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Vaccination Timeliness in Preterm Infants

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Helen Sisson

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Dedication

This work is dedicated to all the infants and parents whose data have contributed to these findings.

It is also dedicated to those who do the extremely important work of researching, teaching, promoting, and administering vaccines.

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Publications and conference presentations emanating from this work

Sisson, H. (2021) Celebrating World Immunisation Week: Why Vaccination Matters. *Evidence-Based Nursing*. 25 April. Available online: Celebrating World Immunisation Week: Why Vaccination Matters | Evidence-Based Nursing blog (bmj.com) [Accessed 18/08/2021].

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Abstract

Background

Vaccination is a key public health activity, with established programmes primarily aimed at infants and children. Infants born prematurely are particularly vulnerable to infection, therefore the protection vaccination offers these infants is vital. Nonetheless, early reports specified that compared with their full term counterparts, preterm infants experience unwarranted delays in receiving vaccines. A contemporary review of the global literature indicated that the delay persists, however, the review also revealed a lack of research based on UK populations.

Aim

Taking a population-based approach, this study aimed to investigate the existence of a vaccination delay for preterm infants, and identify any factors associated with vaccination timeliness.

Design and methods

Using existing datasets, the study analysed data for infants born over a six-month period; this comprised of 4605 infants, and immunisation timeliness was studied for the primary series at eight, 12 and 16 weeks.

Findings

This study does not support the findings of previous research which has reported a negative correlation between gestational age and birthweight, and vaccination age. However, compared with their full term peers, infants classed as moderate to late preterm, or moderately low birthweight, experience greater delays for some vaccines at some of the series visits. The same delays were not observed in infants classed as very preterm,

extremely preterm, or very low birthweight. None of the additional infant or parental characteristics studied influenced timeliness.

Conclusion

The moderate nature of infants' prematurity and birthweight suggests that the delays observed in these infants more closely reflects immunisation practices in the community. It is important that all health professionals involved with families in the early weeks, regardless of care setting, promote and recommend vaccination. Parents should be offered individualised support with their decision making, which is provided by appropriately trained staff who are also knowledgeable of vaccine coverage in their area.

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Abbreviations

BCG	Bacille Calmette-Guerin (vaccine against tuberculosis)
BW	Birthweight
CAG	Confidentiality Advisory Group
CCG	Clinical Commissioning Group
CDSR	Cochrane Database of Systematic Reviews
CHIS	Child Health Computer System
CINAHL	Cumulated Index to Nursing and Allied Health Literature
CRD	Centre for Reviews and Dissemination
DTP	Diphtheria, Tetanus, Pertussis
DTaP	Diphtheria, Tetanus, acellular Pertussis
ELGAN	Extremely low gestational age neonate
GP	General Practitioner
HepB	Hepatitis B
HEXA	Hexavalent vaccine
Hib	Haemophilus Influenzae type b
HPV	Human Papilloma Virus
HRA	Health Research Authority

IPV	Inactivated Polio Vaccine
IRAS	Integrated Research Application System
LAIV	Live Attenuated Influenza Vaccine
LBW	Low birthweight
MenACWY	Meningococcal groups A, C, W and Y
MenB	Meningococcal group B
MMR	Measles, Mumps and Rubella
MSDS	Maternity Services Dataset
NDS	Neonatal Dataset
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNRD	National Neonatal Research Dataset
NNU	Neonatal Unit
ONS	Office for National Statistics
OPV	Oral Polio Vaccine
PCV	Pneumococcal Conjugate Vaccine
PHE	Public Health England
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SAGE	Strategic Advisory Group of Experts
SOC	Standard Occupation Classification
Td	Tetanus and (low dose) Diphtheria
UK	United Kingdom
US	United States
WHO	World Health Organisation

Chapter 1 Introduction

1.1 The rationale for this study – why this research is needed

Vaccination is central to the prevention of infectious diseases and it is estimated that globally established immunisation programmes prevent between two and three million deaths each year (World Health Organisation (WHO), 2021a). Children are the main focus of such programmes because they are most at risk of certain infections should they contract them. The immunisation schedule in the UK is largely accepted, and this is evidenced by coverage statistics (NHS Digital, 2020). However, there are pockets of poor coverage and it is vital to know where under vaccination is occurring so that work can be initiated to address it.

For optimum protection against vaccine preventable diseases, all infants regardless of gestational age should be vaccinated according to recommendations, yet preterm infants are a population who have been identified at risk of a delay in receiving their vaccines (Sisson, 2014; Gagneur et al., 2015). This is concerning, because preterm infants are more vulnerable to infection (Petty, 2017) making timely vaccination imperative.

This study investigates the existence of a delay in preterm infants in a region of England and explores factors associated with vaccination timeliness. This is done using a secondary data analysis design and accessing data from large existing datasets. The study's findings aim to inform practice and policy, with the overarching intention of reducing any observed vaccination delays in preterm infants.

Exploration of this phenomenon was also influenced by my professional practices; I have spent many years of my nursing career talking with patients and parents about vaccines, administering vaccines, teaching other professionals about vaccines, and have been part of a clinical trials team which has researched vaccines. These experiences have engendered a strong sense of advocacy for vaccination.

1.2 Overview of chapters

Chapter two begins by discussing the key concepts of the study, where prematurity and the increased risk of infection in preterm infants are explored. Current vaccination guidance in relation to all infants (including preterm infants) is presented. This chapter also introduces the role of the theory in supporting research.

The selected theoretical perspective of the determinants of vaccine uptake (Thomson et al., 2016) is described in chapter three. Alternative theories are considered, but the rationale for the selected perspective is argued.

Chapter four presents a detailed review of the literature. This demonstrates a systematic approach which examines published research investigating vaccination timeliness in preterm infants. A narrative analysis of the research is presented which subsequently leads the justification of this study.

Chapters five and six provide details of the study's methodology and methods. The methodology (chapter five) presents the rationale for the approach and design of the study, and defines the research question. The methods (chapter six) define the processes undertaken.

The results of the study are presented in chapter seven and this consists of descriptive and inferential analyses designed to answer the research question. Chapter eight is the discussion chapter where the study's findings are contextualised. The findings are considered in light of previous research and current policy and practice.

The final chapter (chapter 9) concludes the study and emphasises recommendations for practice and further research.

Chapter 2 Background

2.1 Introduction

This chapter introduces concepts which are central to the research topic, namely those of prematurity and vaccination, as well as considering relevant theory. Section 2.2 considers the use of a theoretical framework, following which, sections 2.3, 2.4 and 2.5 discuss aspects relevant to preterm birth and low birthweight, including the incidence and potential causes. The relationship between gestational age and birthweight is examined and the risks associated with both are identified. Specifically, the risk of infection to the preterm infant and importance of vaccination are the focus in sections 2.6 and 2.7, followed by section 2.8 which considers the guidance in place to support the practice of vaccinating preterm infants. An initial exploration of the literature identifies the perception of a delay in vaccination in preterm infants, contrary to established guidance (section 2.9). Whilst section 2.2 discusses the significance of using a theoretical framework, the selected theory is discussed in greater depth in chapter 3.

2.2 Theoretical framework

Aveyard (2019) explains that theory provides structure for the literature review, and that it allows clarification of key concepts. Coughlan and Cronin (2017) define the theoretical framework as a specific relevant theory with the purpose of providing structure to a research study. This definition is supported by the rationale that the literature review and theoretical framework are the foundations of any research project (Rockinson-Szapkiw, n.d.). Whilst the literature exploring the use of theoretical frameworks in research tends to support the views of Aveyard (2019) and Rockinson-Szapkiw (n.d.), it is expressed and may be interpreted differently depending on whether a qualitative or quantitative research approach is used. From a quantitative perspective, Creswell (2014:54) defines theory in research as “an interrelated set of constructs (or variables) formed into propositions, or hypotheses, that specify the relationship among variables (typically in terms of magnitude

or direction).” Essentially, this definition may be translated as providing the rationale as to why, and to what extent does independent variable X influence dependent variable Y; it is this explanation of a theoretical framework in quantitative approaches, that influenced the selected theory which is discussed in chapter three. The remainder of this chapter explores the concepts associated with the vaccination of preterm infants and justifies the use of this particular framework, which is discussed in greater depth in chapter three.

2.3 The preterm infant

In human development, the normal period of gestation is deemed to be between 37 and 40 weeks, with infants born on or after 41 weeks and three days classified as post-term and infants born alive prior to 37 weeks gestation considered to be preterm (Petty, 2017). Based on gestational age, the World Health Organisation (WHO) (2021b) define sub-categories of prematurity: moderate to late preterm (32 - <37 weeks), very preterm (28 - <32 weeks) and extremely preterm (<28 weeks).

Statistics concerning preterm births have been available from countries with established systems for collecting such data for some time; for example, the latest findings show that the rate of preterm births in the United Kingdom (UK) varies between areas from 4 – 11% (NHS Digital, 2019) with data from the first quarter of 2021 averaging at approximately 7-8% (NHS Digital, 2021). In the United States (US), this is greater at 10% (Centers for Disease Control and Prevention, (CDC), 2020). Bronstein et al. (2018) suggest that the rate is higher in the US compared with other developed countries because of poorer maternal health and greater financial disparity; the rate of multiple birth is also greater with more assisted pregnancies. The wider international picture regarding preterm birth was less well known until a collaboration between the WHO and member states published an analysis of worldwide estimated preterm birth rates, and the findings of this analysis suggested a global increasing trend in preterm births (Blencowe et al., 2012). However, a more recent analysis

of global birthweight data suggests some decrease in the rate of infants born with a birth weight considered to be low (Blencowe et al., 2019); the relationship between birthweight and gestational age is explored in section 2.4.

In up to half of the cases of spontaneous preterm birth the cause is unknown (Menon, 2008), although epidemiological studies have identified that an individual and family history of preterm birth are strong risk factors (Plunkett & Muglia, 2008). Other associations point towards maternal aspects such as the age of the mother, multiple pregnancy, low maternal body-mass index and maternal infections (Goldenberg et al., 2008; Mugila & Katz, 2010). Petty (2017) highlights maternal lifestyle and low socioeconomic status as contributory factors to preterm birth. In high income countries half of all infants born prior to 25 weeks survive (Petrou et al., 2006); conversely, in low-income and many middle-income countries, infants do not have access to basic care facilities and many of these infants die as a result of their prematurity (Blencowe et al., 2012).

2.4 Prematurity and birthweight

At birth, infants may also be grouped according to their weight with a weight of less than 2500g considered as low (Blencowe et al., 2019). Further sub-divisions are also cited as 1500g-2499g being defined as a moderately low birthweight, and <1500g as a very low birthweight (Martin et al., 2015). The identification and classification of prematurity has been variable because the relationship between preterm birth and birthweight is complex; even in the scientific literature between the 1920s and the 1960s the terms ‘premature’ and ‘low birthweight’ were used interchangeably (Wilcox, 2001). Preterm birth is a major cause of low birthweight (WHO, 2021b), but infants can be born at term yet small for gestational age (Lissauer & Clayden, 2012). Clearly described by Meeks and Cusack (2013) and Lissauer et al. (2020) infants are considered to be small for gestational age if they have a birthweight below a defined centile on an appropriate growth chart; these infants are fully

developed and have not been born prematurely. The term intrauterine growth restriction (IUGR) is used to describe infants who have failed to meet their predicted growth potential *in utero* and this may be due to maternal factors such as diabetes, chronic hypertension, substance abuse or other autoimmune conditions. IUGR can also be caused by placental abnormalities such as chorioangioma, infarction or circumvallation, or foetal factors (for example infection, malformation) (Guiliano et al., 2014). These infants are often also small for gestational age but this is not always the case (Meeks & Cusack, 2013).

Historically, infants were defined as preterm if their weight at birth was 2500g or less (Pusey & Haworth, 1969), but it soon became clear that not all infants weighing less than the defined 2500g were actually preterm and the notion of prematurity was replaced with one of low birthweight (Wilcox, 2001). Estimated delivery dates are now calculated in early pregnancy, and these are often confirmed by an ultrasound scan during the first trimester when certain foetal measurements are taken (Boyle, 2011). This advanced monitoring during pregnancy allows gestational ages to be assessed with much greater accuracy.

Birthweight is still widely used as an important public health indicator because it provides a measure which summarises maternal problems including poor nutrition, ill health and antenatal care (Blencowe et al., 2019). An infant's birthweight is a precise measure which is often freely available in large quantities making it a popular variable to study (Wilcox, 2001). Although there is an association between gestational age and birthweight, they are not synonymous. For instance, in South Asia a substantial proportion of infants are born with a low birthweight in spite of having reached gestational maturity; these are full term infants who are small for gestational age (Barros et al., 2011) but only compared with infants from the UK for example. To address this, in the UK it is recommended that the ongoing monitoring of intrauterine growth is recorded on customised growth charts (Royal

College of Obstetricians and Gynaecologists (RCOG), 2014). The customisation of growth charts allows for adjustments to maternal characteristics such as height, weight, parity and ethnic group, making these growth charts better predictors for infants at risk of being born small for gestational age (RCOG, 2014).

Whether at birth, infants are classified according to gestational age or birthweight, it is generally accepted that it is detrimental for an infant to be born with a low birthweight and that preterm birth is the primary cause of death, morbidity and disability (Blencowe et al., 2012). It is estimated that 50,000 infants are born prematurely each year in England and Wales (Office for National Statistics, 2020a).

2.5 Complications of preterm birth

Infants born prematurely face specific risks which are dependent on the extent of their prematurity. For example, respiratory distress syndrome is a condition commonly associated with infants born below 32 weeks gestation, and for infants born before 34 weeks gestation which is when the coordinated suck and swallow process develops, feeding difficulties are common (Lissauer et al., 2020). Added conditions associated with prematurity include jaundice, brain injury and thermoregulation, all of which require immediate intensive therapy (Lissauer & Clayden, 2012). Prematurity can also have a lifelong impact on an individual in terms of neurodevelopmental functioning, impaired learning and visual disorders as well as an increased risk of chronic disease in adulthood (Mwaniki et al., 2012). In addition to the clinical issues associated with preterm birth, the economic cost of care provision is high, from the initial neonatal intensive care provided, through to the provision of services aimed at meeting continuing health and educational needs of individuals (Blencowe et al., 2012). Hodek et al. (2011) outline the cost incurred by parents of preterm infants, from both a monetary and quality of life perspective. However, it is the immediate threat to life which remains the primary concern and one such

threat is infection (Petty, 2017), the incidence of which increases nine-fold for the preterm infant (Sinha et al., 2012).

2.6 Infection in preterm infants

Infants of all gestational ages are vulnerable to infection. This is because although the immune system begins developing very early in foetal life, it is not sufficiently matured to function effectively until at least one year of age (Sinha et al., 2012), and this fact alone means that the infant is already disadvantaged should an infection occur. Table 2.1 is adapted from work by Sinha et al. (2012) and Lissauer et al. (2020) and it outlines some of the additional endogenous and exogenous factors which predispose the infant to infection.

Table 2.1 Infection risk factors

Endogenous factors	Exogenous factors
Decrease in number and function of neutrophils Phagocytosis less effective Decreased complement levels Low levels of IgM and IgA (antibody type) Less effectively functioning lymphocytes	Clinical procedures causing a breach in skin barrier Medication use which may impair immune function

The likelihood of the factors listed in Table 2.1 are increased in the preterm infant; for example, repeated clinical procedures such as venepuncture are more possible. Compared with their full term peers, preterm infants are also more at risk of the listed endogenous factors, increasing their susceptibility to infection and vaccine preventable diseases (Bonhoeffer et al., 2006).

Protection against infection via placental antibody transfer provides the infant with vital immunity in the first few weeks of life (Blackburn, 2013; Albrecht & Arch, 2020). This process begins *in utero* as early as 13 weeks and is remarkably efficient with the cord blood

of term infants showing IgG levels which correlate with maternal levels (Palmeira et al., 2012). This mode of passive protection has been exploited more recently through the concept of maternal immunisation, with pertussis vaccination routinely recommended for all pregnant women (PHE, 2016a). The vast majority of transplacental transfer occurs after week 32 of gestation (Healy & Baker, 2006), meaning that infants born before this time have not benefitted from this important protection, leaving them even more vulnerable to infection; indeed a systematic review by van den Berg et al. (2011) investigating the transplacental transfer of IgG against vaccine preventable diseases, found that levels of IgG increase with gestational age, which suggests that the earliest born infants are afforded the least protection.

In the postnatal period and without being specific, the life span of antibodies acquired *in utero* is difficult to predict (Glezen, 2003). Edwards (2003) found that whilst at birth, cord blood IgG levels in term infants for pertussis almost equated to maternal levels, by four months of age the rate of decay was such that almost no antibody could be detected in infants; furthermore, van den Berg et al. (2011) suggest that this rate of antibody decay may be even more rapid in preterm infants as their study found that IgG levels fall below protective levels earlier in life for this population compared with their full term peers.

2.7 Vaccination in preterm infants

For infants, an immunisation programme needs to be timed to provide optimal protection at the earliest opportunity; equally, the existence of maternal antibodies may interfere with the infant's immune response to vaccination (Glezen, 2003), so identifying the ideal time to commence an immunisation programme is a challenge. Although immunisation schedules vary globally (WHO, 2019), the widely accepted age at which to commence vaccination is at six to eight weeks of age. Table 2.2 illustrates the specified age at first vaccination from some selected countries. These are shown to demonstrate that regardless

of the country, the age at which the vaccine programme is started is consistent across the globe. Those countries where the programme is initiated earlier do so due to epidemiological data which indicate a greater risk of infection.

Table 2.2 Age at first vaccination in selected countries.

Country	Age at first vaccination
Argentina	8 weeks
Australia	8 weeks
India	6 weeks
Nigeria	6 weeks
South Africa	6 weeks
UK	8 weeks
USA	8 weeks

The current routine childhood vaccination schedule in the UK is illustrated in Table 2.3. This is an up to date schedule at the time of writing (Summer 2021). The first vaccines routinely offered at eight, 12 and 16 weeks are referred to as the primary course or primary series. The vaccines programmed for this time offer protection against nine infections: diphtheria, tetanus, pertussis, polio, haemophilus influenzae type b, hepatitis B, pneumococcal disease, meningococcal disease group B and rotavirus.

Table 2.3 Routine childhood vaccination schedule in the UK (PHE, 2020a).

Age vaccine(s) offered	Vaccine
8 weeks	DTaP/IPV/Hib/HepB + MenB + Rotavirus
12 weeks	DTaP/IPV/Hib/HepB + PCV + Rotavirus
16 weeks	DTaP/IPV/Hib/HepB + MenB
1 year	Hib/MenC + MenB + PCV + MMR

Those in eligible year group	LAIV
3 years 4 months	DTaP/IPV + MMR
12-13 years	HPV
14 years	Td/IPV + MenACWY

When the current vaccines scheduled as part of the primary course are considered, studies have previously indicated that generally, the ability of the preterm infant to mount an effective immune response to them is good. It is explained that the prevention of infection (or protection) correlates with the stimulation of specified antibodies, or immune response (Plotkin, 2010), and it is the level of these antibodies which are used as a measure of protection. Gagneur et al. (2015) reviewed the evidence available on several vaccines, and with the exception of MenB, these included all the vaccines given as a primary course in the UK; the review reported that the preterm immune response to these vaccines shows adequate levels of protection. More specifically, Saari et al. (2003), Bonhoeffer et al. (2006) and D'Angio (2007) all reported immune responses to the DTP/IPV/Hib components of the vaccines which were considered to be at a protective level, but they also reported that as prematurity increased, protective levels decreased. Similarly, Rouers et al. (2020) described a decrease in protective levels alongside an increase in prematurity, but they also reported found lower levels of protection in preterm infants for the Hib component of the vaccine, even after a booster dose at 12 months.

Vaccinating preterm infants with the PCV also produces an adequate level of protection, although this is lower than the level seen in term infants (Saari, 2003; Bonhoeffer et al., 2006; D'Angio, 2007; Rouers et al., 2020). The data available for the rotavirus vaccine are limited although one study has reported that the preterm infant's immune response is comparable to that of a term infant (Omenaca et al., 2012). It is acknowledged that data examining the preterm immune response to MenB vaccination is also limited (this is could

still be considered as novel having just been used for the first time anywhere in 2015), and studies are ongoing (Kent et al., 2019).

In September 2019, HepB was introduced to the UK schedule and combined with DTaP/IPV/Hib into a hexavalent vaccine: DTaP/IPV/Hib/HepB. This particular vaccine has also been studied to look at its immunogenicity and reactogenicity in preterm infants (Omenaca et al., 2005). Here it was reported that preterm infants demonstrated a good immune response to all of the antigens in the vaccine, and that there was no difference observed with reactogenicity between term and preterm infants. Tan et al. (2017) studied the single HepB vaccine in preterm infants and reported adequate immune responses in preterm infants born to Hepatitis B surface antigen-positive mothers. It is worth noting that the studies cited here express their findings in terms of immunogenicity (the immune response to vaccination) and whilst this is not synonymous with the efficacy of the vaccine, or its ability to reduce the incidence of disease (Hannoun et al., 2004), in the science of vaccinology, immunogenicity is thought to be a reliable predictor of vaccine efficacy (Marshall, 2010).

For all infants, there is a risk of an adverse event following immunisation (AEFI) and the WHO (2020) classifies such adverse events into four categories (Table 2.4).

Table 2.4 Categories of AEFI (WHO, 2020).

