abscess, staphylococcal meningitis	Infections	Skin and systematic infection
Dosage regimen	< 7 days: 25-50mg/kg 12 hourly, 7-21 days: 25-50 mg/kg 8 hourly > 21 days:25-50 mg/kg 6 hourly	< 7 days: 50mg/kg 12 hourly 7-21 days: 50mg/kg 8 hourly	< 7 days: 25 mg/kg 12 hourly 7-21 days: 25mg/kg 8 hourly > 21 days: 25mg/kg 6 hourly	< 7 days: 25-100 mg/kg 12 hourly 7-21 days: 25-100 mg/kg 8 hourly 21-28 days: 25-100 mg/kg 6 hourly		Not stated	< 7 days: 25 mg/kg 12 hourly 7 to < 21 days: 25mg/kg 8 hourly ≥21 to < 28 days: 25mg/kg 6 hourly	Skin infections: < 7 days: 25mg/kg 12 hourly 7-21 days: 25mg/kg 8 hourly ≥21 days: 25mg/kg 6 hourly
Instruction for administration	IV over 3-5 minutes	IV over 3-5 minutes	Not stated	IV	Not stated	Over 3-5 minutes	IV bolus over 3-4 minutes. Or intermittent IV infusion over 30 minutes	Not stated
Contraindications	Not stated	Not stated		Not stated		Not stated	Not stated	

Cautions	Cholestatic jaundice may occur several weeks after treatment stopped	Not stated	Caution in hepatic impairment	Not stated	Cholestatic jaundice	
Monitoring for adverse effects	Cholestatic jaundice	Not stated	Adjust in renal impairment	Not stated	Not stated	
IV, intravenous						

9.46 Caffeine (citrate) in neonatal formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2	UNIT-3	UNIT-4	UNIT-5A	UNIT-5B	UNIT-6	UNIT-7	UNIT-8
Indication	Neonatal Apnoea								
Dose regimen	Loading: 20mg/kg (IV/oral) Maintenance: 10mg/kg/day. Maximum: 10mg/kg twice a day	Loading: 20mg/kg Maintenance: 5mg/kg once daily Maximum: 10mg/kg daily		Loading: 20 mg/kg (IV/oral) Maintenance (24 hour post loading): 5 - 10 mg/kg	Loading: 20 mg/kg (IV/oral) Maintenance: 10mg/kg once to twice daily		Loading: Neonate to 6 months: 20mg/kg/dose (IV) Maintenance: 5mg/kg/dose once daily	Loading: 20mg/kg (IV infusion) over 30 minutes Maintenance : 5mg/kg once daily IV infusion over 10 minutes Same for oral	Loading: 20mg/kg infusion over 1 hour Maintenance: 10mg/kg once daily bolus over 5 minutes. For oral: loading 20mg/kg as two doses 10mg/kg two hours apart then maintenance 10mg/kg daily
Instruction for administration	Slow IV over 30 minutes.	IV or oral centrally due to low pH but can be given peripherally. Loading: IV over 30 minutes		IV slowly over 30 minutes.	Not stated	Not stated	Slow IV over 3 – 5 minutes centrally	IV infusion over 30minutes or slow IV over 10 minutes	Not stated
Contraindications	Not stated	Not stated		Not stated			Not stated	Not stated	Not stated

Cautions	Not stated	Stop if symptoms resolved and at corrected GA of 34 weeks	Not stated		Care with calculating doses and administration volumes	IV bolus cause sudden changes in blood pressure	Seizures and death reported at levels >50mg/l (255µmol/L)
Monitoring for adverse effects	if levels required, trough taken once the patient stabilised on maintenance dose. Therapeutic range: 8-30mg/L. Toxicity: > 50mg/L.	Monitor levels if not responding to treatment, or evidence of toxicity.	Range 10-35 mg/l. Monitor levels if not responding to treatment, or evidence of toxicity.		Extravasation risk. Tachycardia is first sign of toxicity. Seizures, circulatory collapse and death occur with ten times the recommended dose	Only request levels if suspect possible toxicity	Monitor levels if not responding to treatment, or evidence of toxicity. Half life is approximately 100 hours. Discontinue for at least 5 days before discharge with monitoring