Programme related	These are adverse events which are as a result of poor/inappropriate practices related to the provision of vaccinations

Vaccine induced	A reaction in an individual which is as a direct result of the vaccine administered or any of its component parts
Coincidental	These are not true adverse reactions to the vaccine but are events that would have occurred anyway, even if the vaccine had not been administered
Unknown	These are AEFIs for which there is not enough evidence to classify into any of the other categories

From a vaccine safety perspective, the focus rests with the AEFIs which are vaccine induced (WHO, 2020) and common events include local reactions such as erythema, pain and swelling at the site of the injection. Additional systemic reactions may also occur, and these can comprise of pyrexia, myalgia and irritability (PHE, 2012), however, an increase risk of fever is observed for MenB when administered alongside the other routine vaccinations at two and four months (PHE, 2016b). Much rarer vaccine induced AEFIs include anaphylaxis; the risk of this happening is reported as approximately one in a million and in the UK, of the cases where vaccination has resulted in anaphylaxis, no deaths have occurred (PHE, 2012). A review of cases of anaphylaxis occurring between 2008-2009 in the UK and Ireland reported that none of the recorded cases were related to the infant and preschool vaccination schedule (Erlewyn-Lajeunesse et al., 2012). Additionally, studying adults and children over a two-year period, McNeil et al. (2016) reported a rate of anaphylaxis as 1.31 per million doses; this emphasises the rarity of this event occurring. It is the whole cell pertussis component of DTP vaccination combinations which has been responsible for most of the more commonly seen vaccine induced AEFIs (WHO, 2014), and to address this problem less reactogenic acellular pertussis vaccines have been developed, since when, such events are much less regularly reported (WHO, 2014). When less serious adverse events do occur, these tend to be self-limiting and do not require

treatment although the administration of antipyretic and analgesic medications can be considered (PHE, 2012).

Compared with full term infants, preterm infants are able to tolerate the administration of routine vaccinations and an increase in the vaccine induced AEFIs previously described are not observed (Esposito et al., 2009; Chiappini et al., 2019; Kent et al., 2019). However, there have been several studies which have investigated the occurrence of apnoeic, bradycardic and desaturation events post immunisation and these have reported mixed results. Carbone et al. (2008) conducted a randomised controlled trial where no increase in apnoeic or bradycardic episodes were observed after administration of the DTP vaccination. Conversely, Schulzke et al. (2005) reported an increase in apnoeic and bradycardic episodes with Lee et al. (2006) and Faldella et al. (2007) also reporting an increase in desaturations. In these three studies reporting an increase in cardiorespiratory events, the vaccinations administered were DTP, Hib and IPV with two of the studies also including HepB (Schulzke et al., 2005; Faldella et al., 2007). Klein et al. (2008) studied DTP, Hib, HepB and PCV in preterm infants found that a history of pre-immunisation apnoea was a predictor for apnoeic events post-immunisation; furthermore, Hacking et al. (2010) reported an increase in apnoeic events only in preterm infants who had a history of septicaemia and prolonged ventilation after they had been vaccinated with DTP, Hib, OPV, PCV and HepB. Where such cardiorespiratory events occurred, these were reported as mainly being self-limiting and requiring minimal intervention, and a period of monitoring post-vaccination is recommended (Schulzke et al., 2005; Lee et al., 2006; Faldella et al., 2007). DeMeo et al. (2015) undertook a population-based study on extremely low birthweight infants. In this study the occurrence of sepsis evaluations, increased need for respiratory support, intubation, seizures and death were measured in the three days prior to and the three days post-immunisation. An increase in the amount of respiratory support and intubation was observed post vaccination, as was the incidence of sepsis evaluations.

However, similar to the findings of Hacking et al. (2010) who reported an increase in apnoeic events where a prior history of septicaemia and apnoea were recorded, DeMeo et al. (2015) observed that the rise in sepsis evaluations post-immunisation were associated with a former history of sepsis. Following the administration of MenB, findings in infants <28 weeks suggest an increased need for respiratory support (Mukherjee et al., 2018), although this has not been observed for infants with a greater gestational age (<35 weeks) (Kent et al., 2017). Most recently, Molanus et al. (2021) studied infants <33 weeks post discharge after the administration of the first DTaP/IPV/Hib/HepB and PCV at two months of age. Infants had their heart rate, respiratory rate and oxygen saturations constantly monitored for 24 hours post-vaccination and the incidence of clinically relevant cardiorespiratory events was not increased. The conflicting findings reported by the studies cited may be explained by heterogeneity in the methods used, such as differences between samples, data collection methods, and outcome measures.

The World Health Organisation reiterate the view that a vaccine which protects everyone and is entirely safe does not exist (WHO, 2020), but given the increased risk of infection associated with vulnerable preterm infants there is no apparent rationalisation for withholding vaccination (Esposito et al., 2009).

2.8 Current vaccination guidance

For the reasons already discussed in this chapter, prematurity is not a justification for delaying vaccination, and this is reflected in policies worldwide. Guidelines from the UK and the US, Canada and Australia all emphasise the importance of vaccinating preterm infants according to their chronological age (and not adjusting for prematurity). The American Academy of Pediatrics (2021) recognises that at a cellular level, preterm infants may not respond as well to vaccination as their full term peers, but that neither low birth weight nor low gestational age are contraindications to vaccination. Australian guidance

acknowledges the possibility of increased cardiorespiratory events post- immunisation and recommends a period of monitoring (Australian Government, 2020). Similarly, in the UK, PHE (2019a) highlight that the benefits of vaccination far outweigh the risk of non-vaccination and advise a period of monitoring after immunisation where indicated. This guidance corresponds with Canadian recommendations where additionally, owing to a potential lack of maternally derived antibodies, the vulnerability of preterm infants is emphasised (Public Health Agency of Canada, 2015). Whilst this current guidance regarding vaccinating preterm infants is resolute, this has not always been the case. It is suggested by Nicoll et al. (1988) and Begg and Nicoll (1994) that previously, a lack of evidence-based guidance and immunisation training created confusion around vaccination practices, including when to vaccinate "undeveloped" infants.

For all individuals, there are very few circumstances under which vaccination should delayed or not be administered at all. Generally, if a confirmed case of anaphylaxis has been attributed to a previous vaccine or any of its components, then vaccination is unequivocally contraindicated, and the decision to defer vaccination with a live vaccine is also justified if the individual is immunocompromised (owing to a disorder causing the immunodeficiency or because of immunosuppressive treatment) (PHE, 2017). Additional reasons for deferring vaccination which may result in a delay, are cited as recent receipt of immunoglobulin and cases where evolving or unstable neurological conditions are present. The presence of an acute illness characterised by systemic symptoms including a pyrexia may also be a reason to delay vaccination, although this is only to avoid incorrectly attributing any symptoms relating to the existing illness to the vaccination, rather than for immunological reasons (PHE, 2017). Yet, whilst these cited reasons for non-vaccination or deferral of vaccination apply to all individuals, not just preterm infants, it could be argued that preterm infants may warrant more vaccination delays compared with their full

term peers owing to the increased risk of prematurity related brain injuries and infection resulting in acute systemic symptoms (Sinha et al., 2012).

2.9 Vaccination practices in preterm infants

Much of the published material on vaccination in preterm infants acknowledges the immaturity of the infant's immune system and subsequent vulnerability to infection (Sinha et al., 2012). Equally, the immune response and safety of the vaccines are also considered, with the overarching message being that of the importance of timely vaccination in this population (PHE, 2017). However, the literature also indicates that vaccination in preterm infants is delayed.

Preliminary enquiries undertaken in the both US and the UK reported delays in this population as far back as 30 years ago. Vohr and Oh (1986) observed a delay in children who had been admitted to the special care nursery as neonates, and Wariyar et al. (1989) reported similar delays. Both studies acknowledged the existence of national guidance indicating that preterm infants should be vaccinated at the same time as their full term peers, but recognised the lack of local policies to support the countries' respective initiatives. The recommendation that preterm infants are vaccinated along with their full term peers was only introduced in the UK in 1988 which may account for the delay seen in the study by Wariyar et al. (1989). Additionally, Vohr and Oh (1986) cite the absence of local guidelines as a key influence behind vaccination delay and also attributes the lack of policy to the wide variations seen in practice in the US, both between neonatal centres and paediatricians.

Some contemporary enquiries have focused on practices concerning the rotavirus vaccination in the neonatal unit (Ladhani & Ramsey, 2014). This has been of particular interest because the vaccine is a fairly recent addition to the schedule, and because the two scheduled doses must be administered within specified timeframes to avert the debated risk of intussusception (PHE, 2015). Furthermore, this is a live attenuated vaccine which is

given orally and therefore, there is a theoretical risk of shedding the virus in the stool; a risk which may be magnified for vulnerable hospitalised infants. However, transmission is considered to be low risk and no additional measures other than the standard infection control practices are recommended (PHE, 2015), and Ladhani and Ramsay (2014) assert the importance of timely rotavirus immunisation for preterm infants, whether or not they are hospitalised. This recommendation is supported by Stumpf et al. (2013) whose study found that 63% of the preterm infants included did not receive the rotavirus vaccine because they were too old and had fallen outside of the recommended timeframe for administration.

The presence of a delay in vaccination among preterm infants can be seen as far back as three decades ago (Vohr & Oh, 1986; Wariyar et al., 1989), and although focussing on the rotavirus vaccination in the neonatal unit, more recently, the literature appears to support the notion that a delay still exists (Stumpf et al., 2013; Ladhani & Ramsay, 2014).

2.10 Conclusion

This chapter has explored concepts associated with the vaccination of preterm infants. The susceptibility of preterm infants to vaccine preventable diseases as discussed in section 2.5, and timeliness of vaccination in this population warrants further investigation. This is initially by way of a review of the literature, which is presented in chapter four. However, fundamental to this chapter has been the importance of timely vaccines for preterm infants, and the existence of a delay in them receiving them. This suggests that theories which have sought to explain this phenomenon are valuable in understanding and explaining it. Therefore, to support, guide and provide context to the remainder of this study, the determinants of vaccine uptake are identified, and chapter three explores this theoretical perspective in detail.

Chapter 3 Determinants of vaccine uptake: a theoretical perspective

3.1 Introduction

This chapter reiterates the position of a theoretical perspective, following which the rationale for the identified theory to support and guide the remainder of the study is presented. Initially, to further understand and explore the idea of a delay in vaccination, the use of an appropriate theory was deemed essential. Creswell and Creswell (2018) say that theory in quantitative research helps to explain phenomena and more specifically, can bridge the gap between dependent and independent variables. In such quantitative research approaches, the theoretical perspective is tested or verified, which is in contrast to qualitative approaches where the theory is developed (Creswell & Creswell, 2018). However, in reality, it was difficult to integrate any identified theory consistently throughout the work; this appeared at times to be counterintuitive, becoming a hindrance rather than a helpful guide. As a result, elements of the selected theoretical perspective were incorporated where this was relevant and appropriate, and this can be seen predominantly in chapters four, five and eight. Furthermore, being able to select a theory at the conceptual stage of the study was a challenge; it was hard to know what would be a helpful perspective without broadly knowing what it needed to feature. As a result, the consideration of theory was an iterative process, which evolved as the study progressed.

Whilst chapter two focused on the idea of vaccination delay in preterm infants, the issue of vaccination uptake has been more widely studied across populations. This has led to the term ‘vaccine hesitancy’ being identified as a concept associated with vaccine uptake. The theoretical perspective of vaccine hesitancy was initially proposed as a framework to help explain the findings, connecting them to what is already known on this theory. However, it became clear that vaccine hesitancy is not congruent with uptake, and that a broader perspective was required. This chapter explores the concept of vaccine hesitancy, which

leads to a discussion on the determinants of vaccine uptake, and identification of the selected framework.

3.2 Vaccine hesitancy

There is a wealth of evidence reporting on the significant impact vaccination has in the prevention of disease and associated morbidity and mortality, and public confidence in vaccination remains largely high in developed countries (Williamson & Glaab, 2018). Yet, there are still areas where vaccine uptake is low, and this is frequently explained through the lens of vaccine hesitancy. Whilst this is not a new phenomenon, it is one which is being used increasingly to explore the reasons behind why people may be resistant to vaccines – this could result in a delay in acceptance, or the refusal of vaccines completely.

Resistance to, and skepticism about vaccination are occurrences which have been observed for as long as vaccines have existed (Dube et al., 2021). The 1853 Compulsory Vaccination Act attempted to make small pox vaccination mandatory in England but was met with opposition from all sections of Victorian society; the arguments against this were based on enforced class legislation (Durbach, 2000). Some vaccines (smallpox in particular) also had very poor safety profiles, resulting in incapacitating side effects, and sometimes, even death (Gainty & Arnold-Foster, 2020). Such events from history perhaps reflect on some of the influences around hesitancy today, for example, fears about vaccine safety and the notion that vaccination is a political, rather than public health activity (Strategic Advisory Group of Experts, 2014). The distinction between hesitancy and the anti-vaccination movement is important to make; these paradigms are not the same, but anti-vaccination is a term often used interchangeably with vaccine hesitancy. Dube et al. (2021) state that vaccine hesitancy represents the space between the opposing stances of pro-vaccination and anti-vaccination. To understand reasons behind vaccine uptake, the term vaccine hesitancy has become a catchall notion, and one that has been widely explored to identify

strategies to increase coverage (Getman et al., 2018; Vrdelja et al., 2018; Kerrigan et al., 2020).

Dube et al. (2013) highlighted the model of a spectrum, that vaccine hesitancy exists on a continuum ranging from active demand for vaccines, to complete refusal of all vaccines. In 2011, the Strategic Advisory Group of Experts (SAGE) on Immunization observed that hesitancy to accept vaccinations was impacting on vaccine uptake in both developed and developing countries. This led to the formation of a working group specifically to investigate vaccine hesitancy, and the result was the publication of the 2014 Report of the SAGE Working Group on Vaccine Hesitancy (SAGE, 2014). The report quotes a definition of vaccine hesitancy, which is extensively cited in work exploring the phenomenon:

"Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccine services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence." (SAGE, 2014:7).

It was also once again noted that vaccine hesitancy could be viewed on a continuum ranging from full acceptance through to full refusal of all vaccines (Figure 3.1).

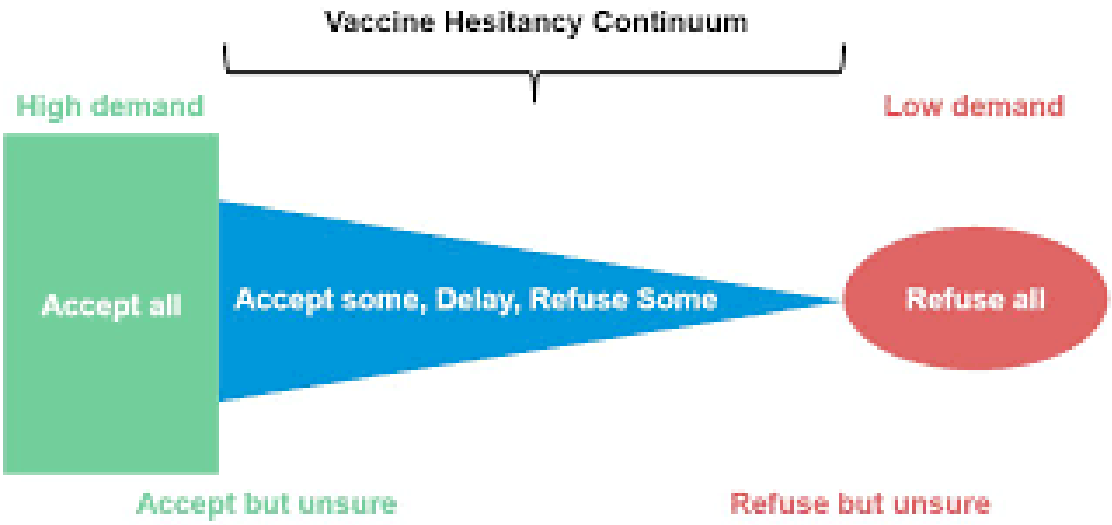


Figure 3.1 Vaccine hesitancy continuum (SAGE, 2014).

SAGE (2014) cite the influences of complacency, convenience and confidence (referred to as the "3Cs"), which are viewed as central components in the decision-making process and can be defined as followed:

Complacency – this influence emerges from the perception that the risk associated with vaccine preventable diseases is low, and therefore, vaccination is not a necessary action to take.

Convenience – this influence is defined as incorporating factors such as physical and geographical availability, affordability, understanding and vaccination appeal; more specifically, how these affect vaccine uptake.

Confidence – this is simply defined as trust; trust in the vaccines, trust in the service that delivers the vaccines and more widely, and trust in those who make the decisions around vaccine policy.

SAGE (2014) also developed a more comprehensive matrix to describe the complex nature of influences associated with context, individuals and groups, and specific vaccines, and

an overview of this is presented in Figure 3.2. McIntosh et al. (2016) say how important it is to be able to measure vaccine hesitancy so that appropriate solutions may be used to address the issues and based on the matrix (Figure 3.2) Larson et al. (2015) developed a survey tool to do just this.

Contextual influences Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors.	a. Communication and media environment b. Influential leaders, immunization programme gatekeepers and anti- or pro- vaccination lobbies. c. Historical influences d. Religion/culture/gender/socio-economic e. Politics/policies f. Geographical barriers g. Perception of the pharmaceutical industry
Individual and Group influences Influences arising from personal perception of the vaccine or influences of the social/peer environment.	a. Personal, family and/or community members' experience b. Beliefs, attitudes about health and prevention c. Knowledge/awareness d. Health system and providers-trust and personal experience. e. Risk/benefit (perceived, heuristic) f. Immunisation as a social norm vs. not needed/harmful
Vaccine/vaccination-specific issues Directly related to vaccine or vaccination	a. Risk/benefit (epidemiological and scientific evidence) b. Introduction of a new vaccine or new formulation or a new recommendation for an existing vaccine c. Mode of administration d. Design of vaccination programme e. Reliability and/or source of supply of vaccine and/or vaccination equipment f. Vaccination schedule g. Costs h. The strength of the recommendation and/or knowledge base and/or attitude of healthcare professionals

Figure 3.2 Vaccine hesitancy matrix (SAGE, 2014).

Whilst the meaning and scope of vaccine hesitancy have been described by SAGE (2014), there is some conflict with these descriptions. SAGE (2014) state that vaccine hesitancy is a behavioural phenomenon which results from the decision-making process, yet it is argued that hesitancy is actually a psychological state (Leask, 2015; Bedford et al., 2018). Whilst there are some differences here in the interpretation of this term, it is viewed that hesitancy is a natural part of the decision-making process, and Dube et al. (2021) state that ambivalence towards vaccination is based on legitimate doubts. Peretti-Watel et al. (2015) acknowledge that vaccine hesitancy is an ambiguous concept, and is not simply a behaviour, but can be associated with other behaviours (for example, information seeking). They go on to suggest that vaccine hesitancy may be better understood as a decision-making process. This is a psychological activity where the advantages and disadvantages of an action are weighed up, prior to arriving at a decision about a behaviour. There are links here to health promotion theory, specifically, decision-making about health actions. Many health promotion models consider how people have arrived at decisions about their health choices. Widely accepted and established health promotion models by Becker (1974) and Prochaska and DiClemente (1984) both cited in Green and Tones (2010), describe the processes an individual works through to arrive at their decision, with some indication of the process followed should a behaviour not be maintained (Prochaska & Di Clemente, 1984). The point here being that if vaccine hesitancy extends beyond matters associated with decision-making, over which an individual has no control, then actions developed to address it may be ineffective. Furthermore, Bedford et al. (2018) express concern about how the word 'hesitancy' has been interpreted, arguing that this term is frequently and inappropriately used when referring to uptake. For example, even though vaccination services may exist, some individuals or populations may face challenges with access for a variety of reasons, so the reason for delay is as a direct result of pragmatic issues, not an informed choice.

It is stated that the scope of the SAGE Working Group was to "categorize factors that influence the behavioral decision to accept a vaccine" (MacDonald & SAGE, 2015:4161), and there is a section in the report where the scope of vaccine hesitancy is reported as not applying in situations where the demand is low based on availability issues, such as lack of vaccines or access to them, unreasonable travel to receive vaccines and poor communication associated with the programmes. However, as previously established the term 'hesitancy' is incorrectly used to explain reasons associated with poor demand in populations, when in fact, reasons for this may be due to practical issues such as access (Bedford et al., 2018). This issue is emphasised when the influence identified as 'convenience' is considered in light of the definition provided for 'hesitancy'. To describe this, SAGE (2014) refer to concepts relating to both decision-making and system-level issues, such as geographical availability, despite also saying that such travel issues were not within the scope of the report. Therefore, vaccine hesitancy and under vaccination due to other determinants need to be distinguished to enable appropriate solutions to be put into place (Bedford et al. 2018).

The concept of vaccine hesitancy is important to investigate to address the causes of under-vaccination, but greater clarity in the delineation of choice and availability is needed. Some central terms are also open to interpretation, and may mean that certain influences are addressed inadequately. Because of this inconsistency, whilst some aspects of vaccine hesitancy may be of use to help explain both the findings of the literature review and the current study, it falls short of addressing other factors associated with sub-optimal coverage. It is acknowledged that vaccine hesitancy is not the same as vaccine uptake, but that also understanding the influences on hesitancy may provide an indication of actions needed to address low uptake. Leask et al. (2012) identify two broad factors associated with under-vaccination; the first is socioeconomic disadvantage, which may contribute towards a lack of access to the support and resources to get their children vaccinated (such as transport or

childcare), and second, factors due to parental concerns, perhaps about the safety of vaccines and need for vaccination are cited. Whilst there is ambiguity in the report (SAGE, 2014) over the inclusion of some factors associated with the influence of 'convenience', these are important reasons to consider if the aim of any subsequent recommendations is to increase demand; regardless of whether the causes are due to choice or access.

3.3 The determinants of vaccine uptake

It is argued that any attempt to better understand vaccine coverage must examine all influences. Therefore, the need for a theoretical perspective which encompasses all potential determinants was deemed important to elucidate the study's findings, and the ability of vaccine hesitancy to be able to do this was questioned. This led to the identification of the 5As (Table 3.1), a taxonomy for the determinants of vaccine uptake which was the result of a narrative review (Thomson et al., 2016).

Table 3.1 Definitions of the 5As

5As/Determinants	Definition
Access	How vaccines reach, or are reached by individuals
Affordability	Refers to financial and non-financial ability of individuals to afford vaccines
Awareness	How much knowledge individuals have of the need for and availability of vaccines, including the benefits and risks
Acceptance	The degree to which people either accept, question or refuse vaccines
Activation	The degree to which people are nudged towards vaccination

Further details relating to each determinant are characterised as follows:

Access – this includes where infants are born (acute or community settings), as well as geographical location. The level of contact with health care systems was also appropriate here, and convenience was a contributing factor, which included appointment availability.

Affordability – this not only refers to the ability to pay for or having the means to cover any financial costs, but also cost in terms of time. The need to take time off work (and not get paid as a result) to attend is also an issue here.

Awareness – educational level and poor knowledge about the vaccination programme are relevant barriers to timely immunisation, whereas conversely, those more informed may also not comply with recommendations. The amount of information and contact with a health professional are important influences on this determinant.

Acceptance – factors related to this determinant featured most commonly in the review findings, and include concerns about the vaccines (efficacy, safety, side-effects), and attitudes towards vaccination are also predictors in this determinant. Of equal relevance here, are perceived susceptibility and severity of the disease. Health beliefs are key components of this determinant, including the belief that natural infection is better than vaccination. Omission bias is also highlighted, meaning that the harmful result of any action is viewed less favourably than any negative outcome as a result of inaction. Trust is a feature of this determinant – trust in health professionals and vaccine policies. Acceptance aspects related to the social context include social responsibility, peer influence, and personal recommendations to vaccinate by a health professional were a strong normative influence.

Activation – this determinant includes processes such as reminder services, personal prompts and providing information in other contexts.

Some of these determinants seem to relate directly to pragmatic actions, such as access and affordability, whereas, acceptance appears more akin to vaccine hesitancy. It is reported that the determinant of activation was later added to encompass specific facilitators for vaccination (Thomson et al., 2016). This taxonomy was developed for practical application and as such, socio-demographic factors were excluded; it is stated that these factors cannot be influenced by interventions (Thomson et al., 2016). Even though socio-demographic characteristics may be challenging and even impossible to change, knowing how they might influence uptake is important so that targeted strategies can be developed. However, it could be viewed that these factors are implicit within some of the determinants. For example, access, affordability and awareness may all be influenced by socio-economic status or educational level, and it is recommended that a flexible approach is taken, rather than being accepted as a definitive categorisation.

This taxonomy of the determinants of vaccine uptake was deemed to be the most appropriate perspective to provide context and meaning to the topic area under scrutiny in this work.

3.4 Conclusion

This chapter has explained the need for theory to support research and identified the preferred theoretical framework to be used in the study. The overarching research question guiding this study is *'are vaccinations in preterm infants delayed and what are the factors associated with vaccination timeliness?'*

For the reasons discussed, the use of vaccine hesitancy as a theory on its own was not considered as an appropriate theoretical perspective to understand this, given its focus on decision-making and omission of other influential factors. Therefore, the taxonomy developed by Thomson et al. (2016) which characterises the broader determinants of vaccine uptake was selected. As previously noted, socio-demographic characteristics are

not included as a distinct aspect of this, but may be implicitly relevant. It is possible that explicitly acknowledging these characteristics would enhance the application of this taxonomy.

The following chapter explores published research on the question of a delay in vaccination for preterm infants. This is presented as a review of the literature, where Thomson et al's. (2016) taxonomy is referred to provide some meaning and highlight the significance of the findings.

Chapter 4 Literature Review

4.1 Introduction

The issues discussed in chapter two emphasise the necessity of immunising preterm infants, however, some of the literature suggests that vaccinations in this population are delayed. To investigate this concept thoroughly, this chapter presents a review of the published literature on this topic. Coughlan and Cronin (2017) consider that the literature review needs to adopt a systematic approach to demonstrate transparency in the process and methods chosen. An important point here is to distinguish between a literature review with a systematic approach and a systematic review. Aveyard (2019) defines a systematic review as being the most detailed way of reviewing the literature, and one where a team of dedicated researchers adhere to a strict protocol. Aveyard (2019) also describes characteristics of a systematic review such as a clearly defined search strategy and the development of inclusion and exclusion criteria. Whilst the review presented in this chapter adopts a systematic approach and may share some common characteristics, it is not an attempt at a systematic review.

The chapter describes the development of the review question and presents the search strategy which clearly defines how the studies included in the review were selected. The chosen method of appraisal is considered and a summary of the studies is presented, then the decision to use narrative synthesis as the method of analysis is justified and the analysis is presented. Finally, the discussion section interprets the findings of the review and identifies how these warrant further empirical investigation.

4.2 Search Strategy

The use of acronyms to guide the development of a review question is recommended and Aveyard (2019) suggests PICO(T) (population, intervention, comparison, outcome, (time)) and SPIDER (sample, phenomena of interest, design, evaluation, research). Bettany-Saltikov and McSherry (2016) also suggest PICO and as well as PE(I)O (population,

exposure (or issue), outcome). Both perspectives distinguish between the use of these acronyms, with PICO(T) being a suitable guide in the development of quantitative questions and SPIDER and PE(I)O being more suited to questions with a qualitative approach. Given that the aim of this review was to observe the timeliness of vaccination in preterm infants, the use of SPIDER and PE(I)O which support the development of a qualitative question initially seemed redundant. Equally, for quantitative approaches, PICO implies an intervention and comparison intervention need to be present. Again, the value of this acronym to the aim of the review was not immediately clear; whilst the identification of some of the component parts of PICO was relatively easy, this was less apparent elsewhere:

Population - The population of interest was preterm infants.

Intervention or **E**xposure – The term exposure was considered to be more suitable than intervention, because intervention implies an experimental element. Bettany-Saltikov and McSherry (2016) suggest that if an exposure is being studied, that this term should be used loosely. Therefore, when applied to the review question, this component was translated as vaccination.

Comparative intervention – Bettany-Saltikov and McSherry (2016) advise that it is possible to observe interventions without the inclusion of a comparative intervention and in these cases, this component can be omitted. Therefore, it seemed appropriate to disregard this.

Outcome – The outcome of interest was to identify any delay in vaccination, which may be measured as the time between the recommended age of vaccination and the actual age of the infant at the time of the scheduled vaccination.

The process of using one of the established acronyms to aid the development of the review question was complex and the result was that the review question actually took the form of the PEO acronym, previously associated with qualitative questions. Using these acronyms helped to ensure comprehensiveness and precision, but this required flexibility in the translation of the components.

The search strategy was guided by the question: *'are vaccinations in preterm infants delayed?'* Bell and Waters (2018) stress that one of the basic principles of literature searching is the development of focussed key words to allow the identification of relevant sources. Therefore, from this question, key words and related synonyms were identified and these are illustrated in Table 4.1. Boolean logic and truncation were applied to ensure that the search remained focused whilst still facilitating the capture of relevant studies (Machi & McEvoy, 2012).

Table 4.1 Search terms

	Key terms	OR	OR	OR	OR
	Vaccination*	Immunisation*	Immunization*		
AND	Preterm infant*	Pre-term infant*	Premature infant*	Premature	
AND	Delay*	Rate*	Uptake	Coverage	Timing

4.2.1 Databases searched

The decision to search the identified databases was made based on their relevance to the topic and subsequent potential to yield significant literature. The databases selected were Academic Search Premier, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Database of Systematic Reviews (CDSR) and Medline. Aveyard (2019) recommends the use of CINAHL given its propensity to nursing-based literature whist Medline also holds medical literature. It was felt that by searching both of these databases, most of the relevant literature on the topic would be identified. In addition,

Academic Search Premier was searched because of its multidisciplinary approach; vaccination is essentially a public health activity, thus not exclusive to nursing or medicine. The decision to search the CDSR presented a dilemma. Initially, because one of the inclusion criteria was that the literature included in the review needed to be primary research and that systematic reviews are summaries of existing evidence (Aveyard, 2019; Cochrane Library, 2021), it was considered inappropriate. However, the decision to search this database was justified by ascertaining if systematic reviews on the topic of vaccinating preterm infants had already been undertaken because this could have influenced the focus of the review. Searching these databases also ensured a global perspective to gain an idea of the wider practice of vaccinating preterm infants. The search terms cited in Table 4.1 were applied to the title and abstracts of the literature identified in the databases in December 2014; using the same methods, the search was repeated in June 2021 and nine additional papers were retrieved. Details relating to the second search are annotated in italics in the following search detail presented. It should be observed at this point that the decision not to include grey literature was made for pragmatics reasons. Both searches produced a number of studies which was deemed adequate for the review, although it is also noted that this decision may have excluded some insightful perspectives. The number of papers found in each database is illustrated in Table 4.2.

Table 4.2 Number of hits from both database searches.

Database	Number of papers
Academic search premier	154 + *157*
CINAHL	97 + *108*
Cochrane Library	234 + *271*
Medline	404 + *415*
Total	889 + *951*
After removal of duplicates (*n*=128 and *n=258*)	761 + *693*

4.3 Identification of the selected studies

The Preferred Reporting System for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009a) was adhered to during the process of selecting the relevant literature (Figure 4.1). Although this reporting system was developed for systematic reviews and meta-analyses, its use in this literature review can be justified by the principle that all research should be fully and transparently reported (Moher et al., 2009b). This review takes a systematic approach to reviewing the literature and the use of PRISMA (Moher et al., 2009a) provides assurance that it has been undertaken in a rigorous manner (Aveyard, 2019). As well as searching the identified databases, the reference lists of the selected studies were checked for any additional research which may have been included in the review, and this identified a further four sources. After the removal of duplicates, 1454 items of literature were screened by reading the abstracts to ascertain relevance, a process which was guided by the use of inclusion and exclusion criteria.

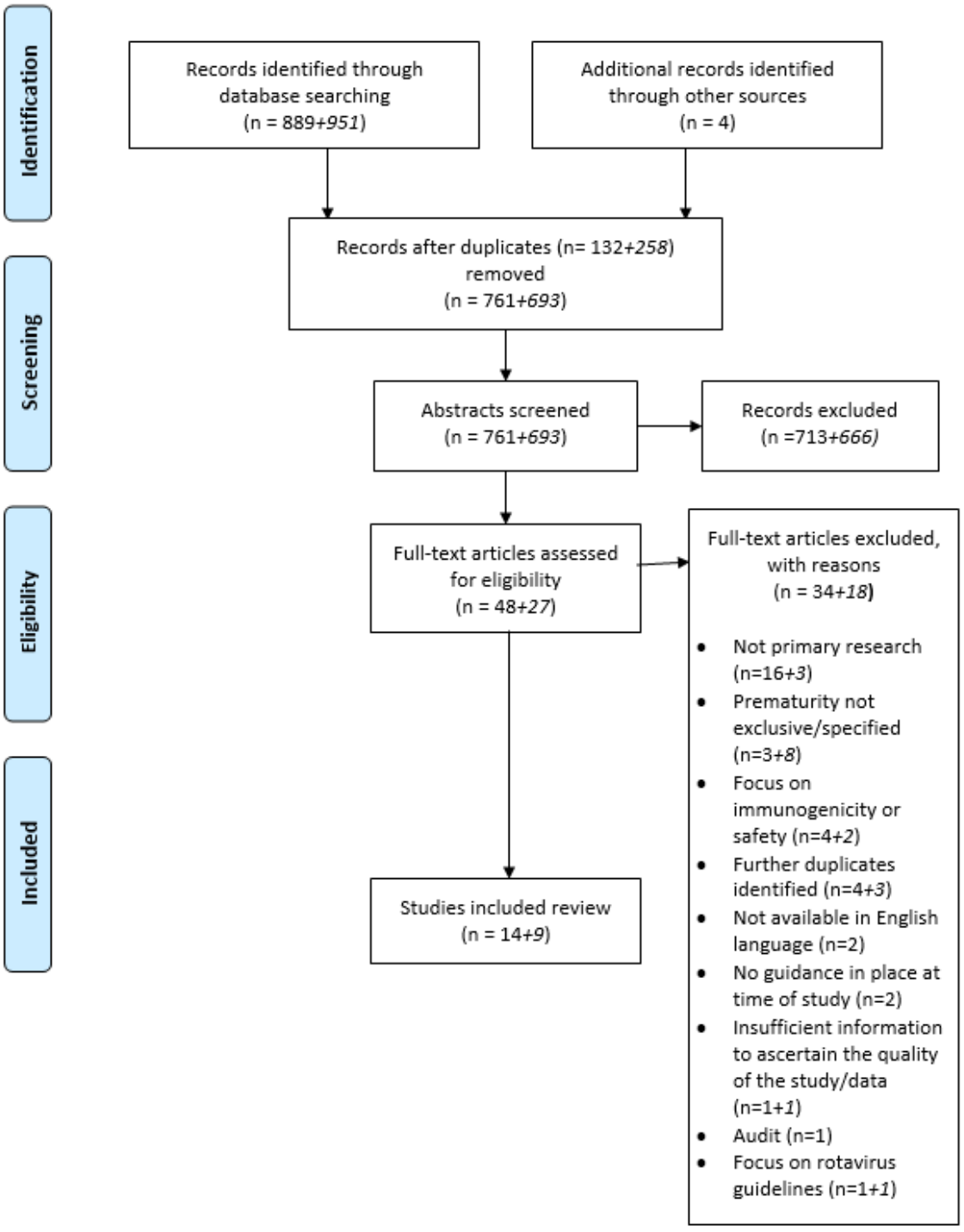


Figure 4.1 PRISMA flow diagram. (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009a).

4.4 Criteria for inclusion and exclusion of literature and selection process.

The use of inclusion and exclusion criteria is recommended to keep the review focussed and to avoid being drawn towards irrelevant literature (Aveyard, 2019). Oliver (2012) points out that given the nature of academia, the decision of whether or not to include certain literature is likely to be highly subjective therefore the validation of set criteria must be evident. A pragmatic approach was taken in the development of the criteria; it was important to retain the focus of the review whilst simultaneously justifying the associated criteria (Table 4.3).

Table 4.3 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Primary research Research addressing vaccination rates/timeliness in preterm infants Focus on routine scheduled vaccines Peer reviewed research Available in English language	Sources not peer reviewed No guidance in place regarding the timing of vaccinating preterm infants at time of study

It is widely acknowledged that the types of literature included in a review will be influenced by the topic and review question (Bettany-Saltikov & McSherry, 2012; Machi & McEvoy, 2012). The importance of primary research is asserted by Aveyard et al. (2016) due to it being the most reliable source of evidence which can be related to practice. Aveyard (2019) also refers to the concept of empiricism because primary research has been undertaken and reported first hand using a systematic approach. For this reason, it was deemed important to make this an inclusion criterion. Additionally, given the review question: 'are vaccinations in pre-term infants delayed?' it was important that any retrieved studies were able to directly address this. It was deemed appropriate to include both qualitative and quantitative research; it was possible that important insights could be gained from either at this stage of the study. Research which had been peer reviewed was an essential criterion

to ensure the quality of the studies included had been considered (Jolley, 2013). Oliver (2012) argues that even research which has been peer reviewed does not guarantee perfection although it has been subject to a degree of scrutiny by informed peers which does mean that quality checks will have been made. Incidentally, none of the papers were excluded on the basis that they were not peer reviewed; they were all published in peer reviewed journals. As established in chapter two, the vaccinations in focus for this review are routine scheduled vaccinations. Therefore, any research reporting on immunisation rates of unscheduled vaccines in preterm infants was excluded. The existence of established guidelines regarding the practice of vaccinating preterm infants at the time of the studies was also an important inclusion criterion. For the purpose of this review, it would be difficult to determine whether or not preterm infants were being vaccinated later than scheduled without having a standard against which to measure this outcome. Equally, it would be impossible to explore any findings alongside the determinants of vaccine uptake without the existence of any recommendations.

No date parameters were applied so that vaccination timeliness in preterm infants could be observed over time. Furthermore, whilst it is acknowledged that prematurity may be a risk factor for timely vaccination, the focus was to specifically explore this issue in these infants in comparison to full-term infants. For this reason, studies which reported on other reasons for vaccination delay in infants of all gestational ages were not included in the review.

For both searches a total of 1454 abstracts were screened and 1379 papers were excluded. The majority were excluded because they did not feature vaccination rates but rather, were focussed on the immunogenicity of the vaccines in preterm infants. The remainder were not research studies and were therefore also excluded. This left 75 studies for further scrutiny at which point the full text versions of each were accessed and read to ascertain suitability using the inclusion and exclusion criteria. This led to the exclusion of a further

52 papers on the basis that they were not primary studies (*n*=19), did not feature preterm infants exclusively (*n*=11) or were not focussed on routine vaccination, but rather immunogenicity or safety (*n*=6). Two of the studies were not available in English and seven more duplicates were identified. Two more studies were excluded because there was no guidance on vaccinating preterm infants in place at the time they were undertaken. A further five papers were excluded; one of which was an audit. There is debate about using audit findings as if they were research findings, as Jolley (2013) writes that audits often do not meet the standards required of scientific research. Conversely, Naughton (2013) argues that research and audit share the same methodological principles and aim to produce data which are both reliable and valid. This issue is worthy of consideration, but the purpose of the audit in question was to establish the practice of vaccinating with a specific vaccine in an identified neonatal unit. Whilst it is recognised that a proportion of the infants in the unit may have been born prematurely, this was not specified and it was for this reason that the paper was excluded. Two further papers were excluded because they were published as post scripts and contained insufficient information on which to make a judgement regarding their quality. The final exclusions were due to the papers examining the patterns of rotavirus vaccination in preterm infants with a view to assessing practice or relaxing the guidance around the scheduling of this vaccine to increase eligibility in this population.

By undertaking a systematic approach to searching the literature via database searching and checking the selected studies' reference lists, and subsequently applying inclusion and exclusion criteria, 23 studies were identified and deemed suitable for inclusion in the review.

4.4.1 Studies included in the review

All of the selected studies took a quantitative approach and were undertaken in the United Kingdom (UK) (*n*=3) , United States (US) (*n*=7), Australia (*n*=1), Germany (*n*=1), Italy (*n*=2), Israel (*n*=1), France (*n*=2), Canada (*n*=1), Switzerland (*n*=1), Peru (*n*=1), South

Africa (*n*=1) and The Netherlands (*n*=2) between the years of 1988 and 2021. Table 4.4 provides a basic summary of the included studies.

Table 4.4 Authors, date, country and title of studies.

Authors	Country	Title of Study
Bary-Weisberg & Stein-Zamir (2021)	Israel	Vaccination timeliness and completeness among preterm and low birthweight infants: a national cohort study.
Batra et al. (2009)	US	Evaluation of Vaccine Coverage for Low Birth Weight Infants During the First Year of Life in a Large Managed Care Population.
Crawford et al. (2009)	Australia	Immunisation practice in infants born prematurely: Neonatologists' survey and clinical audit.
Davis et al. (1999)	US	Immunization Levels Among Premature and Low-Birth-Weight Infants and Risk Factors for Delayed Up-to-Date Immunization status.
Denziot et al. (2011)	France	Hospital initiation of a vaccinal schedule improves the long-term vaccinal coverage of ex-pre-term children.
Fortmann et al. (2021)	Germany	Five Year Follow Up of Extremely Low Gestational Age Infants after Timely or Delayed Administration of Routine Vaccinations.
Hofstetter et al (2019)	US	Early Childhood Vaccination Status of Preterm Infants.
Laforgia et al. (2018)	Italy	Are pre-terms born timely and right immunized? Results of an Italian cohort study.
Langkamp et al. (2001)	US	Delays in Receipt of Immunizations in Low-Birth-Weight Children.
Magoon et al. (1995)	US	Delays in Immunizations of High-Risk Infants During the First Two Years of Life: Special Care for the High-Risk Infant Should Not Mean Special Immunization Schedules.
McKechnie and Finlay (1999)	UK	Uptake and timing of immunisations in preterm and term infants.
Nestander et al. (2018)	US	Immunization Completion in Infants Born at Low Birth Weight
Ochoa et al. (2015)	Peru	Vaccine schedule compliance among very low birth weight infants in Lima, Peru.
Pinquier et al. (2009)	France	Vaccination rate of premature infants at 6 and 24 months of age: a pilot study.
Roper & Day (1988)	UK	Uptake of immunisations in low birthweight infants.
Rouers et al. (2019)	Netherlands	Timeliness of immunisations in preterm infants in the Netherlands.
Ruiz et al. (1991)	US	Pertussis Immunization Patterns in Special Care Nursery Graduates.

Slack & Thwaites (2000)	UK	Timing of immunisation of premature infants on the neonatal unit and after discharge to the community.
Tillmann et al. (2001)	Switzerland	Vaccination rate and age of premature infants weighing <1500 g: a pilot study in north-western Switzerland.
Tooke & Louw (2019)	South Africa	A successful preterm vaccination program in a neonatal unit in a developing country.
Tozzi et al. (2014)	Italy	Timeliness of routine immunization in a population-based Italian cohort of very preterm infants: Results of the ACTION follow-up project.
Wilson et al. (2012)	Canada	On-time Vaccination Coverage in Premature Infants in Ontario, 2002-2009.
Woestenberg et al. (2014)	Netherlands	Delayed Start of Diphtheria, Tetanus, Acellular Pertussis and Inactivated Polio Vaccination in Preterm and Low Birth Weight Infants in the Netherlands.

A detailed table featuring more information on the selected studies can be found in Appendix 1.

4.5 Critical appraisal and data extraction

Critical appraisal is an important element of the literature review process, and Aveyard (2019) identifies three key questions that the appraisal process needs to address: firstly, do the selected studies feature highly in the hierarchy of evidence? Secondly, what are the main findings in the studies? And finally, what are their strengths and weaknesses? When combined, consideration of these aspects then provides an indication of the feasibility of a study's findings to practice based on its quality (Moule, 2018). There are numerous templates and tools available to facilitate the appraisal process, but Facchiano and Hoffman-Snyder (2012) stipulate three key issues in the appraisal of a quantitative study; its validity, the reliability and importance of its results, and the applicability of the results to other populations. To assess the quality of the studies in this review, an appraisal tool based on the framework developed by Coughlan et al. (2007) was used. This particular framework was selected owing to its consideration of the three central issues cited by Facchiano and Hoffman-Snyder (2012) and also because of the degree of flexibility it offers; many quantitative appraisal tools are design specific, asking questions which are

only relevant to certain methodologies (Critical Appraisal Skills Programme, 2021). Furthermore, most of the 23 selected studies used either wholly or partly, secondary data on which to base their analyses and the appraisal framework by Coughlan et al. (2007) only considers methods concerning the collection of primary data. Therefore, it was necessary to adapt this section of the framework to facilitate a thorough appraisal of the data collection methods where secondary data were used. This adaptation was based on suggestions by Mongan (2013) which have been made to encourage researchers to determine whether there is an appropriate fit between the dataset and the research question. Mongan (2013) specifies the following considerations:

- Are there sufficient data?
- What was the original purpose for which the data were collected?
- When and how were they collected?
- Are the variables of interest included in the dataset?
- What is the level of data aggregation?
- What data cleaning procedures have been applied (which according to Mongan (2013) refers to the reliability and validity of the dataset)?
- What sampling procedures were used?