9.47 Morphine in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2	UNIT-3	UNIT-4	UNIT-5A	UNIT-5B
Indication	• Analgesia (moderate to severe pain) • NAS	Not stated	• Pain/sedation • NAS	• Intubation • NAS	• Analgesia • NAS	• Sedation • Intubation • NAS
Dose regimen	• Analgesia: IV, 100 mcg/kg 6 hourly adjusted according to response • NAS: 40 mcg/kg 4 hourly, increase by 20mcg/kg/dose until stabilise. Continue for at least a week. Reduce frequency at 2-7 day basis to 6, 8,12, and 24 hourly. Discontinue at a dose of 40mcg/kg/daily.	loading dose: 100mcg/kg infused over 1 hour. Maintenance dose: 10 mcg/kg/hr. (maximum 40mcg/kg/hr)	• Pain/sedation: IV: 50-100 mcg/kg • NAS: 40 mcg/kg every 4 hours	• Intubation: 100 mcg/kg reduce to 50 mcg/kg if on infusion • NAS: 0.5 mg/kg/day in 4 divided doses- adjust to response	• Analgesia: Bolus: 50 - 100 mcg/kg • NAS: 40 mcg/kg 4 hourly -adjust to response	• Sedation: 50 mcg/kg over 5 minutes, follow by infusion between 10 - 40 mcg/kg/hr • Intubation: 50-100 mcg/kg for term neonate. 25-50mcg/kg for preterm neonate. • NAS: oral morphine solution 0.2 - 0.5mg/kg/day
Instruction for administration	IV over at least 5-10 minutes	Not stated	Not stated	Slow IV bolus	Not stated	Not stated
Contraindications	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Cautions	Increased susceptibility to	Not stated	Not stated	Not stated	Not stated	Not stated

	respiratory depression					
Monitoring for adverse effects	Respiration	Not stated	Not stated	Do not use if hypotensive	Not stated	Not stated

Comparison	**UNIT-6**	**UNIT-7**	**UNIT-8**
Indication	• Sedation • Pain • Intubation	• Intubation • Analgesia • NAS	• Pain • Sedation • NAS
Dose regimen	• Sedation/analgesia: continuous IV in neonate-6 months: 5-40mcg/kg/hour. • Intubation: IV 100mcg/kg/dose One dose only. Repeated once if necessary	• Intubation: IV 100 mcg/kg/dose, repeat if required • Pain: loading IV 50 mcg/kg/dose over at least 5 minutes then continuous IV infusion 5 - 20 mcg/kg/hour adjusted according to response • NAS: Oral 40mcg/kg 4 hourly,30mcg/kg 4 hourly then 20mcg/kg 4 hourly then 10mcg/kg 4 hourly. Reduced every 24-48 hours if feeding well and settling between feeds	• General dosing; IV bolus of 25 – 100mcg/kg/dose over at least 5 – 10 minutes. Infusion: Loading 50 – 100mcg/kg IV over 30 minutes then 5-40 mcg/hour • Oral short-term pain relief: 200mcg/kg orally, then 50mcg/kg/dose 6 hourly if required
Instruction for administration	Pain: IV preferred, IM used when no IV access.	Not stated	Not stated
Contraindications	Not stated	Not stated	Not stated
Cautions	Do not flush a line containing morphine (potent drug)	Not stated	Not stated
Monitoring for adverse effects	Not stated	Neonates with increased susceptibility to respiratory depression, have increased sensitivity and decreased metabolism of morphine	Not stated

NAS, neonatal abstinence syndrome; IV, intravenous

9.48 Poractant in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2	UNIT-3	UNIT-4	UNIT-5A	UNIT-5B	UNIT-6	UNIT-7	UNIT-8
Indication	RDS (treatment and prophylaxis)			Not stated	RDS		RDS (treatment and prophylaxis)	RDS	RDS-also term neonates with significant lung disease (meconium aspiration, pneumonia)
Dosage regimen	Treatment: 200mg/kg, then 100mg/kg 12, 24 hourly if necessary. Maximum: 300-400mg/kg. Prophylaxis: 100-200mg/kg (within 15 minutes of birth) Maximum: 300-400mg/kg	Not stated		Treatment: 100- 200 mg/kg, repeat within 12 hours if still intubated at 100mg/kg. Maximum: 300-400 mg/kg. Prophylaxis :100 - 200 mg/kg (within 15 minutes of birth); 100 mg/kg repeated 6 - 12 hours if still intubated	First dose: 100 – 200 mg/kg. then 100mg/kg for second and subsequent doses. Maximum: 400 mg/kg	Not stated	Treatment: 100-200mg/kg/ dose Prophylaxis: 100 -200 mg/kg for all neonates (BW: 600g - 1200g)	Unable to access the information	First dose :120 mg in delivery suite to all neonates GA < 30 weeks require intubation and ventilation for presumed RDS