Given the lack of a suitable appraisal tool for the studies included in this review, the development of this adapted version based on the framework by Coughlan et al. (2007) and with the additional elements suggested by Mongan (2013), was essential. The process of appraising each study required the extraction of certain data. Therefore, at this stage it seemed both sensible and practical to develop a template which would serve a dual purpose; that of guiding the extraction of relevant information, whilst also facilitating the critical appraisal of the studies. Bettany-Saltikov and McSherry (2016) considers data extraction as a challenging phase in the literature review process which should be guided by a useful

and appropriate data extraction form to ensure standardisation and validity of the results. If the purpose of data extraction is considered as: "highlighting the relevant information that will answer the research question" (Bettany-Saltikov & McSherry, 2016:140), then the form presented in

Figure 4.2 serves this purpose. As suggested by the Centre for Reviews and Dissemination (CRD) (2009) the data extraction form may need to be piloted and refined, and as such, the final version of the form used in this review was not produced without some revision. These refinements were primarily needed around the outcomes of the included studies. In the literature, critical appraisal and data extraction are not expressed as activities which may occur concurrently; neither is it suggested that there may be some mutual benefits of undertaking these two activities at the same time (Bettany-Saltikov & McSherry, 2016). In this review, these activities naturally overlapped and any attempts to undertake them separately seemed futile; in fact, the CRD (2009) write that data extraction is linked to the assessment of study quality and that both processes are often undertaken simultaneously.

Elements influencing the credibility of the study	
Study details	
Author(s)	

Source	
Writing style	
Report title	
Abstract	
Elements influencing the robustness of the research	
Purpose/research problem	
Logical consistency	
Literature review	
Theoretical framework	
Aims/objectives/research question/hypotheses	
Sample	
Ethical considerations	
Operational definitions	
Methodology Design Is secondary data used? If yes then consider: Is there sufficient data? What was the original purpose for which the data were collected? When and how were they collected? Are the variables of interest included in the dataset? What is the level of data aggregation? What data cleaning procedures have been applied? What sampling procedures were used?	
Data analysis/results Results expressed in terms of prematurity, birthweight or both? Degree of prematurity and/or birthweight classified? Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)? Are predictors in rates or delay explored?	
Discussion	
References	

Figure 4.2 Data extraction form template

Whilst the quality of the studies was variable, they were all considered to have adopted appropriate methodologies and methods to support their inclusion in the review. Full appraisals of each study using the template presented in

Figure 4.2 can be found in Appendix 2.

4.6 Method of analysis

Several methods of analysis may be used in a literature review. Aveyard (2019) suggests three approaches: meta-analysis, meta-ethnography and integrative review. Meta-analysis refers to the application of statistical techniques which combine and synthesise the results of several quantitative studies. Conversely, meta-ethnography and integrative review may be applied to bring together the findings of qualitative enquiries. These approaches rely on the studies included being either quantitative or qualitative. Given that the studies in this review are entirely quantitative, consideration was given to adopting an approach akin to meta-analysis. However, the review question *'are vaccinations in preterm infants delayed?'* is open to translation; indeed, the studies included in this review have interpreted this differently, and Cooper (2010) cites the characteristic of studies sharing an identical conceptual hypothesis as a fundamental requirement for meta-analysis. Furthermore, the included studies used a range of methodologies and outcome measures, and although Littell et al. (2009) state that there will always be some substantive clinical heterogeneity in a meta-analysis, both Eysenck (2001) and Cooper (2010) argue that methods and outcomes should be homogeneous to avoid overlooking important differences between studies. Bettany-Saltikov and McSherry (2016) cite the inability to undertake a meta-analysis as a common problem in disciplines such as nursing and suggests narrative synthesis as an alternative approach. Narrative synthesis is similar to thematic analysis in that it uses a textual rather than a statistical approach to synthesise the evidence and involves a higher level of synthesis by attempting to generate novel insights and knowledge (Coughlan and Cronin, 2017). Popay et al. (2006) also propose that narrative synthesis can be used when the studies included in a review are too diverse for meta-analysis and include a range of research designs. To support the systematic approach adopted in this literature review, narrative synthesis was chosen as an appropriate method of analysis and this process was

guided by the framework developed by Popay et al. (2006). This was also thought to be an appropriate framework given the complex nature of vaccine hesitancy; the detailed analysis entailed would allow for a greater synthesis of ideas and conclusions. Popay et al. (2006) acknowledged that owing to the lack of an authoritative body of knowledge and in the absence of a recognised process for undertaking a narrative synthesis, a methodological foundation on which to base this process was essential. Therefore, basing this analysis on this framework enhanced the robustness and trustworthiness of this review by systematically organising, describing and interpreting the data (Coughlan et al., 2007). The framework developed by Popay et al. (2006) was designed to complement the systematic review process where a meta-analysis would also be undertaken. However, the value of undertaking a narrative synthesis solely (in the absence of homogeneity between studies included in a review) has emerged as an equally legitimate method of analysis in its own right (Popay et al., 2006; Bettany-Saltikov & McSherry, 2016; Coughlan and Cronin, 2017).

The narrative synthesis undertaken in this review used a process adapted from the guidance published by Popay et al. (2006) and included methods such as textual description, grouping similar data and data transformation. Exactly how the process as described by Popay et al. (2006) translated into the methods used in the review is presented in Table 4.5:

Table 4.5 The narrative synthesis process.

Narrative synthesis framework (Described by Popay et al., 2006).	Narrative synthesis methods undertaken in this review.
Element 1 - Developing a theory	The development theory for this review was shaped by the context described in the primary studies. Whilst none of the studies identified a theoretical

This is concerned with identifying a theory to inform the review, for example, addressing how (for a systematic review) an intervention works. *Tools and techniques:* None identified.	framework, the implicit hypothesis in all of them was that vaccinations in preterm and/or low birthweight infants are delayed. *Tools and techniques:* No specific tools used.
Element 2 - Preliminary synthesis Explained as the initial description of studies and the identification of patterns in terms of size and effect. *Tools and techniques:* Textual description of studies Tabulation Groupings and clusters Transforming data into a common rubric Vote counting as a descriptive tool Translating data: thematic analysis Translating data: content analysis	*Tools and techniques:* Tabulation Groupings and clusters Vote counting and data translation
Element 3 - Exploring relationships This is the discovery of similarities and differences between the studies (findings and methods) and the identification of factors which may explain them. *Tools and techniques:* Graphs, frequency distributions, funnel plots, forest plots and L'Abbe plots Moderator variables and sub-group analyses Idea webbing and conceptual mapping Reciprocal and refutational translation Qualitative case descriptions Investigator/methodological triangulation	Some of the techniques described in this element had already inadvertently been carried out. Greater detail is provided in the 'Exploring relationships' section *Tools and techniques:* Idea webbing and conceptual mapping Investigator triangulation
Element 4 - Assessing the robustness of the synthesis This is a complex stage concerning not only the assessment of studies in terms of quality and quantity (which has an obvious influence on the trustworthiness of the emerging synthesis), but also concerns the synthesis methods used and the extent	As with element 3, many of the methods described here had already been employed, however more details are provided in the section 'Assessing the robustness of the synthesis'

to which studies have been justly included based on inclusion criteria. *Tools and techniques:* Weight of evidence Best evidence synthesis Use of validity assessment Critical reflection on synthesis process Checking synthesis with authors of primary studies	

4.7 Analysis of included studies

4.7.1 Element 1 - Theory development

The authors of the studies included in the review all justified the basis for their research by acknowledging the possible existence of a delay in the vaccination of preterm or low birthweight infants. Whilst none of the studies explicitly defined vaccination delay as theory which guided their research, this notion was implicit throughout, and has a fundamental association with the determinants of vaccine uptake. This was assessed independently by a thorough familiarisation of each study, after which it was possible to connect the determinant of awareness, and most strikingly, the determinant of acceptance to the studies' findings and conclusions. This process cannot be defined as objective, but there is merit in the rigour of this approach.

4.7.2 Element 2 - Preliminary synthesis

Textual description of studies:

Popay et al. (2006) say that the purpose of this is to systematically describe each of the studies included in the review. Given that the data required in this description were the same data that had already been highlighted in the data extraction process, this would have been a duplication of effort which would not have added to the synthesis process and was subsequently deemed unnecessary.

Tabulation

Tabulation is recognised by Popay et al. (2006) as both a useful and common approach in the synthesis process. It enables description and also highlights the emergence of patterns across studies, and may be used where both quantitative and qualitative data are represented. Tabulation was particularly useful in this review because any tables could be developed specifically around the review focus. Therefore, the formulation of a table (appendix 1) to gain an initial overview of the studies was deemed to be an important starting point of the synthesis. It facilitated familiarity of each study and the similarities and differences between the studies' methods and findings began to emerge. In fact, this table was in essence already developed, as this was undertaken whilst simultaneously appraising each of the studies and extracting key data. The data extracted related to the studies' designs, samples, data collection and analysis methods, findings, and also the studies' methodological strengths and limitations. The quality of the studies was not discussed in detail in this table although detailed appraisals were undertaken (see appendix 2). Tabulation was also extensively used in the following 'groupings and clusters' section to provide structure to the analysis and to begin to identify patterns across the studies.

Groupings and clusters

Popay et al. (2006) acknowledge that in a systematic review, the synthesis of a large number of studies is easily practicable owing to the statistical analysis methods applied; however, this is not the case where a narrative synthesis is undertaken. Therefore, the development and organisation of the studies into smaller groups makes this process more manageable. Using the data extraction table as a starting point facilitated the identification of common characteristics between the studies, and thus, guided this 'grouping' process. Furthermore, Popay et al. (2006) highlight the importance of referring to the review question as a way of informing decision making around grouping the studies. Therefore, three aspects of the review question: "*are vaccinations in preterm infants delayed?"* were

also used to guide how the studies were grouped, and these were *vaccinations*, *preterm infants* and *delayed*. Additionally, the contexts of the studies were deemed important here (including studies' rationale and data collection method), as were the identification of any factors associated with a delay.

Vaccinations

Rather than citing each vaccination, Table 4.6 illustrates which antigens were included in each of the studies. These were administered differently according to the country where the study took place and the availability of the vaccines at the time of the study. For example, HepB was only included as part of the UK schedule in 2017 (PHE, 2020b) explaining why it had not been included in earlier studies. Additionally, the development over time of combination vaccines reflects the different vaccines investigated across the studies. The scheduled vaccines were the main focus in all of the studies included in the review, and these varied according to the country where the study was undertaken and also when it was undertaken. Eleven of the studies investigated all of the scheduled childhood vaccines recommended in their respective countries in the time period studied (Tillmann et al., 2001; Crawford et al., 2009; Pinquier et al., 2009; Wilson et al., 2012; Tozzi et al., 2014; Laforgia et al., 2018; Hofstetter et al., 2019; Rouers et al., 2019; Tooke & Louw, 2019; Bary-Weisberg & Stein-Zamir, 2021 & Fortmann et al., 2021). Davis et al. (1999), Slack and Thwaites (2000) implied that all of the scheduled vaccinations were studied but this is not explicitly stated. Additionally, Langkamp et al. (2001) used data which were more than ten years old, and it is unclear if the vaccines studied included all of those scheduled at the time. Batra et al. (2009) include all scheduled vaccines apart from the PCV, but they explain that this was because this vaccine was introduced during the study period. Similarly, Ochoa et al. (2015) explain that they excluded the scheduled MMR and BCG for reasons related to data incompleteness, and Nestander et al. (2018) excluded Hib in their analysis

due to a shortage of the vaccine during the study period. Whilst Roper and Day (1988), Ruiz et al. (1991), Magoon et al. (1995) and McKechnie and Finlay (1999) include scheduled vaccinations in their research, it is unclear if this actually includes all of those that are recommended. One study examines the "major vaccines administered during the first two years of life" (Denziot et al., 2011:383), and whilst HepB vaccine is excluded, it is explained that this was because uptake rates for this had been affected generally for reasons associated with a possible link between the vaccination and demyelination events in adults. However, in spite of being scheduled, Denziot et al. (2011) exclude the MMR vaccine without explanation. Similarly, Woestenberg et al. (2014) only study DTaP-IPV when Hib and PCV are also scheduled and no reason for this is provided.

Table 4.6 Antigens analysed in the studies.

	DTP or DTaP	Hib	Polio	Hep B	PCV	Men C	MMR	Varicella	Rotavirus
Bary-Weisberg & Stein-Zamir (2021)	✓	✓	✓	✓	✓		✓	✓	
Batra et al. (2009)	✓	✓	✓	✓					
Crawford et al. 2009)	✓	✓	✓	✓	✓	✓	✓	✓	
Davis et al. (1999)	✓	✓	✓				✓		
Denziot et al. (2011)	✓	✓	✓		✓				

Fortmann et al. (2021)	✓	✓	✓	✓	✓				
Hofstetter et al. (2019)	✓	✓	✓	✓	✓		✓	✓	✓
Laforgia et al. (2018)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Langkamp et al. (2001)	✓		✓				✓		
Magoon et al. (1995)	✓	✓	✓				✓		
McKechnie & Finlay (1999)	✓	✓	✓						
Nestander et al. (2018)	✓	✓	✓	✓			✓	✓	
Ochoa et al. (2015)	✓	✓	✓	✓	✓				✓
Pinquier et al. (2009)	✓	✓		✓			✓		
Roper & Day (1988)	✓								
Rouers et al. (2019)	✓	✓	✓	✓					
Ruiz et al. (1991)	✓								
Slack & Thwaites (2000)	✓	✓				✓			
Tillmann et al. (2001)	✓	✓	✓				✓		
Tooke & Louw (2019)	✓	✓	✓	✓	✓				✓
Tozzi et al. (2014)	✓	✓	✓	✓	✓	✓	✓	✓	
Wilson et al. (2012)	✓	✓	✓		✓				
Woestenberg et al. (2014)	✓		✓						

Preterm infants

The term ‘preterm infants’ was translated as concerning the study population and how this was identified; initially, the data sources were explored. All of the studies used secondary data to identify the study population, and whilst the advantages and limitations of using these data are not discussed fully here, the source of the data is considered (Table 4.7). For

eleven of the studies, data were drawn from local sources, namely neonatal unit (NNU) records (Roper & Day, 1988; Ruiz et al., 1991; Magoon et al., 1995; McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Tillmann et al, 2001; Crawford et al., 2009; Denziot et al., 2011; Ochoa et al., 2015; Laforgia et al., 2018; Tooke & Louw, 2019). Of these studies, Crawford et al. (2009) and Ochoa et al. (2015) used data from multiple units, where the remainder used data from a single NNU. The data used in the study by Roper and Day (1988) were from a London borough and although the sample size suggested that this covered several units it was not possible to determine this. Other studies used much larger data sets from what were considered as regional sources (Davis et al., 1999; Batra et al., 2009; Pinquier et al., 2009; Wilson et al., 2012; Hofstetter et al., 2019). Tozzi et al. (2014), Woestenberg et al. (2014), Rouers et al. (2019) and Bary-Weisberg and Stein-Zamir (2021) all used national data in their analyses. A further study claimed to have used a "nationally representative sample" (Langkamp et al., 2001:168). Based on a national population, Nestander et al (2018) used data for those registered with the national military health system. Finally, whilst also taking a national approach, Fortmann et al. (2021) took data from a national database for preterm infants.

Table 4.7 An overview of how study populations were identified.

Scope of data	Study
National	Langkamp et al. (2001) Tozzi et al. (2014) Woestenberg et al. (2014) Nestander et al. (2018) Rouers et al. (2019) Bary-Weisberg & Stein-Zamir (2021)

	Fortmann et al. (2021)
Regional	Davis et al. (1999) Batra et al. (2009) Pinquier et al. (2009) Wilson et al. (2012) Hofstetter et al. (2019)
A neonatal unit	Roper & Day (1988) Ruiz et al. (1991) Magoon et al. (1995) McKechnie & Finlay (1999) Slack & Thwaites (2000) Tillmann et al. (2001) *Crawford et al. (2009) Denziot et al. (2011) *Ochoa et al. (2015) Laforgia et al. (2018) Tooke & Louw (2019)

*These studies included multiple NNUs.

With the exception of one study (Ruiz et al., 1991) the samples were identified by either the infants' birthweight, gestational age or both (Table 4.8). Birthweight was used to identify infants by Magoon et al. (1995), Langkamp et al. (2001), Batra et al. (2009), Nestander et al. (2018) and Tooke and Louw (2019); these studies did not discuss the relationship between gestational age and birthweight, however the existence of an association was implied. Ten of the studies identified infants by their gestational age (McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Crawford et al., 2009; Pinquier et al., 2009; Denziot et al., 2011; Wilson et al., 2012; Tozzi et al., 2014; Laforgia et al., 2018; Hofstetter et al., 2019; Rouers et al., 2019). Of these ten studies, four of them did not feature birthweight at all (McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Wilson et al., 2012; Laforgia et al., 2018), whereas the remainder factored birthweight into their analyses. Roper and Day (1988), Davis et al. (1999), Tillmann et al. (2001), Woestenberg et al. (2014), Ochoa et al. (2015), Nestander et al. (2018), Fortmann et al. (2021) and Bary-Weisberg and Stein-Zamir (2021) used both birthweight and gestational age as identifying factors. Based on admissions to a neonatal unit (NNU), Ruiz et al. (1991) classified infants

as either high risk, low risk or normal risk, and one of the criteria for being high risk was a birthweight of less than or equal to 1500g.

Table 4.8 Method of identification of sample

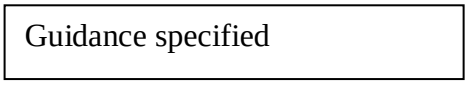
	Gestational age	Birthweight	Other
Bary-Weisberg & Stein-Zamir (2021)	✓	✓	
Batra et al. (2009)		✓	
Crawford et al. (2009)	✓		
Davis et al. (1999)	✓	✓	

Denziot et al. (2011)	✓		
Fortmann et al. (2021)	✓	✓	
Hofstetter et al. (2019)	✓	✓	
Laforgia et al. (2018)	✓		
Langkamp et al. (2001)		✓	
Magoon et al. (1995)		✓	
McKechnie & Finlay (1999)	✓		
Nestander et al. (2018)		✓	
Ochoa et al. (2015)	✓	✓	
Pinquier et al. (2009)	✓		
Roper & Day (1988)	✓	✓	
Rouers et al. (2019)	✓		
Ruiz et al. (1991)			✓
Slack & Thwaites (2000)	✓		
Tillmann et al. (2001)	✓	✓	
Tooke & Louw (2019)		✓	
Tozzi et al. (2014)	✓		
Wilson et al. (2012)	✓		
Woestenberg et al. (2014)	✓	✓	

Defining 'delayed'

How the studies determined vaccination practices in preterm infants was variable. Some of the studies investigated this in terms of 'age specific immunisation status' or simply whether or not infants were 'up-to-date' with the identified vaccinations at a defined age (Roper & Day, 1988; Ruiz et al., 1991; Davis et al., 1999; Crawford et al., 2009; Pinquier et al. 2009; Denziot et al., 2011; Nestander et al., 2018; Hofstetter et al., 2019). Others explored the infants' age at vaccination to determine whether a delay occurred or to report on the 'age appropriateness' of the vaccination (Magoon et al., 1995; McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Wilson et al., 2012; Woestenberg et al., 2014; Ochoa et al., 2015; Rouers et al., 2019; Tooke & Louw, 2019; Fortmann et al., 2021). Six of the studies used both of these approaches (Langkamp et al., 2001; Tillmann et al., 2001; Batra et al.,

2009; Tozzi et al., 2014; Laforgia et al., 2018; Bary-Weisberg & Stein-Zamir, 2021), with the advantage of being able to distinguish the timeliness of vaccination as well as the rates of coverage; an infant having received the correct amount of vaccines at one year of age does not necessarily indicate that they were given 'on-time'. How each of the studies defined an up-to-date status or delay was also considered important so that some level of consistency could be determined between them. Some studies had based their definitions of a delay or up-to-date status on guidance, whereas others had not been specific about what was considered delayed or indeed, specified any guidance or recommendations (Figure 4.3). As previously discussed, each of the studies included in this review needed to acknowledge that there were guidelines in place regarding the vaccination of preterm infants; it would be impossible to measure a delay without a standard to measure this against, and this concept is central to vaccine hesitancy. Whilst all of them acknowledged the existence of guidance, not all of them named the guidance or indeed, what it specified. In these cases, the concept of unwarranted delays was accepted.



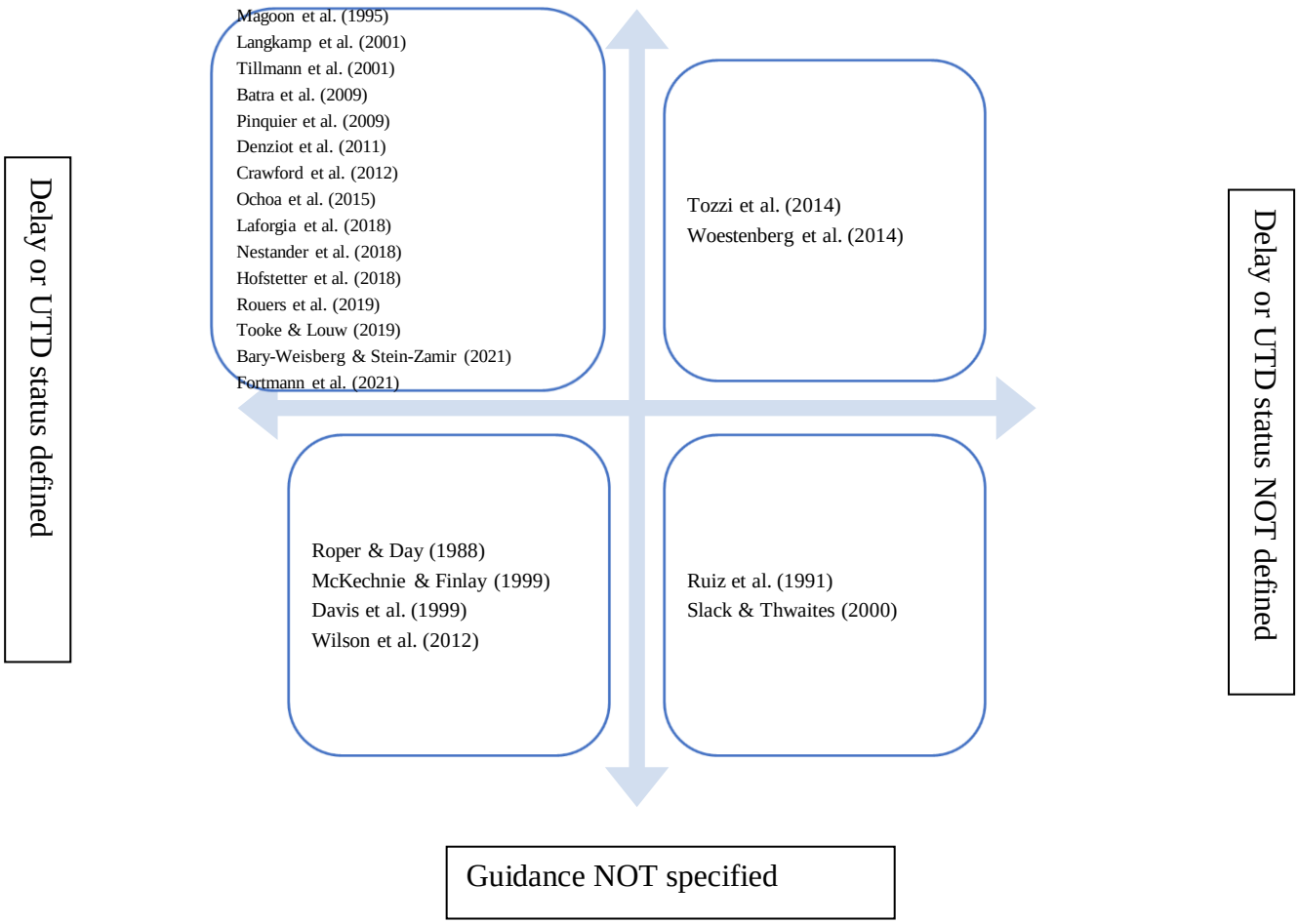


Figure 4.3 Identification of how up-to-date (UTD) status or delay in vaccination were defined.

Context of the studies

As highlighted in element 1 – *Theory development*, all of the studies justify the basis for their research by acknowledging the possible existence of a delay in vaccinating preterm or low birthweight infants. This justification is strengthened by all but one of the studies (Roper & Day, 1988) with evidence of a literature review. Again, with the exception of Roper and Day (1988) all of the authors add to the rationale of their studies by indicating that preterm or low birthweight infants are at a higher risk of vaccine preventable diseases compared with the general population. Davis et al. (1999) and Langkamp et al. (2001) further validate their population-based studies, by highlighting that previous enquiries into

vaccination rates in preterm infants had been largely based on single neonatal units. Bary-Weisberg and Stein-Zamir (2021) acknowledge that published studies have had small sample sizes (and highlight issues associated with inaccurate or incomplete data), hence their population-based approach. Ochoa et al. (2015) state that their study is set in a developing country as all previous studies have investigated this issue in developed countries. Finally, Tooke and Louw (2019) set out to evaluate practice after a new policy was introduced for vaccinations to be administered on the neonatal unit, also in a developing country. Although thought to be an established idea (as discussed in chapter three), not all of the studies discuss vaccine hesitancy. The term is used by Laforgia et al. (2018) and Hofstetter et al. (2019), but not explored in relation to the studies' findings in any depth.

Although all of the studies used secondary data sources from which to identify their samples, not all of them exclusively used these data in their analyses. Table 4.9 outlines how the study data were obtained and gives a brief overview of the databases used. It also identifies the timeliness of the data from point of collection to analyses (where this information was available).

Table 4.9 Data collection details

	Data source used	Other data collection methods	'Date' of data	Date of analyses/study publication	'Age of data'
Bary-Weisberg & Stein-Zamir (2021)	National Immunisation Registry		Born during 2016	Study published in 2021	5 years
Batra et al. (2009)	Vaccine Safety Datalink Project database		Born 1997-2002	Study published in 2009	7-12 years
Crawford et al. (2009)	Australian Childhood Immunisation Register and hospital records	GP questionnaires and parental telephone interviews	Born 2003-2005	2006-2007	1-3 years
Davis et al. (1999)	Vaccine Safety Datalink Project database		Data tracked 1991-1997	Study published in 1999	2-8 years
Denziot et al. (2011)	Some data extracted from NICU database (not immunisation data)	Immunisation data from parental questionnaire	Born 2003-2005	Study published in 2011	6-8 years
Fortmann et al. (2021)	Neonatal network	Annual parental questionnaires	Born 2010-2019	Study published in 2021	2-11 years
Hofstetter et al. (2019)	Immunisation information system		Admitted infants 2008-2013	Study published 2019	6-11 years
Laforgia et al. (2018)	Regional vaccination and hospital register		Infants discharged during 2013	Study published 2018	5 years
Langkamp et al. (2001)	Two databases (1988 NMIHS & 1991 Longitudinal Follow-up Survey) identified infants whose parents were then contacted and asked to provide health care providers information - the health care		Only the dates of the databases are stated – 1988 & 1991	Study published in 2001	10-13 years

	providers then supplied the researchers with the data regarding immunisation status				
Magoon et al. (1995)	Infants identified via a clinic database then parents contacted	Immunisation data from parental questionnaire	Born 1982-1991	Study published in 1995	4-13 years
McKechnie & Finlay (1999)	Child Health Department computer system		Born in 1996	Study published in 1999	3 years
Nestander et al. (2018)	Military database		Infants born between Oct 2007-Sept 2011	Study published 2018	7-11 years
Ochoa et al. (2015)	Hospital records and follow up over a year		Infants assessed for eligibility 2009-2012	Study published 2015	3-6 years
Pinquier et al. (2009)	Based on a birth cohort but data source unclear		Born in 2000	Study published 2009	9 years
Roper & Day (1988)	Child Health Department computer system		Born 1984	Study published in 1988	4 years
Rouers et al. (2019)		Parental questionnaires and medical notes	Recruited 2015-2017	Study published in 2019	2-4 years
Ruiz et al. (1991)	Infants identified via an admissions database then parents contacted	Immunisation data from parental questionnaire	Admissions to NICU 1985-1986	Study published in 1991	5-6 years
Slack & Thwaites (2000)	Child Health Department computer system and hospital records	Parents contacted (no further detail provided)	Born in 1998	Study published in 2000	2 years
Tillmann et al. (2001)	Infants identified via an admissions database then	Immunisation data from	Born 1994-1995	Observation period – a day in 1999	4-5 years

	parents contacted	parental questionnaire			
Tooke & Louw (2019)	Hospital data		Admitted infants between Oct 2014-Apr 2015	Study published 2019	4-5 years
Tozzi et al. (2014)	Data from a larger cohort study (ACTION Project) but not immunisation data	Immunisation data relied on parents providing vaccination certificate	Children enrolled onto database during 2003-2005 and invited to clinic where data were obtained from parents	Clinic invitations at child's corrected age of 2 years	Approx. 2 years
Wilson et al. (2012)	Immunisation data from OHIP database (insurance administration database)		Born 2002-2009	Study published in 2012	3-10 years
Woestenberg et al. (2014)	National immunisation database (Præventis)		Born 2006-2010	Study published in 2014	4-8 years

Table 4.9 demonstrates which studies used data exclusively from existing databases. Although databases were used for some information and to identify the target population, six of the studies relied on parents to supply the data needed (Ruiz et al., 1991; Magoon et al., 1995; Tillmann et al., 2001; Denziot et al., 2011; Tozzi et al., 2014; Rouers et al., 2019). Crawford et al. (2009) accessed an immunisation database and hospital records to establish vaccination status as well as contacting parents and general practitioners (GPs). It is not stated why parents and GPs were also contacted but it could be assumed that this was done as a measure of validating the data obtained from the other sources. Similarly, Slack and Thwaites (2000) contacted parents in addition to using a database and hospital records, and again, although the justification for this lacking, it may be assumed that was for data checking purposes. It was unclear in the study by Pinquier et al. (2009) exactly where data

were obtained. Knowledge of how vaccination data were obtained is important in understanding how reliable the data are. It could be argued that some methods used for recording and recalling this information are more reliable than others. There is no recommended procedure, but it is evident in Table 4.9 that the variety of methods used may affect that accuracy of the data.

Given many of the studies in this review use secondary data, it was important to identify the timeliness of the data used. Knowing this was important to ensure that any inferences the studies' authors made were relevant. To establish this, Table 4.9 lists the 'date' of the data and when they were analysed or published and then gives an approximate 'age' of the data; this is in an attempt to identify the time period between when data were collected or recorded, and subsequent analyses undertaken. Firstly, most studies extracted their data based on the birth dates of infants (Roper & Day, 1988; Magoon et al., 1995; McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Tillmann et al., 2001; Batra et al., 2009; Crawford et al., 2009; Pinquier et al., 2009; Denziot et al., 2011; Wilson et al., 2012; Woestenberg et al., 2014; Nestander et al., 2018; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021; Fortmann et al., 2021). Ochoa et al. (2015) based their sample on infants born in one of the four hospitals in the study; infants who were born elsewhere but transferred to one of the participating hospitals were also eligible. Davis et al. (1999) tracked the data over a fixed time period, whilst Ruiz et al. (1991) based their analyses on data obtained from parents of admissions to the NNU, and Laforgia et al. (2018), Hofstetter et al. (2019) identified infants from admission over a defined time period. Infants were eligible in the study by Tooke and Louw (2019) if they were still inpatients by six weeks of age (over a defined time period). Tozzi et al. (2014) used data based on when the infants were enrolled onto the identified database. Finally, Langkamp et al. (2001) used information from two databases which in spite of being dated 1988 and 1991, give no further detail of the time points or periods over which these data were taken from.

It was not possible to pinpoint the exact date of analyses in most of the studies. However, Crawford et al. (2009) do specify by giving the time period of when the data were analysed and Tillmann et al. (2001) also give an exact date of analysis. Tozzi et al. (2014) identified infants from a database during 2003-2005 and then these children were invited to a clinic at their corrected age of two years at which point immunisation information was obtained; this suggests that the data were approximately two years old at analysis. Some of the studies used data which could be considered outdated. Both Magoon et al. (1995) and Langkamp et al. (2001) include data which is potentially up to thirteen years old. Furthermore, Batra et al. (2009) and Wilson et al. (2012) include data which is up to twelve and ten years old respectively, and the data in the studies by Hofstetter et al. (2019) and Fortmann et al. (2021) use data which are up to 11 years old.

Factors associated with up-to-date status and vaccination delay

All of the studies reported their findings on vaccination timeliness or completion in relation to either birthweight or gestational age (and some referred to both). However, infants were grouped in terms of risk by Ruiz et al. (1991) and a birthweight of less than or equal to 1500g was a criterion for being high risk.

Some studies explored additional factors associated with up-to-date vaccination status or delay. The length of hospitalisation and its impact on vaccination timeliness and uptake was explored by Slack and Thwaites (2000), Davis et al. (2001), Crawford et al. (2009), Laforgia et al. (2018), Rouers et al. (2019) and Fortmann et al. (2021). Initiation of the vaccination series whilst hospitalised was a feature in six of the studies (Pinquier et al., 2009; Denziot et al., 2011; Wilson et al., 2012; Tozzi et al., 2014; Woestenberg et al., 2014; Bary-Weisberg & Stein-Zamir, 2021). Other diagnoses and oxygen therapy were also considered by Magoon et al. (1995), Davis et al. (1999), Pinquier et al. (2009), Tozzi et al. (2014) and Fortmann et al. (2021).

Just three studies investigated ethnicity (Batra et al., 2009; Hofstetter et al., 2019; Bary-Weisberg & Stein Zamir, 2021), whilst seven investigated socioeconomic status or parental educational levels (Magoon et al., 1995; Langkamp et al., 2001; Denziot et al., 2011; Tozzi et al., 2014; Woestenberg et al., 2014; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021). Davis et al. (1999) and Nestander et al. (2018) studied the influence of well-child visits on uptake and timeliness, and three studies examined the influence of practices (Ruiz et al., 1991; Magoon et al., 1995; Crawford et al., 2009).

Transforming data into a common rubric

Popay et al. (2006) suggest that transforming data into a common rubric allows for a more comprehensive and robust comparison of findings. However, this was not considered appropriate here owing to the differences between the studies' methods and subsequent results.

Vote counting and data translation

Vote counting is described by Popay et al. (2006) as a method of calculating the frequency of different results across the studies. This is not without some controversy however, and the main line of argument against vote counting concerns the complexity associated with the various methods reviewers may choose to interpret the results. Haddaway et al. (2015) promote the avoidance of vote counting in literature reviews by arguing that equal weight may be given to studies of varying quality leading to unreliable and misleading conclusions. What is recommended is a consideration of the study findings in light of the effect size, sample size and variability (Haddaway et al., 2015). Whilst Haddaway et al. (2015) make an important point, the concept of vote counting was considered a key element in this synthesis as it allowed for an initial combination of the results of all of the studies. Equally, as highlighted by Haddaway et al. (2015) it was important to consider the quality of the

studies at this stage (although this is considered in greater depth in element 4 – *Assessing the robustness of the synthesis*). Furthermore, the purpose of this narrative synthesis is to describe the findings of the included studies; it is not an attempt to synthesise the findings using statistical methods. Therefore here, an element of vote counting was adopted by grouping similar findings and, additionally conclusions were drawn whilst simultaneously considering the quality of the studies identified. This process naturally drew on the stage of the narrative synthesis process described by Popay et al. (2006) as translating data. Thematic analysis is central to this stage and this helped to provide a structured method of organising and summarising the findings from all of the studies. To facilitate this process a findings matrix (featured in Appendix 3) was developed where the results of all of the studies were brought together. This enabled similarities and differences between them to be more easily identified whilst ascertaining the frequency of occurrence. The different coloured text in the matrix indicates whether or not vaccination timeliness or completion was affected by the characteristic identified.

In the following sections, the findings are discussed under the headings: birthweight, gestational age, hospitalisation and other diagnoses/treatments, infant and family characteristics and additional findings.

Birthweight

Birthweight was a key feature in some of the studies' findings (Roper & Day, 1988; Ruiz et al., 1991; Magoon et al., 1995; Davis et al., 1999; Slack & Thwaites, 2000; Langkamp et al., 2001; Batra et al., 2009; Tozzi et al., 2014; Woestenberg et al., 2014; Bary-Weisberg & Stein-Zamir, 2021), and some of them categorised this. Batra et al. (2009), Woestenberg et al. (2014) and Nestander et al. (2018) classify and label birthweights using the same criteria as follows: extremely low birthweight <1000g, very low birthweight 1000-1499g, low birthweight 1500-2499g and normal birthweight ≥2500g. Rouers et al. (2019) and

Bary-Weisberg and Stein-Zamir (2021) also stratify infant weights in this way, although they are not labelled. Langkamp et al. (2001) use different criteria; normal birthweight remains the same (≥2500g) but very low birthweight is classed as <1500g and weights in between (1500-2500g) are considered as moderately low birthweight or low birthweight; Hofstetter et al. (2019) define similar categories. Magoon et al. (1995) and Davis et al. (1999) separate into weight categories: <1500g, 1500-2500g, >2500g and <1000g, 1000-1499g, 1500-1749g, 1750-2499g, >2500g respectively, and although some of these categories are similar, they are not labelled as extremely low birthweight, very low birthweight, low birthweight or normal birthweight. Ochoa et al. (2015) define two birthweight groups; as <1000g and 1000-1500g. Roper and Day (1988) define 2000g as a cut-off point with infants weighing less being considered as low birthweight and those ≥2000g as normal birthweight. In the study by Ruiz et al. (1991) infants were classified in term of risk (high, low and normal risk) and birthweight featured only in the high-risk category, where infants with a birthweight ≤1500g were included. Slack and Thwaites (2000) and Tozzi et al. (2014) give no details on how low birthweight was determined.

Nestander et al. (2018) reported that the odds of completion of the schedule (at two years) were significantly decreased in low birthweight infants, and that infants with the lowest birthweights had the greatest odds of non-completion. Batra et al. (2009) found that extremely low birthweight infants consistently experienced significant delays in vaccination relative to normal birthweight infants. Furthermore, these infants were also significantly less up-to-date compared with normal birthweight infants. However, the same study did not find a significant difference in delays or up-to-date rates between low birthweight and normal birthweight infants. These findings are comparable with those reported by Langkamp et al. (2001) that very low and low birthweight infants received their first and second scheduled vaccinations later than normal birthweight infants. Similarly, Ruiz et al. (1991) reported that the rate of vaccination at one year for high risk infants

(which include those with a birthweight ≤1500g) was significantly lower than infants in the normal and low risk categories. In the study by Woestenberg et al. (2014), extremely low birthweight infants were reported to have a higher median age at first vaccination relative to normal birthweight infants, for whom, the median age at first vaccination was lower. These findings agree with those of Slack and Thwaites (2000) who report a significant negative correlation between median age at first and third vaccination and birthweight. Likewise, Bary-Weisberg and Stein-Zamir (2021) and Roper and Day (1988) reported that the uptake of the first vaccination was significantly delayed in low birthweight infants compared with normal birthweight infants; in fact, Bary-Weisberg and Stein-Zamir found that delay rates were highest in the <1000g birthweight group. Likewise, Ochoa et al. (2015) found that infants in the <1000g group were significantly less likely to be immunised compared with the 1000-1500g group for all vaccines apart from the second dose of Rotavirus. Rouers et al. (2019) reported a higher mean time to first vaccination in the <1000g birthweight category when compared with the other categories. Also relevant to the timing of the first vaccination, Magoon et al. (1995) reported significant delays for the first scheduled vaccinations which increased as birthweights decreased. Davis et al. (1999) found that low birthweight infants (<1500g) had a significantly lower up-to-date status at all ages assessed, and Tozzi et al. (2014) found that timeliness of vaccination was associated with birthweight, and more specifically, through multivariable hazard modelling that low birthweight was associated with a delay in starting the course of HEXA. Whilst Hofstetter et al. (2019) described birthweight characteristics of the sample, this was not included in their multivariable analysis because of its strong correlation with gestational age. Similarly, Tooke and Louw (2019) and Pinquier et al. (2009) describe birthweight characteristics of the infants in their study, but no explicit findings related to this are reported.

These studies featuring birthweight report findings which are consistent; birthweight is associated with delays in vaccination and lower up-to-date vaccination status. Some of the studies reported that infants with the lowest birthweights experienced the greatest delays and were less likely to be up-to-date (Magoon et al., 1995; Slack & Thwaites, 2000; Batra et al., 2009; Ochoa et al., 2015; Nestander et al., 2018; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021). Whilst all of the studies were considered methodologically sound, there were variations in the methods used within the studies which need to be considered. With the exception of the studies by Ruiz et al. (1991) and Magoon et al. (1995), the remainder featured here use secondary data and furthermore, some include data which are up to 13 years old. Problems regarding the accuracy and timeliness associated with the use of secondary data are well documented (Vogt, 2007; Cooper, 2010), however, secondary data sources can provide large amounts of data (Mongan, 2013). Indeed, the studies by Davis et al. (1999), Langkamp et al. (2001), Batra et al. (2009), Woestenberg et al. (2014), Nestander et al. (2018), Rouers et al. (2019) and Bary-Weisberg and Stein-Zamir (2021) all have large sample sizes based on regional or national cohorts. Contrary to these findings regarding birthweight is the conclusion in the study by Crawford et al. (2009) that birthweight is not associated with up-to-date status. In this study, the sample consists of 100 infants and it relies on GP and parental recall as well as existing records. Additionally, the questionnaire distributed to GPs and parents was not tested for validity or reliability.

The association between birthweight and delays in vaccination and lower up-to-date vaccination rates, is considered to be a significant finding. Despite the variable methods and quality of the studies involved, the frequency and consistency of its occurrence strengthens this finding. Of equal significance is the date range of the relevant studies with the earliest having been published in 1988 (Roper & Day) and the most recent in 2021 (Bary-Weisberg & Stein-Zamir); this suggests that the association between birthweight and vaccination delay and completeness is a long-standing issue.

Gestational age

Prematurity featured in the findings of 17 of the 23 studies included in this review (Roper & Day, 1988; Magoon et al., 1995; Davis et al., 1999, McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Tillmann et al., 2001; Crawford et al., 2009; Pinquier et al., 2009; Denziot et al., 2011; Wilson et al., 2012; Tozzi et al., 2014; Woestenberg et al., 2014; Nestander et al., 2018; Hofstetter et al., 2019; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021; Fortmann et al., 2021). As with birthweight, the degree of prematurity was categorised by some of the researchers, and for clarity this is illustrated in Table 4.10.

Table 4.10 Studies' categorisation of prematurity.

	Gestational age (in weeks) categories
Bary-Weisberg & Stein-Zamir (2021)	<28, 28-31, 32-36, ≥37
Crawford et al (2009)	<28 and 28-32

Davis et al. (1999)	Preterm described only as <38 but also with birthweight of more than 2500g
Denziot et al. (2011)	<28, 28-30, 31-32, 33-34
Fortmann et al. (2021)	<29 weeks only, described as extremely low gestational age neonates (EGLANs)
Hofstetter et al. (2019)	23-33 Early preterm 34-36 Late preterm
Magoon et al. (1995)	<29, 30-31, 32-33, 34-37, ≥38
McKechnie & Finlay (1999)	<28, 28-29, 30-31, 32-33, 34-35
Nestander et al, (2018)	≤32, 33-36, ≥37
Pinquier et al. (2009)	<33 (only studied infants born less than 33 weeks)
Roper & Day (1988)	≤31, 32-37, ≥38
Rouers et al. (2019)	<28, 28-32, 32-36
Slack & Thwaites (2000)	24-27, 28-31, 32-35
Tillmann et al. (2011)	Unclear
Tozzi et al. (2014)	Included infants born between 22-31 weeks - no further categorisation
Wilson et al. (2012)	≤27- ≥37 Extremely preterm 28-32 Very preterm preterm 33-36 Near term
Woestenberg et al. (2014)	<32 Extremely preterm 32-36 Preterm ≥37 Full term

Table 4.10 demonstrates some variation between the studies regarding the categorisation of prematurity. Most of the studies classified full term as ≥37 or 38 weeks gestational age and the most preterm infants have been considered to have a gestational age of less than approximately 28 weeks, although Slack and Thwaites (2000) further identify infants born between 24-27 weeks, and Hofstetter et al. (2019) define infants born between 23-33 weeks.