Instruction for administration	Intra-tracheal		Intra-tracheal	Not stated	Intra-tracheal		Not stated
Contraindications	Not stated		Not stated		Not stated		
Cautions							
Monitoring for adverse effects							

RDS, respiratory distress syndrome

9.49 Indomethacin in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-5A	UNIT-5B	UNIT-6	UNIT-8	
Indication	PDA-second line after ibuprofen	PDA	PDA	PDA	PDA-first line	
Dose regimen	All doses IV at 12-24 hours. Depending on the age at time of first dose: <48 hours: 200-100 -100 mcg/kg 2-7 days: 200 - 200 - 200 mcg/kg > 7 days: 200-250-250 mcg/kg Or IV injection 100mcg/kg 24 hourly for six doses	IV: 100 mcg/kg once daily for six doses Alternative short course (if normal renal function): same UNIT-1	Not stated	Prophylaxis: IV 200mcg/kg, then 100mcg/kg 12, 24, 48 hourly Early symptoms (2-6 days): IV 200 mcg/kg -100 mcg/kg 12, 24, 48 hourly. If PDA persisted after 4th dose, continue with 5th and 6th dose at 100mcg/kg 24 and 48 hourly Late symptomatic (> 7 days): IV 200mcg/kg , repeated every 12, 24, 48 hourly. Further course given if required	Not stated	No available information in UNIT 2 to UNIT 4, and UNIT 7
Instruction for administration	Over 20 minutes	Not stated		Over 20 – 30 minutes		
Contraindications	History of asthma, angioedema, urticaria and rhinitis to aspirin or any other NSAID or with coagulation defect	Not stated		Not stated		
Cautions	Reduces in cerebral blood flow (20-minute infusion preferred to bolus)	Avoid in severe hepatic impairment		Not stated		
Monitoring for adverse effects	Reduces glomerular filtration	Monitor renal function		Withhold dose if urine output <1 ml/kg/hr during the preceding 8 hours		

9.50 Ibuprofen in neonatal drug formularies and clinical practice guidelines

Comparison	UNIT-1	UNIT-2	UNIT-3	UNIT-5A	UNIT-5B	UNIT-6	UNIT-7	UNIT-8
Indication	PDA	PDA	PDA	PDA	PDA	PDA	PDA	PDA (2nd line)
Dose regimen	IV doses 10-5-5 mg/kg 24 hourly. Repeat if PDA persisted after 48 hours of first course				Not stated	IV doses 10-5-5 mg/kg 24 hourly. Repeat if PDA persisted after 48 hours of first course		
Instruction for administration	IV injection over 15 minutes	Short infusion over 15 minutes	Short infusion over 15 minutes	Not stated		Short infusion over 15 minutes	Slow IV injection over 15 minutes	Not stated
Contra-indications	History of asthma, angioedema, urticaria or rhinitis to aspirin or any NSAIDs or coagulation defect				Not stated			Abdominal distension, NEC, platelet count < 100,000, bleeding problem, renal impairment
Cautions	Use in renal, cardiac or hepatic failure	Not stated		Avoid in severe hepatic failure	Not stated	Use in renal, cardiac or hepatic failure	Not stated	Not stated
Monitoring for adverse effects	Weight, urine output, platelet function and severe hyper-bilirubinaemia	Not stated		Monitor renal function	Not stated	Monitor renal and GI function. Extra-vasation risk	Bleeding. If anuria or oliguria (<0.5ml/kg/hour) after 1st or 2nd dose, withhold next dose until urine output rises at least 0.5ml/kg/hr	Stop treatment if bleeding. Monitor platelet, creatinine, lactate, and electrolytes
No available information from UNIT-4								

THE END