The details regarding gestational age in the studies by Davis et al. (1999), Tillmann et al. (2001), Pinquier et al. (2009), Tozzi et al. (2014), were less clear and it was not possible to identify any additional classifications. Four studies (Wilson et al., 2012; Woestenberg et al., 2014; Hofstetter et al., 2019; Fortmann et al., 2021) named the defined categories; whilst Wilson et al. (2012) and Woestenberg et al. (2014) labelled infants born ≥37 as full term, the remaining definitions of near term, preterm, very preterm and extremely preterm are very different (Table 4.10). Laforgia et al. (2018) did not categorise gestational age; it was analysed as a continuous variable only. Gestational age was included in the description of the sample in Ochoa et al's. (2015) study, but not defined in detail. Laforgia et al. (2018) and Tooke and Louw (2019) do not define preterm but studied 159 and 60 preterm infants respectively who had been admitted to an identified NNU.

Whilst observing an overall delay in vaccination uptake in preterm infants, Denziot et al. (2011) found that infants with a gestational age of <28 weeks were significantly less likely to be up-to-date at five months of age. Similarly, Fortmann et al. (2021) found that infants <29 weeks faced delays in receiving the first vaccines (HEXA and PCV), and Ochoa et al. (2015) reported that infants <32 weeks were less likely to immunised on time, or have an up-to date vaccination status at seven months of age. Pinquier et al. (2009) found that seven out of ten infants born <33 weeks were not up-to date at the age of two years. Although not significant, this finding was echoed by Tillmann et al. (2001) in that relative to full term infants, preterm infants had lower up-to-date statuses. Similarly, Wilson et al. (2012) reported an association between gestational age and lower rates of vaccination, but this was only in conjunction with the infant being hospitalised. They observed lower rates at two and four months in extremely preterm infants who were in hospital at the time the vaccination was due, and lower rates at two months in very preterm infants. This is in contrast to the finding reported by Crawford et al. (2009) who through logistic regression found that hospitalisation meant that infants with a gestational age of <28 weeks were

significantly more likely to be up-to-date at two months. Hofstetter et al. (2019) studied up-to-date status at two timepoints, 19 and 36 months. They found that both early preterm and late preterm infants had lower completion rates when compared with term infants, at both timepoints. Magoon et al. (1995) and Rouers et al. (2019) reported a significant delay in the first vaccinations however, this was not observed in subsequent doses. Rouers et al. (2019) also found that the greatest delays were seen in infants in the lowest gestational age category of <28 weeks. Similarly, McKechnie and Finlay (1999) observed that delays were greater as gestational ages decreased, but that this was not only significant for the first scheduled vaccination, but also for the second and third vaccinations. Although not reported as significant, Roper and Day (1988) also saw a delay in the uptake of the first scheduled vaccination for preterm infants relative to full term infants. Similarly, Nestander et al. (2018) reported lower coverage for preterm infants in all identified low gestational age categories. Slack and Thwaites (2000) found that median age at first and third scheduled vaccinations negatively correlated to gestational age. Likewise, Woestenberg et al. (2014) also reported a higher median age at first vaccination in extremely preterm infants (<32 weeks) relative to full term infants. Tozzi et al. (2014) did not find an association between timeliness of vaccination and gestational age; accordingly, neither did Davis et al. (1999). However, although Davis et al. (1999) defined preterm infants as those with a gestational age of less than 38 weeks, they were required to have a birthweight of >2500g. Bary-Weisberg and Stein-Zamir (2021) found that gestational age strongly correlated with birthweight, and all subsequent analyses were undertaken using the birthweight categories. Translating these findings, it could be assumed that infants in the lower gestational age groups experienced the greatest delays, although this is not explicitly stated in the findings. Although Laforgia et al. (2018) reported delays in preterm infants, they found that completeness at 24 months equalled or was better in preterm infants compared with term infants. However, their study was undertaken to evaluate a strategy

aimed at increasing timeliness in preterm infants. Tooke and Louw (2019) were also evaluating a new initiative around vaccinating on the NNU, reporting that 68% of infants received their vaccines on time.

Several of the studies report an association between gestational age and delays in vaccination and lower up-to-date vaccination rates. Furthermore, Magoon et al. (1995), McKechnie and Finlay (1999), Slack and Thwaites (2000), Rouers et al. (2019) and Bary-Weisberg and Stein-Zamir (2021) all observed that as gestational age decreased, delays in vaccination increased and up-to-date vaccination rates were lower. Four of the studies did not find an association between gestational age and vaccination delays or up-to-date rates (Davis et al., 1999; Tozzi et al., 2014; Laforgia et al., 2018; Tooke & Louw, 2019).

Again, these findings should be considered in light of the quality and context of the studies concerned. Of note are the studies by Magoon et al. (1995), Tillmann et al. (2001) and Denziot et al. (2011) which rely solely on parental recall for immunisation history; additionally, the questionnaires used in the studies do not appear to have been tested for validity and reliability. An initiative to increase coverage and timeliness was evaluated in the study by Laforgia et al. (2018), and Tooke and Louw (2019) were also evaluating a new practice on the NNU. Roper and Day (1988) do not claim that their findings are significant and there are some missing data, meaning that these findings should be viewed with caution. Finally, the controls used in the study by McKechnie and Finlay (1999) were term infants also admitted to the unit; it could be argued that the 'normal' health status of these infants cannot be confirmed compromising their value as a control.

Interestingly, the studies by Langkamp et al. (2001) and Batra et al. (2009) do not feature gestational age in their findings. This is however implicit in the introduction, discussion and conclusion of each study, and whilst it appears sensible to assume that infants of a certain weight must also possess a degree of prematurity this association is only implied.

This association is explained by Bary-Weisberg and Stein-Zamir (2021) and accounts for the lack of gestational age having been reported explicitly. Similarly, Ruiz et al. (1991) do not highlight gestational age anywhere in their study, however, some of the characteristics used to define an infant as 'high-risk' may be also associated with prematurity (such as birthweight ≤1500g, intraventricular haemorrhage and bronchopulmonary dysplasia).

Although the methods and quality of the studies varies, there seems to be an important association between gestational age and delays in vaccination or lower up-to-date vaccination rates. This association features in several of the studies, and as previously noted is important as it occurs in studies across a wide date range (1988 – 2021), suggesting a persistent association.

Hospitalisation and other diagnoses/treatments

Some of the studies featured hospitalisation and other diagnoses and treatments, to explore how these factors may influence vaccination patterns in preterm and low birthweight infants. The length of time spent on the NNU featured in several studies. Through logistic regression, Crawford et al. (2009) demonstrated that infants <28 weeks who were hospitalised for a period of more than 30 days were significantly more likely to be up-to-date at two months. Equally, Fortmann et al. (2021) studied length of stay and found that infants were more likely to be timely immunised with longer hospitalisation, and Woestenberg et al. (2014) reported this finding among extremely preterm infants. Hospitalisation was also reported by Davis et al. (1999) as a significant factor; infants hospitalised for eight-14 days in the first month of life were significantly more likely to be up to date at six months. This finding is only reported as occurring in "low birth weight and/or premature children" (Davis et al., 1999:551) making it impossible to conclude whether the degree of prematurity or weight at birth is significant. Conversely, Laforgia et al. (2018) and Rouers et al. (2019) reported that a greater length of stay in hospital equated

to an increase in age at vaccination. Slack and Thwaites (2000) found that the median age at vaccination positively correlated to duration of stay on the neonatal unit. Furthermore, most of the infants in this study had been discharged, meaning that they were in the community at the time their vaccinations were due. Therefore, it is highlighted that these delays "reflect more closely on community practice" (Slack & Thwaites, 2000:304).

Considering where the immunisation series was initiated, Denziot et al. (2011) found that the administration of a primary vaccine before discharge was linked with better coverage after discharge, and Woestenberg et al. (2014) concluded that hospitalised extremely preterm infants (gestational age <32 weeks) were more likely to receive their vaccinations on time relative to preterm infants (gestational age 32-36 weeks). In contrast, Pinquier et al. (2009) and Wilson et al. (2012) observed lower immunisation rates in hospitalised children, in particular, very premature children (gestational age 28-32 weeks) at two months and extremely premature children (gestational age ≤27 weeks) at two and four months (Wilson et al., 2012). Bary-Weisberg and Stein-Zamir (2021) reported similar findings; only a third of infants eligible for first vaccines whilst still inpatients were vaccinated as recommended – subsequent doses for infants who remained on the NNU for 60 days or more were also not completed in a timely fashion when measured at two years of age. Similarly, by logistic regression Tozzi et al. (2014) reported an association between delays in vaccination with HEXA and MMR in low birthweight infants and hospitalisation.

Other diagnoses and oxygen therapy were also featured in some of the studies. Davis et al. (1999) found that a diagnosis of bronchopulmonary dysplasia or hyaline membrane disease was not associated with up-to-date status. Conversely, by a similar analysis, Magoon et al. (1995) did find an association between a delay in OPV vaccination and a diagnosis of bronchopulmonary dysplasia. Furthermore, in this study, a diagnosis of intraventricular haemorrhage was significantly associated with a delay in DTP vaccination and the number

of diagnoses at discharge was significantly associated with a delay in both DTP and OPV vaccinations. Tozzi et al. (2014) reported that delays of the MMR vaccination were associated with the presence of cerebral palsy. Fortmann et al. (2021) investigated associated diagnoses and reported that being small for gestational age, having impaired growth, and more complex health needs were risk factors for delayed vaccination. Tooke and Louw (2019) and Fortmann et al. (2021) also reported that infants discharged still in receipt of oxygen therapy experienced delays in vaccination, and whilst Pinquier et al. (2009) described the number of infants in receipt of oxygen therapy in their study, there are no further analyses of this variable with vaccination timeliness.

There is a lack of consensus in the studies featuring hospitalisation in their findings. Although the details of the findings differ, the studies by Davis et al. (1999), Crawford et al. (2009), Woestenberg et al. (2014) and Fortmann et al. (2021) appear to suggest that in certain circumstances, hospitalisation actually promotes timely vaccination. Alternatively, Slack and Thwaites (2000), Laforgia et al. (2018) and Rouers et al. (2019) suggest the opposite, and associate hospitalisation with delays in vaccination or lower up-to-date vaccination rates. There is also some discord regarding the initiation of the vaccination series; Denziot et al. (2011) and Woestenberg et al. (2014) reported that starting this on the NNU was associated with better, timelier uptake, but Pinquier et al. (2009), Wilson et al. (2012), Tozzi et al. (2014) and Bary-Weisberg and Stein-Zamir (2021) reported the opposite; that being on the NNU equated to less timely vaccination. All of these studies were considered to be methodologically sound to be included in this review; indeed, six of them are population-based studies featuring large samples (Davis et al., 1999; Wilson et al., 2012; Tozzi et al., 2014; Woestenberg et al., 2014; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021). It may therefore be suggested that the impact of hospitalisation on vaccination timeliness and rates in preterm infants requires further investigation. Where

studied, certain diagnoses and oxygen therapy appear to negatively impact on timeliness and completeness.

Infant and family characteristics

Three of the studies in this review explored infant and family characteristics in relation to delays in vaccination or lower up-to-date vaccination rates in preterm and low birthweight infants. Batra et al. (2009) studied ethnicity and race; for all races and ethnicities studied, significant delays were experienced among extremely low birthweight infants in comparison to normal birthweight infants. Furthermore, relative to extremely low birthweight White infants, extremely low birthweight Black and Hispanic infants had the lowest up-to-date vaccination rates. Again, relative to White infants, very low birthweight infants of all other ethnicities and races demonstrated significantly lower up-to-date vaccination levels. For all infants classed as low birthweight and normal birthweight lower up-to-date levels were demonstrated among Black and Hispanic infants when compared with white infants. Logistic regression analyses reported significant predictors of delay as extremely low birthweight, very low birthweight, Hispanic ethnicity, Black race and born before 2001. After adjusting for ethnicity (Black, Hispanic or Asian), Hofstetter et al. (2019) found that preterm infants still had lower odds of completing their vaccination series when assessed at 19 months. Bary-Weisberg and Stein-Zamir (2021) reported that infants of Jewish ethnicity experienced greater delays in receiving their vaccines.

Langkamp et al. (2001) found that vaccination rates for very low birthweight infants without health insurance were significantly lower than the rates seen in very low birthweight infants with health insurance. However, Hofstetter et al. (2019) did not find any significant association between those insured or uninsured and vaccination completeness. Langkamp et al. (2001) also reported that very low birthweight infants whose mothers had not completed high school education were significantly less up-to-date

than very low birthweight infants whose mothers had completed high school. This finding appears at odds with the finding reported by Magoon et al. (1995) that the level of parental education was not associated with delays in vaccination. Tozzi et al. (2014) explored parental employment status and found that infants of unemployed mothers were more likely to experience delays in receipt of the MMR vaccine and infants of unemployed fathers were more likely to experience a delay in receiving the HEXA vaccination. Tozzi et al. (2014) also found that a greater number of siblings in the family was associated with a delay in starting the HEXA vaccination and not being the first-born infant in the family was also associated with a delay (Bary-Weisberg & Stein-Zamir, 2021). Woestenberg et al. (2014) investigated parental education and employment under the wider term of socioeconomic status (SES), which also included average income per household. Although it was only a significant finding in extremely preterm infants, Woestenberg et al. (2014) found that a lower SES was associated with lower vaccination rates; this finding has resonance with the findings reported by Langkamp et al. (2001), Tozzi et al. (2014), Rouers et al. (2019) and Bary-Weisberg and Stein-Zamir (2021). This inference is contrary to the finding of Magoon et al. (1995) that the level of parental education was not associated with delays in vaccination; additionally, Denziot et al. (2011) reported that a lower family income was associated with greater up-to-date vaccination levels. The study by Woestenberg et al. (2014) took place in the Netherlands and it also reported that infants were more likely to be vaccinated on time if the parental country of birth was the Netherlands.

Although not investigated in many of the studies, the population-based enquires by Batra et al. (2009) and Bary-Weisberg and Stein-Zamir (2021) provide a strong indication that race and ethnicity are factors which influence vaccination patterns in preterm and low birthweight infants. Two different large population-based studies reported an association between mothers' educational level and vaccination patterns in preterm and low

birthweight infants (Langkamp et al., 2001; Woestenberg et al., 2014); conversely, Magoon et al. (1995) did not find any association but this was an older smaller scale study which relied on parental and primary care provider responses for data. Findings by Woestenberg et al. (2014) that parental employment status or socioeconomic status was associated with vaccination delay and rates concur with the findings of Tozzi et al. (2014), Rouers et al. (2019) and Bary-Weisberg and Stein-Zamir (2021). Again, the strength of these large population-based studies signifies that this is an important finding.

Additional findings

The care received by the infant after discharge also appeared to have an effect on vaccination rates and timeliness. Davis et al. (1999) found that children were more likely to be up-to-date at two years of age if they had received more than three well-child visits than those having received less than three visits. Likewise, Nestander et al. (2018) reported that rates of vaccination completion increased with scheduled well-child visits. Similarly, Denziot et al. (2011) reported significantly better coverage of the PCV vaccine in infants followed up by a network vaccinator.

In addition to studying vaccination patterns, three of the studies explored other elements of practice around vaccinating preterm or low birthweight infants and potential reasons for a delay. Crawford et al. (2009) undertook a postal survey among neonatologists (*n*=76, 68% response rate) investigating practice in accordance with national recommendations. Nearly all of the respondents (89%) reported that they recommended vaccination in agreement with national policy, and a further 95% stated that they had a policy in place to support this in practice. However, the questioning in the survey revealed a lack of adherence to the guidance. Magoon et al. (1995) focused on standards of practice among care providers by surveying paediatricians, family physicians, neonatologists and public health clinics. It was found that compared with the other care providers, a higher proportion of family

practitioners deviated from the national standards; for preterm infants, they used a different schedule (48%) and vaccinated according to the infants corrected age (52%) rather than chronological age as recommended. When questioned regarding contraindications to DTP vaccination, paediatricians and family physicians listed factors which were not in keeping with national standards. Magoon et al. (1995) also questioned parents regarding delays in the vaccination of their infants. This survey revealed that the proportion of parents who perceived a delay was less than the actual proportion of infants who experienced a delay. Furthermore, some of the reasons for delay cited by parents concurred with the contraindications given by care providers, namely, gestational age, low birthweight, otitis media and upper respiratory tract infection. Ruiz et al. (1991) contacted the primary health care provider by telephone to establish reasons for non-vaccination. Of the 14 infants who never received any vaccinations against pertussis, nine could have received the vaccine in accordance with national recommendations. The remaining five could have also received the vaccine; in these cases, it should have been deferred rather than omitted completely. Each of the clinicians responsible for the care of these children (n=14) cited concern over their liability should the vaccine cause some neurologic injury as the reason the why vaccine was not given.

The small number of responders in these studies (Ruiz et al., 1991; Magoon et al., 1995; Crawford et al., 2009) means that caution should be applied when drawing inferences from these findings. Crawford et al. (2009) only include neonatologists in their study meaning that other care providers of preterm and low birthweight infants are not represented here. Additionally, the studies by Ruiz et al. (1991) and Magoon et al. (1995) are quite dated, so the value of these findings in relation to current practice are questionable as attitudes may have shifted. Nonetheless, the studies do provide possible insights into immunisation practices in preterm and low birthweight infants, along with some potential reasons why vaccination may be withheld or delayed.

4.7.3 Element 3 – Exploring relationships

At this stage of the synthesis, Popay et al. (2006) describe moving away from identifying, tabulating, counting and listing results, towards exploring the relationships between them. Two broad types of relationships are identified: those between individual study characteristics and those between the findings of different studies. Having reached this stage of the synthesis, it was apparent that much of this had already been done. Both the groupings and clusters and the vote counting and data translation sections compared and contrasted relationships between the studies methods and findings. This process emphasised the heterogeneity across the studies included, and even at this stage, provided further validation for using this narrative synthesis approach as the method of analysis in this review. Several tools are described to support the process of exploring relationships (Popay et al., 2006), including graphs, frequency distributions, funnel plots, forest plots and L'Abbe plots**,** however, these techniques were considered to be of particular use when undertaking a meta-analysis and were therefore in this instance inappropriate.

Moderator variables and sub-group analyses

When analysing interventions, reviewers need to consider "what works, for whom, and in what circumstances" (Popay et al., 2006:19), a notion originally developed by Pawson and Tilley (2004). Doing this includes analysing moderator variables, or those variables which are expected to moderate the effect under question in the review. Whilst none of the studies in this review are intervention studies, the principle described here can still be applied. Some moderator variables (factors associated with timeliness or completeness) spontaneously emerged in the process of exploring vaccination rates in preterm and low birthweight infants and these are discussed in the vote counting and data translation section. Furthermore, many of the tables presented in the groupings and clusters section examine characteristics across the studies, another method of identifying the circumstances and contexts of the studies.

Idea webbing and concept mapping

Popay et al. (2006) provide two fundamental reasons for using tools such as concept maps: to group findings considered conceptually similar and to identify relationships between them. Visual methods are recommended so that relationships can be clearly illustrated and to create a representation of the final product. In this synthesis process, doing this served two purposes. Firstly, and as Popay et al. (2006) explain, it enabled a visual representation of the grouped findings and illustrated the relationship between them, and secondly it served as a method of verifying that the discussion in element two (vote counting and data translation) was comprehensive and accurate. This review was guided by the question: *'are vaccinations in preterm infants delayed?'* and the dichotomous nature of this question suggested that the findings from the selected studies would indicate that either vaccinations were or were not delayed in this population. However, this was not as straightforward as anticipated, and findings were much more dependent on circumstances; it was at this stage that findings were aligned to a visual representation and the concept map featured in

Figure 4.4. This illustrates the key findings, and their influence on vaccination timeliness and uptake. It also highlights in the corresponding colours where factors served to both facilitate and serve as a barrier to uptake and timeliness.

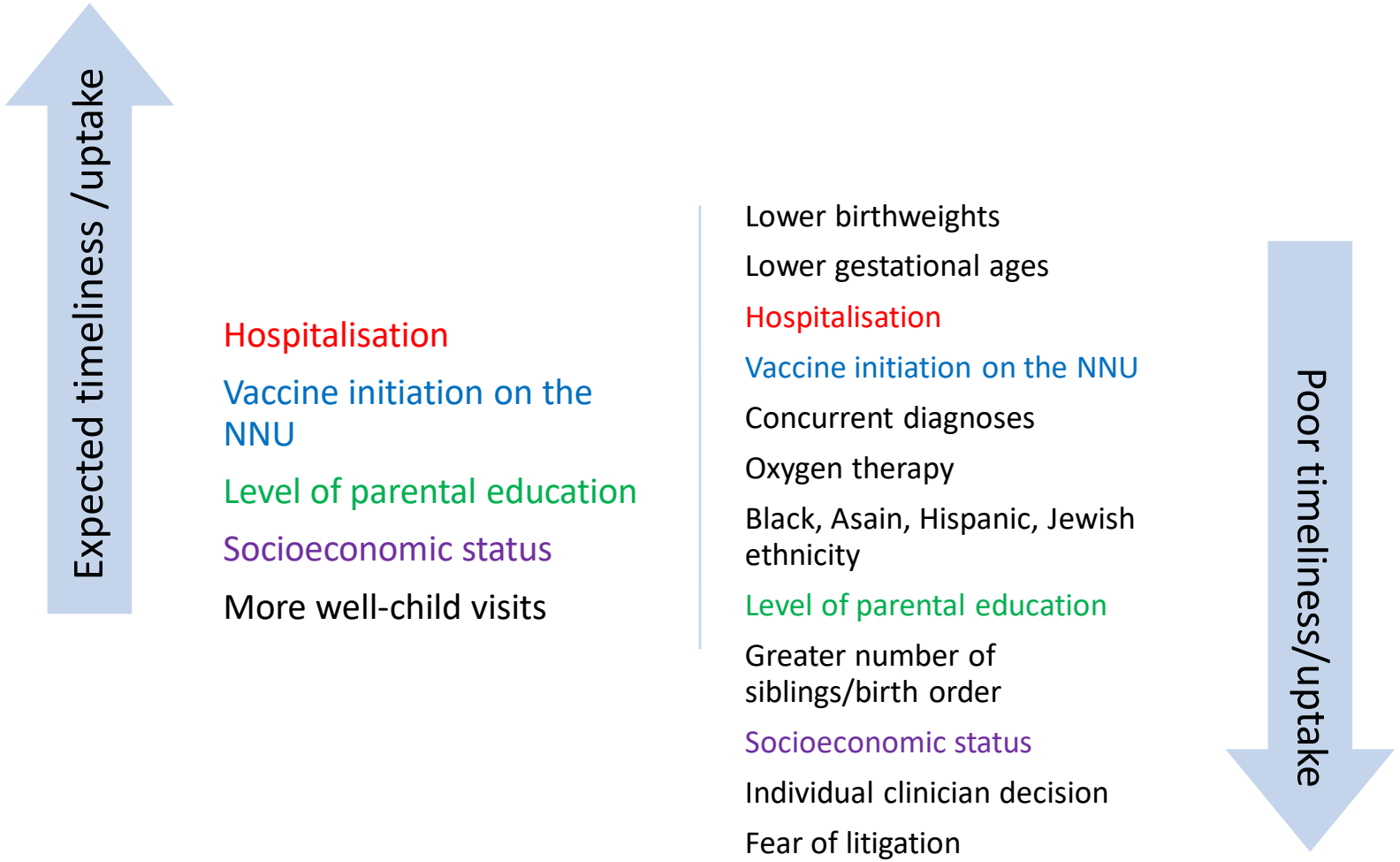


Figure 4.4 Concept map of findings

Data translation: reciprocal and refutational

Data translation is described as a method of "using qualitative research techniques to synthesise findings from multiple studies" which is "typically based on the work of Noblit and Hare" (Popay et al., 2006:20). A fundamental aspect of this involves the translation of the studies into each other, and although commonly associated with qualitative designs, this technique can be used when the review includes a combination of both qualitative and quantitative approaches; however, the nature of this review meant that there was insufficient qualitative evidence for this to be of any value.

Qualitative case descriptions

This is described as the process of using descriptive data from the studies which has attempted to explain or make sense of the findings (Popay et al. 2006), and in published studies, these data most usually come after the results section. It was considered that this element would be most appropriately incorporated into the discussion section of this chapter (section 4.8) to allow for a broader insights which would encompass the findings from across the studies.

Investigator/methodological triangulation

Investigator and methodological triangulation refer to the methods used by researchers across the studies in a review (Popay et al. 2006). This may help to explain why the results are reported in a certain way. Many of the aspects relative to methodological triangulation have been explored already in the *groupings and clusters* section, but investigator triangulation is relevant here. The purpose of this is to consider the data in relation to the context and disciplinary perspective of the researchers, although it could be argued that this is of greater concern where qualitative approaches have been used. Even though the researchers' credentials were considered in the earlier appraisals of each study, revisiting

this here was regarded as a useful way of checking for anything unusual in light of the methods used and the findings. Table 4.11 provides an overview.

Table 4.11 Disciplinary and practice background of researchers.

Bary-Weisberg & Stein-Zamir (2021)	Public health and community medicine and district health
Batra et al. (2009)	Vaccine research and paediatrics
Crawford et al. 2009)	Research institutes, infectious diseases and neonatal unit
Davis et al. (1999)	Government disease control centre and vaccine safety project
Denziot et al. (2011)	Neonatal medicine, research institute, and paediatrics
Fortmann et al. (2021)	Paediatrics, neonatology and research
Hofstetter et al. (2019)	Paediatrics, research and immunisation office
Laforgia et al. (2018)	Biomedical science
Langkamp et al. (2001)	Paediatrics, biostatistics and pharmacology
Magoon et al. (1995)	Neonatology
McKechnie & Finlay (1999)	Paediatrics
Nestander et al. (2018)	Paediatrics
Ochoa et al. (2015)	Public health and 'hospital' settings
Pinquier et al. (2009)	Paediatrics and neonatology
Roper & Day (1988)	Epidemiology
Rouers et al. (2019)	Infectious diseases, primary care and paediatrics
Ruiz et al. (1991)	Disabilities centre and paediatrics
Slack & Thwaites (2000)	Paediatrics
Tillmann et al. (2001)	Paediatrics
Tooke & Louw (2019)	Neonatology
Tozzi et al. (2014)	Epidemiology, birth defects and prematurity centre, maternal and child health institute and neonatal units
Wilson et al. (2012)	Research institute, epidemiology, public health, family and community medicine
Woestenberg et al. (2014)	Epidemiology and surveillance and disease control centre

The backgrounds of the researchers are relevant to the topic of this review and the range of backgrounds may explain the heterogeneity seen across the studies. The context of the studies tended to reflect the researchers' disciplines; the authors of the studies which were

based on data from neonatal units, tended to be from a neonatal or paediatric background (Ruiz et al., 1991; Magoon et al., 1995; McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Tillmann et al., 2001; Crawford et al., 2009; Tooke & Louw., 2019). Some of the population-based studies were undertaken by researchers from public health or epidemiological disciplines (Davis et al., 1999; Langkamp et al., 2001; Batra et al., 2009; Wilson et al., 2012; Tozzi et al., 2014; Woestenberg et al., 2014; Bary-Weisberg & Stein-Zamir, 2021). Furthermore, it could be argued that the studies conducted by researchers from a range of disciplines make inferences from their findings which consider wider clinical and public health perspectives, and this is considered in section 4.8.

4.7.4 Element 4 – Assessing the robustness of the synthesis

The robustness of the synthesis can be scrutinised at different levels. Initially, the methodological quality of the included studies can be reviewed on an individual basis; this then obviously impacts on the quality of the synthesis that is based on these studies. So, the trustworthiness of this synthesis is highly dependent on the quality of the evidence that it has been based on.

Weight of Evidence

This refers to the selection of studies for inclusion in the review. Here, Popay et al. (2006) describe an approach where relevance criteria are set according to the review question and studies are assessed for suitability on these criteria. This approach has been adopted in section 4.4 - Criteria for inclusion and exclusion and selection process. Using these criteria ensured that the studies included were given equal consideration in a systematic manner.

Best evidence synthesis

The assessment of the included studies' methodological quality is referred to here. Popay et al. (2006) describe that at this stage, information is extracted from each study in the same way, using a standard format. In addition, the quality of the study is assessed by also using systematic methods to promote parity and prevent bias. This process was undertaken using a standardised form (Figure 4.2) and is described in section 4.5.

Use of validity assessment

Popay et al. (2006) refer to this as assessing the strength of the evidence presented and the guidance set out by the Evidence for Policy and Practice Information (EPPI) is referred to. According to the EPPI approach, four criteria are used to determine the weight of evidence a study has to offer. These criteria are: trustworthiness (methodological soundness), appropriateness (ability to answer review question), relevance and overall weight, which result in a score being produced. However, it did not appear appropriate to subject the studies in this review to further quality assessment. The trustworthiness, appropriateness and relevance of each study had already been scrutinised and deciding that the weight of one study was greater or less than another seemed futile. Furthermore, ranking the studies seemed equally misguided; this synthesis considers the weight of all the evidence in its entirety, and values the contribution each study makes to the review question.

Reflecting critically on the synthesis process

The limitations of this review including the synthesis process are considered in section 4.8.

Checking the synthesis with authors of primary studies

Popay et al. (2006) refer to this in the context of qualitative data and it was not considered to be necessary in this synthesis.

4.8 Discussion

This literature review set out to answer the question *'are vaccinations in preterm infants delayed?'* and the studies included used a range of methods. All of them studied all or some of the scheduled vaccines, although these varied according to the country and year when the studies were set. The scope of the studies also differed with samples being selected from admissions to single neonatal units to wider, population-based samples. Whilst some of the studies focussed on the birthweight of infants included as the independent variable, others concentrated on gestational age. This presented some difficulty in translating the findings of the studies into one another, and thus, the findings of these studies were considered separately. With the exception of three of the studies (Ruiz et al., 1991; Langkamp et al., 2001; Batra et al., 2009) the remainder implied that birthweight and gestational age were associated. A low birthweight is not necessarily suggestive of prematurity; infants may be born full term but be small for gestational age (Lissauer & Carroll, 2018). However, premature birth is recognised as a leading cause of low birthweight therefore, in their entirety, the findings of all of the studies contribute to answering the review question. Whilst the data collection methods of the studies varied all but one (Rouers et al., 2019) used secondary data sources. Some used a combination, also relying on parents or health care providers to supply the required information (Ruiz et al., 1991; Magoon et al., 1995; Slack & Thwaites, 2000; Tillmann et al., 2001; Crawford et al., 2009; Denziot et al., 2011; Tozzi et al., 2014; Fortmann et al., 2021).

This literature review has some limitations. The heterogeneity of the studies included meant that a more traditional meta-analysis was not possible and a narrative synthesis

was undertaken instead. Whilst this is considered a legitimate method of analysis and followed established guidance, there were some elements of the synthesis (such as data transformation) which were not appropriate, and other elements were adapted prior to use (vote counting and data translation). The methods used, and indeed those not used, have been justified; however, it is possible that in this interpretation and adaptation of the elements suggested by Popay et al. (2006), some objectivity has been lost.

Whilst an assessment of the methodological quality of each of the studies has been undertaken, it is worth considering some of the limitations associated with the secondary data used in them. According to Mongan (2013) among the commonly cited disadvantages are differences in the classification of the variables, the lack of assurance around the completeness, quality and accuracy of the data and the potential for the data to be out-of-date. These are all issues which were identified in the studies included and it could be disputed that they may have compromised the synthesis of this review. However, Mongan (2013) also writes that the quality of data from large scale surveys is likely to be high given that such projects often involve the expertise of experienced researchers.

Many of the studies revealed a significant association between birthweight and vaccination schedule completeness. Furthermore, seven studies suggest the lowest birthweights are associated with increased delay and non-completion (Magoon et al., 1995; Slack & Thwaites, 2000; Batra et al., 2009; Ochoa et al., 2015; Nestander et al., 2018; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021). Similarly, some findings reported an association between gestational age and vaccination status with Magoon et al. (1995), McKechnie and Finlay (1999) and Slack and Thwaites (2000), Rouers et al., (2019) and Bary-Weisberg and Stein-Zamir (2021) also suggesting a negative correlation between these variables. Several studies hypothesised reasons for poor uptake which were directly related to the infants' prematurity or birthweight. Batra et al. (2009) inferred that

an infants' weight directly influenced decisions of whether or not to vaccinate and Langkamp et al. (2001) described infants of low birthweights as having special health care needs; it is suggested that immunisation campaigns need to be broad enough to encompass low birthweight infants. Similarly, Rouers et al. (2019) cited hospitalisation as a significant barrier to timeliness and completeness. Rather than not vaccinating due to true contraindications, Roper and Day (1988) propose that delays occur because of parents' "inappropriate worries" relating to the infants' weight or gestational age. Although the review found some opposing findings, in the determinant of access, Thomson et al. (2016) found that hospitalisation (more specifically being born in hospital) facilitated more timely vaccination. Vaccinating infants with a lower birthweight or gestational age may be seen as risky, and with the presence of any other comorbidities, it is possible that vaccination is not deemed as important as other treatments. This could be from both a parental and provider viewpoint. Thomson et al. (2016) discuss omission bias in the determinant of acceptance, which has strong connotations with this suggestion. Fortmann et al. (2021) postulate that uncertainty and lack of knowledge on the part of parents and providers contributes to delays, which relates to the determinant of awareness (Thomson et al., 2016). The studies by Slack and Thwaites (2000) and McKechnie and Finlay (1999) both report that illnesses associated with prematurity could be a cause for delay. It is asserted that although illness may potentially be a cause for delay at the first scheduled vaccination, it is unlikely it would account for subsequent delays (McKechnie & Finlay, 1999). Slack and Thwaites (2000) suggest that preterm infants may have more respiratory symptoms which prompt unwarranted delays. Again, these findings suggest that omission bias could be relevant here, but also that that greater awareness of the vaccination programme could play a part for some (Thomson et al., 2016). Ruiz et al. (1991) studied high risk infants and in this study the term 'high risk' referred to several criteria (including low birthweight) associated with the risk of occurrence of

developmental delay. It is implied that labelling infants as ‘high risk’ creates confusion in that it could be interpreted as the infant being at a higher risk of adverse reactions following pertussis vaccination. However, this may be a notion associated with all vaccinations for preterm infants and Crawford et al. (2009) and Nestander et al. (2018) refer to the perceived fragility of the infant (from parent and provider perspective) as a potential reason for a delay in vaccination. Once again, this has strong connotations with the element of omission bias cited with the determinant of acceptance (Thomson et al., 2016). Paradoxically, Glanz et al. (2009) found that parents who refused to give consent for pertussis vaccination were more likely to have infants at an increased risk of pertussis infection, and this includes preterm infants. Increased support to enhance timeliness and uptake was suggested by two studies; this was to support parents with their decision making about vaccination (Hofstetter et al., 2019), and also as a way of supporting providers through the introduction of distinct policies and procedures (Bary-Weisberg & Stein-Zamir, 2021). Support for parents strongly aligns to the determinants of awareness and activation. Awareness highlights that an appropriate amount of information and contact with a health professional are important influences, and activation includes the importance of personal prompts and provision of information in alternative contexts (Thomson et al., 2016).

Batra et al. (2009) suggest that negative media coverage and parental beliefs concerning vaccinations may be a barrier to timely immunisation; but it could be said that this may be a cause for delay for all infants and not just in preterm infants. Indeed Holton et al. (2012) examined the fundamental role the media played in the controversy surrounding the MMR vaccination and the negative impact this had on uptake rates for all children. Thomson et al. (2016) do not cite the influence of the media in their taxonomy. However, it could be a relevant factor in the determinants of awareness, and specifically, for the acceptance factors related to the social context. Influencing vaccination decisions either

way, the internet has been identified as a frequent source accessed by mothers searching for vaccination information (Vrdelja et al., 2018).

Discharge planning is identified as a potential influence on vaccine uptake. Tillmann et al. (2001) suggest that parents see their preterm infants as 'needing a rest' after discharge and that health care providers do not prioritise vaccination in discharge care plans. Woestenberg et al. (2014) propose that logistical issues associated with the transference of care contribute to a delay, and in particular, doubt over who is responsible for administering the vaccines. These issues related to discharge suggest that the importance of timely vaccination needs to be reinforced at discharge. Additionally, they imply that vaccination may be viewed as a risky intervention by both parents and health care providers alike, given the ambiguity over the responsibility for administering them, and this has some resonance with omission bias (Thomson et al., 2016). Some studies reported on starting the series of vaccinations on the neonatal unit; Slack and Thwaites (2000) found that this had no bearing on improving the timeliness of subsequent vaccinations after discharge and point towards increased education in the primary care setting as a strategy to address this. Other studies reported that hospitalisation had a negative impact on initiation and subsequent timeliness and uptake; Pinquier et al. (2009), Wilson et al. (2012), Tozzi et al. (2014) and Bary-Weisberg and Stein-Zamir (2021). Conversely, Denziot et al. (2011) and Woestenberg et al. (2014) reported that starting the scheduled vaccinations on the unit did improve future coverage. It could be assumed that primary health care providers are more confident in prescribing and administering the vaccines knowing that the infant has already safely received at least one dose; equally, this may also be true of parents giving consent, who might be assured by the fact that this would not be the first time their child is to be vaccinated. This points towards the determinant of acceptance where trust in vaccine policies and recommendations of a health professional to vaccinate are cited as influences (Thomson et al., 2016). This also suggests the need

for increased support for those tasked with administering vaccines on the NNU, as already proposed by Bary-Weisberg and Stein-Zamir (2021). Laforgia et al. (2018) suggests that neonatologists can play a crucial part in this in three ways; by initiating the immunisations when due should the infants still be hospitalised, reinforcing the need for timely vaccination on discharge, and checking vaccination status at any follow up visits. Thomson et al. (2016) report that contact with healthcare systems (access), recommendations to vaccinate (acceptance) and personal prompts (activation) are all significant factors in influencing vaccination decisions.

Three studies found an association between the amount of follow up the preterm infant receives and immunisation coverage, in that an infant was more likely to be up-to-date having received more frequent visits, regardless of whether the contacts were due to ill health or not (Davis et al., 1999; Denziot et al., 2011; Nestander et al., 2018). These findings are extended and Davis et al. (1999) propose that all children, irrespective of prematurity who are regularly followed up, are more likely to have up-to-date vaccination statuses. Similarly, and perhaps unsurprisingly, Denziot et al. (2011) found that coverage of PCV was better in preterm infants seen by a follow-up network vaccinator and they link this finding to low-income; infants of families with social difficulties including low income, are routinely offered mother-infant welfare visits, during which vaccination status is addressed. These findings strongly align to the determinant of access, where increased engagement with services had an impact on vaccination rates (Thomson et al., 2016). In the UK, frequent core contacts with all children under five years old regardless of gestational age, are written into policy giving primary health care providers the opportunity to consider immunisation status (Department of Health, 2009). However, the identification of any overdue vaccines still relies on the parents having the means as well as the motivation to take their children to receive the vaccines. Domiciliary vaccination is recommended for those families experiencing difficulties accessing vaccination

services but it is not a service which is offered consistently in the UK (National Institute for Health and Care Excellence (NICE), 2009). Convenience (access) and perhaps having to take time off work, expense incurred form attending appointments (affordability) are important considerations here (Thomson et al., 2016).

Several studies reported on the influence of characteristics associated with socioeconomic status. Tozzi et al. (2014) suggest that the higher vaccination rates seen in preterm infants of employed mothers may be due to the improved social contact these mothers have which promotes the exchange of information. Whilst Thomson et al. (2016) deliberately excluded socio-demographic factors, acceptance factors associated with the social context include peer influence, which could play a part in information exchange. Tozzi et al. (2014) also reported lower rates of HEXA in preterm infants of unemployed fathers and propose that this may be due to wider social problems including access to vaccine facilities. It is also reported that HEXA uptake is lower with an increasing number of siblings. Bary-Weisberg and Stein-Zamir (2021) also reported that when the infant was not the first born, delays are more likely. Although no reasons are offered to explain this, it could be explained by logistical reasons; accessing services may be practically challenging with multiple children to care for (Rainey et al., 2011). There is an obvious connection with this finding to the determinants of access and affordability (Thomson et al., 2021). Accessing appointments, and affordability in terms of time and potential expense may all be more challenging for parents with a greater number of children. The studies by Batra et al. (2009), Hofstetter et al. (2019) and Bary-Weisberg and Stein-Zamir (2021) were the only ones included in the review which explored ethnicity and race as predictors for vaccination delay. Hofstetter et al. (2019) and Bary-Weisberg and Stein-Zamir (2021) reported poorer uptake in Black, Hispanic, Asian and Jewish infants respectively, but do not return to this finding in their discussion to offer any explanation. However, Batra et al. (2009) explain the reasons for the identified delays seen in preterm

Black and Hispanic infants by referring to previous investigations into vaccination rates in different racial and ethnic groups where delays are associated with socioeconomic status and poorer access to health care services. In addition, Wagner et al. (2014) identified that infants, irrespective of prematurity, from some ethnic minority groups were at greater risk of being under immunised, particularly if they were not registered with a GP. Whilst there could be connections to particular religious and moral convictions (related to acceptance), Thomson et al's. (2016) determinants of awareness and activation could be of equal importance. For some parents, English may not be their first language meaning that there are some difficulties with the exchange of information and communication in all forms. Furthermore, generic invitations and reminders may not account for ethnic diversity in populations.

The determinant of awareness encompasses knowledge, information and education (Thomson et al., 2016) and an increasing need for appropriate information and education was suggested as a strategy to increase vaccination uptake and rates in preterm infants by some authors (Magoon et al., 1995; Slack & Thwaites, 2000; Tillmann et al., 2001; Denziot et al., 2011; Tozzi et al., 2014; Ochoa et al., 2015; Laforgia et al., 2018; Rouers et al., 2019; Fortmann et al., 2021). This was either education or information aimed at parents and health professionals, and similar strategies have recently been identified as a means of increasing vaccination uptake in the general population (Jarrett et al., 2015). However, tailoring this information and targeting parents of preterm infants and those health care providers working with them could improve its effectiveness.

Conflicting findings were reported among the studies regarding the influence hospitalisation and concurrent illnesses may have on vaccination timeliness and rates. Davis et al. (1999), Crawford et al. (2009), Woestenberg et al. (2014) and Fortmann et al. (2021) reported an increase in age appropriate immunisation based on how long the infant

was hospitalised, although Woestenberg et al. (2014) only reported this finding among extremely preterm infants. The studies do not offer any explanations for this, but it may be argued that the constant monitoring that these infants receive whilst inpatients increases their chances of being vaccinated earlier when compared with preterm infants who have been discharged into the community and may not be under such close observation; this connects with access (Thomson et al., 2016) in that contact with services is deemed an important influence. Of the studies reporting the opposite, that hospitalisation length has a negative impact on vaccination timeliness (Slack & Thwaites, 2000; Laforgia et al., 2018; Rouers et al., 2019), again no potential causes are discussed in the studies. However, one possible explanation may be related to the reasons behind hospitalisation; the infant may have concurrent illnesses or an unstable health status which is seen as a reason to withhold or delay vaccination. Prematurity itself is not a contraindication to vaccination and there are very few reasons which would warrant non-vaccination or a delay (PHE, 2017) therefore it is vital that the genuine contraindications are understood by those caring for preterm infants as inpatients. Acceptance, more specifically, omission bias and perceived risk associated with the vaccine can be considered here (Thomson et al., 2016).

This literature review sought to answer the question *'are vaccinations in preterm infants delayed?'* In their entirety, the studies included support the notion that they are. Infants with the lowest birthweights seem to experience the greatest delays and are less likely to be up-to-date and there is evidence of a negative correlation between birthweight and age at vaccination, and a similar negative correlation is also reported between gestational age and age at vaccination. More specifically, some delays are greatest in extremely low birthweight infants of Black or Hispanic origin, and for infants in the lowest birthweight categories from families with a lower socio-economic status. The studies demonstrate that this delay is not vaccine specific, that it is apparent across countries and has been a

problem over some decades. The variability between individual studies may be explained by amendments to guidance and the constantly changing vaccination schedules; changes which occur to reflect disease epidemiology and the development of novel vaccines. From a UK perspective, the most recent study is from 21 years ago (Slack & Thwaites, 2000), since which time there have been many changes to the routine schedule. The more contemporary studies reviewed support the continued existence of a delay; therefore, it is reasonable to suspect that this may still be the case in the UK. Additionally, of the UK studies reviewed, none of them were population based, so although they contribute to the wider picture of vaccination rates and timeliness in preterm infants, any inferences drawn from them are limited.

There are several parallels between the review findings and the determinants of vaccine uptake described by Thomson et al. (2016). All of the determinants appear, but most prominently, acceptance and the specific element of omission bias was a recurring feature. This suggests that vaccinations are delayed over concern that the vaccine itself may be detrimental to the infant; a decision which may imply that perceptions about disease risk and severity are also influential. The findings of this review have both clinical and public health importance. Vaccination is a fundamental public health activity primarily undertaken in the community where practitioners enact policies aimed at populations of unspecified individuals (Verweij & Dawson, 2007). Equally however, the decision to vaccinate a preterm infant in the acute care setting is likely to be based on clinical judgement centred on individual infants.

4.9 Conclusion

This chapter has presented a review of the literature which set out to answer the question *'are vaccinations in preterm infants delayed?',* and the narrative synthesis used to analyse

the studies facilitated an approach which supported the notion that they are. The review also identified several influences on vaccination timeliness in the preterm population.

As well as using gestational age as a variable, a common characteristic of infants in the studies was birthweight. Both gestational age and birthweight were strong indicators of a delay, with some studies suggesting that lower gestational ages and lower birthweights lead to a greater delay. Within the studies, other characteristics associated with vaccination timeliness were identified and these included hospitalisation of the infants and increased follow up. There was some disagreement between studies as to whether parents' socio-economic status and educational level had any influence on timeliness or uptake. These differences could be explained by the smaller sample used for one of the studies (Magoon et al., 1995), and that another was assessing uptake in an area where there was a vaccination follow up scheme in place (Denziot et al., 2011).

There are several reasons presented across the studies to explain the existence of a delay in the preterm population, and many of the findings can be understood by considering them alongside the determinants of vaccine uptake (Thomson et al., 2016). Some of these are associated with concerns directly related to the infants' gestational age or weight; infants could have long standing or recurrent health needs, which may or may not be authentic reasons for a delay. The suggestion is also made that negative media coverage could influence parental beliefs concerning vaccination, although it is acknowledged that this would apply to all parents, and not just those of preterm infants. The concept of risk is highlighted in some of the studies; either that preterm infants are 'high risk', or that the giving of vaccinations to this population is in itself is perceived as a risky intervention. Where parental socio-economic and educational status were studied, influences and barriers to timely vaccination were suggested as being related to greater social contact and subsequent information exchange, and lack of access to vaccination facilities. Two

of the studies also found that preterm infants with a higher number of siblings were less likely to receive vaccinations, which again, could make attending vaccination appointments more challenging. Ethnicity was explored in some studies and found to be a barrier to vaccination in some cases; it is suggested that this may be for socioeconomic reasons and access to health care.

From a UK perspective, this review has identified a lack of recent research investigating vaccination timeliness in preterm infants. Furthermore, there have been no population-based enquiries in the UK and it is suggested that this is an area requiring attention. Identifying any shortfalls in vaccinating this population could influence policy and inform practice so that preterm infants may receive timely vaccination which will offer them the vital protection against infection that they need. Chapter five presents the methodology for the current study, justifying the research approach and design developed to address the research question.

Chapter 5 Methodology

5.1 Introduction

Chapter two identified the importance of vaccination in the prevention of disease, and explained why preterm infants specifically, are a cohort of the population who are at greater risk of infection. The subsequent literature review presented in chapter four supported the existence of a delay in these infants. However, the studies identified in the literature review were either small scale, not contemporaneous, or not based on a UK population. Therefore, the aim of this study is to investigate this issue further in a UK, regional based study. Knowing that the preterm population may be exposed to risk because of untimely vaccination may facilitate the development of strategies aimed to address this delay.

This chapter presents a rationale for the research approach and design and defines the study population and variables. It also outlines the research process, including a consideration of the key ethical issues associated with the selected design. Fundamentally, it provides the foundation for the selected methodology to address the proposed research question.

5.2 Research question

The study set out to answer the following:

- Is there a mean difference in vaccination age between preterm and full term infants?
- Is there a relationship between gestational age and age at vaccination?
- What are the factors associated with vaccination timeliness?

As the study aimed to investigate this from a regional perspective, this entailed the use of large amounts of data pertaining to full term and preterm infants. The primary aim

addressed the question of the existence of a delay in vaccinating preterm infants, and further investigations aimed to explore the relationships between variables.

5.3 The research approach and design

Given the stated research questions, the selected research approach was quantitative. Quantitative approaches are described as those which use theoretical and methodological techniques and principles where the focus is on measurement using numbers and statistics (Sarantakos, 2013). The study's aims indicate an examination of defined variables; variables which are measurable, resulting in numerical data which for analysis using statistical methods is appropriate.

The data used in this study were derived from secondary sources, and this research design may be described as secondary data analysis. Whilst recognising the existence of many definitions concerning secondary data analysis, Smith (2006) concludes that it is an empirical activity using data which are already compiled. Furthermore, and as is the case in this research, Smith (2006) states that secondary data analysis may include the application of a novel research question, statistical approach or theoretical framework to the existing data; it is this feature which distinguishes it from other designs, characterising it as a research design in its own right. Johnston (2014) describes secondary data analysis as an empirical approach which is subject to the same research principles as studies which use primary data and asserts that it is a viable design provided a systematic process is followed. The decision to use secondary data was influenced by several factors. Fielding et al. (2017) highlight the amount of time, money and other resources which can be saved by using secondary data. Additionally, Smith et al. (2011) emphasise how secondary datasets can provide access to large samples where accessing an equal amount of data first hand would be extremely challenging to replicate (Smith, 2006), and this was certainly the case for this study. The study used secondary data because there are large existing datasets from which the required infant and immunisation information could be

obtained; to also collect the data first hand may not have only been a poor use of resources but it could have even been considered unethical (Triparthy, 2013). Mongan (2013) also writes that expedient and economical research which effectively answers questions relevant to policy makers is being increasingly called for and using secondary data to do this is completely feasible.

When planning this study, these were all reassuring observations. However, there were significant challenges – particularly in relation to time and expense. The amount of time taken to obtain the required data from existing sources was hugely underestimated; this was due to the use of multiple datasets hosted by different organisations, and the approvals required for using patient identifiable data without consent. Using these data also incurred some costs, which although may not have been as much as collecting the data first hand, were still substantial. Furthermore, a process of data linkage between datasets was required (as illustrated in Fig. 5.2). Whilst this was, in principle, the most suitable approach, such linkage processes are also not without their drawbacks. Harron et al. (2017) highlight some common problems and the following was especially relevant in this study. Due to preserving the confidentiality of the data, as the researcher, I was unable to perform this linkage myself, and so this meant relying on a third party to undertake this process (details are provided in chapter 6). The linkage was performed by data analysts, so whilst their skills and expertise of handling large datasets was reassuring, there was little I could do to confirm the reliability of the linkage.

Further disadvantages related to the use of secondary data are acknowledged. Smith et al. (2011) point out that the researcher's lack of control regarding the population and variables under scrutiny can be problematic; because, as Tripathy (2013:1479) states, "the original data was not collected to answer the present research question". The analyses that could be undertaken was confined to the data available, meaning that it was not possible to incorporate any additional variables into the study design. All the associated elements

within the determinants of vaccine uptake cited by Thomson et al. (2016) could not be directly studied (for example aspects related to peer influence or social responsibility).

Issues concerning the timeliness, accuracy and completeness of the data are also raised (Smith, 2006). As previously highlighted, obtaining the data was a protracted process, and in this time, the immunisation schedule changed. This meant that the relevance of any findings relating to these particular vaccines may now be altered. There were also some accuracy and completeness problems with the data; it was obvious where data entry errors had occurred, and it was not always possible to revisit the original source and correct this. Some data were also incomplete because it had not been gathered at the original source, and there was no method of returning to this. Despite these challenges, owing to the large amount of data yielded by the selected datasets, it is still considered that the use of secondary data analysis as the design for this study was the most appropriate choice.

Philips (2013) broaches the argument that to undertake original research, the researcher must collect their own data; otherwise, this limits their researching ability. However, this notion is quickly dismissed as misguided thinking, as the breadth of high-quality studies which have been based on secondary data demonstrate (Philips, 2013), and Smith et al. (2011) maintain that knowledge of the dataset and having a flexible approach to answering the research question are equally important research abilities. To answer the research question, access to three separate datasets was necessary: maternity dataset, neonatal dataset and immunisation dataset. Therefore, the analysis in this study is not confined to a single dataset but required matching and analysis of infant information at an individual level from across all three. Figure 5.1 provides an overview of the research process applied in this study, illustrating how this addressed the research question.

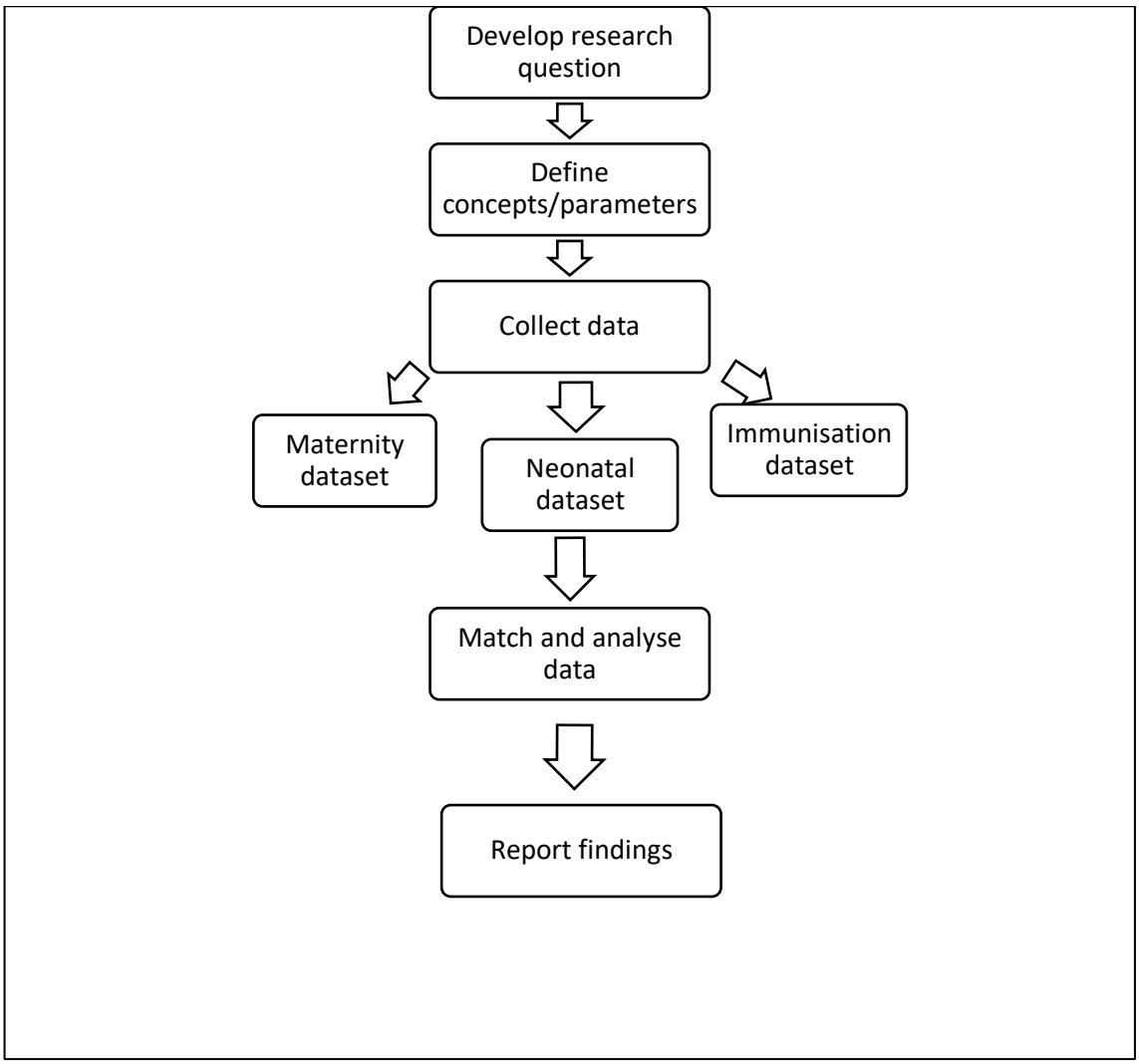


Figure 5.1 Overview of the research process for this study

5.4 Definition of concepts and variables

This section defines the study population, including how it was identified. It also describes the datasets used in the study, providing an overview of how they are linked. The justification for the definition of a delay is presented, and finally, the variables studied are defined. The rationale for all of this is provided and supported by the aims of the study.

5.4.1 The study population

The population of interest in the study was infants, both preterm and full term. As described in chapter two and based on WHO (2021b) classifications, infants born before

37 weeks are considered as preterm. Therefore, for the purpose of determining prematurity in the infants included in this study, those born at or after 37 weeks were deemed full term, and those with a gestational age of < 37 weeks were considered as preterm. Routinely, data for all infants born in England are entered into the Maternity Services Dataset (MSDS), and this is the dataset that was used to identify the infants from the region. More details are provided in section 5.4.2. All infants born over a defined six-month period were eligible for inclusion. It was estimated that the number of eligible infants would be approximately 4000-5000, and that based on UK data, around 8% of these would be born prematurely. Using data from within a defined six-month period meant that enough data for analysis would be yielded, while ensuring that that for pragmatic reasons, the dataset was manageable. More detail on this is in chapter six, but the selected six-month period was identified as during this time, there were no concerns regarding vaccination supply or delivery. Furthermore, there was nothing notable which may have had impact on uptake.

The National Neonatal Research Dataset (NNRD) was used to extract and study additional data to explore factors which may be associated with a delay in preterm infants. Further details regarding this dataset can be found in section 5.4.3. This dataset has specifically been established for research purposes, lending itself to a study with a secondary data analysis design. Figure 5.2 provides an overview of how the data were linked to answer the research question:

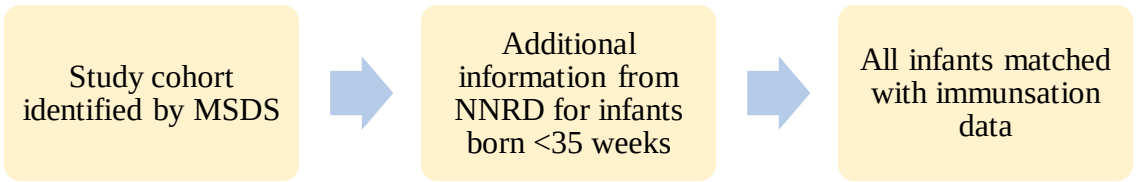


Figure 5.2 How data were identified and linked

Once the study cohort was identified, additional information for infants born under 35 weeks was extracted. Immunisation data was then requested, and all data were then matched using the NHS number (and date of birth if required) as common identifiers for each dataset.

5.4.2 Maternity Services Dataset

The Maternity Services Dataset (MSDS) captures information regarding Maternity Services activity, which relate to both mother and baby at an individual level (NHS Digital, 2021). This was the dataset which enabled initial identification of the study cohort and for this study, there were certain data concerning the specific birth episode that were of interest. Table 5.1 demonstrates the data requested from the MSDS and how this contributed to answering the research question.

Table 5.1 Data from the MSDS with rationale.

MSDS data	Rationale
Infant data: • NHS number • Date of birth • Gender • Gestational age • Birth weight Maternal data: • Date of birth • Ethnicity • Number of previous pregnancies	 Identifier to link to other datasets Identifier Variable of interest Variable of interest Variable of interest Variables of interest

The variables of interest relate to previous research which have identified that they are factors associated with vaccine hesitancy (SAGE, 2014) as well as being identified in the literature review (chapter four) as influencing factors; therefore, were considered relevant in answering this research question. Whilst Thomson et al. (2016) excluded

sociodemographic data in the development of their determinants of vaccine uptake, these were still deemed to be important considerations to enable any subsequent recommendations to be targeted. From the MSDS infants' gestational ages were identified and from this, it was possible to extract further neonatal data from the NNRD for infants with a gestational age of less than 35 weeks.

5.4.3 National Neonatal Research Database

The National Neonatal Research Database (NNRD) was established by the Neonatal Data Analysis Unit to capture clinical episodes in the course of care provision for multiple purposes, including service evaluation and research (Imperial College London, 2021). Data are captured using the Neonatal Data Set (NDS) and all neonatal units across England and Wales submit data to the database via a data entry supplier (Imperial College London, 2021). The NDS comprises data relating to clinical interventions, outcomes and diagnoses, and some demographic information. The data collected from the NNRD and how this contributed to the study are illustrated in Table 5.2.

Table 5.2 Data collected from the NNRD with rationale.

NNRD data	
Infant data: • NHS number • Birth date	Identifiers
• Gestational age and weight • Neonatal unit admitted to • Reason for admission • Diagnosis at admission • Diagnosis at discharge • Discharged on oxygen • Date of discharge	Variables of interest
Parental data: • Mothers' occupation • Fathers 'date of birth • Fathers' ethnicity	Variables of interest

As before, the variables of interest here relating to parental characteristics, are factors associated with vaccine hesitancy (SAGE, 2014), the determinants of vaccine uptake (Thomson et al., 2016), or had been identified as significant in the literature review. For example, characteristics relating to the health of an infant may be associated with the concepts of risk perception (acceptance) and knowledge and information (awareness).

5.4.4 Vaccination data – Child Health Information System

The vaccines studied are defined here in Table 5.3; this is based on the schedule at the time which was operational among the defined study cohort of infants.

Table 5.3 Vaccination schedule from Summer 2016 (PHE, 2020a).

Age of child	Vaccination given
8 weeks	Diphtheria, tetanus, pertussis, polio, Hib and Hep B (DTaP/IPV/Hib/HepB) Meningococcal group B (MenB) Pneumococcal conjugate (PCV) Rotavirus
12 weeks	Diphtheria, tetanus, pertussis, polio, Hib and Hep B (DTaP/IPV/Hib/HepB) Rotavirus
16 weeks	Diphtheria, tetanus, pertussis, polio and Hib (DTaP/IPV/Hib) Meningococcal group B (MenB) Pneumococcal conjugate (PCV)
One year old	Hib/MenC booster Pneumococcal conjugate (PCV) Measles, mumps and rubella (MMR) Meningococcal group B (MenB)
Eligible child age groups	Influenza (annually)
3 years 4 months	Diphtheria, tetanus, pertussis and polio (DTaP/IPV) Measles, mumps and rubella (MMR)
12-13 years	Human papillomavirus vaccine (HPV) 2 doses 6-24 months apart
14 years	Tetanus, diphtheria and polio (Td/IPV) Meningococcal groups A,C,W & Y (Men ACWY)

Table 5.3 demonstrates the breadth of the childhood vaccination programme in the UK, but for the purpose of this study, it is the administration of the primary vaccinations – also referred to as the primary series - given at eight, 12 and 16 weeks which are investigated (highlighted in Table 5.3). These vaccinations have been chosen to study because preterm infants are particularly vulnerable to infection making the earliest months of their life a time when the immunological support which vaccination provides especially vital. Immunisation data are stored on datasets hosted by local Child Health Information Systems (CHIS), and it is possible to extract data from the datasets at an individual level. For each infant, a total of four different vaccines given across three visits are considered, resulting in nine opportunities to study timeliness; this required a vast amount of data which were readily accessible from the CHIS, and using these existing data suited both the purpose and design of this study.

The immunisation schedule frequently alters to reflect changes in disease epidemiology and the development of new vaccines, and at the time of the data extraction based on the study cohort, the primary schedule looked slightly different as it does now. The difference relates to the two-dose pneumococcal vaccine given at eight and 16 weeks in the 2016 schedule which was reduced to a single dose at 12 weeks in the 2020 schedule (Sisson, 2020). It is the primary vaccinations in the Summer 2016 schedule that are analysed in this study (Table 5.3).

5.4.5 Definition of 'delay'

The primary aim of this study is to establish whether preterm infants experience a delay in receiving their vaccines, so it is important to establish what is considered as a delay. Although the primary vaccinations are scheduled for eight, 12 and 16 weeks, the possibility that all infants are vaccinated on the exact day that they would turn these ages is unlikely. In the community, the Child Health Information Service (CHIS) would usually issue an appointment which falls in the week after the date that the child reaches

these ages, meaning for example, that an infant may be eight weeks and six days old by the time the first vaccine is given (depending on which day the vaccination clinic falls). In addition to what almost amounts to a week, it is not unreasonable to assume that in some cases, some infants may be unable to attend on this day, perhaps for logistical reasons, or even for legitimate causes such as those listed in chapter two, even though deferrals associated with genuine reasons as described by PHE (2017) are likely to be uncommon. Nonetheless, experience from practice has demonstrated how vaccines are unjustly delayed based on parental and some staff perceptions of the infant not being well enough to receive their vaccines; this applies to both infants born at a normal gestational age, and to those born prematurely. It is for these reasons that for the purpose of this study, for the first primary vaccination, a delay is defined as being greater than two weeks from the infants' age of eight weeks. Public Health England (2019b) recommend that four weeks is observed between doses of the same vaccines given at eight and 12 weeks (DTaP/IPV/Hib/HepB and Rotavirus) and again for the third dose of DTaP/IPV/Hib/HepB at 16 weeks. Therefore, subsequent delays are also defined as vaccinations given later than two weeks, but for the second and third doses, this is given to mean two weeks from the scheduled date based on when the previous dose was administered. For PCV and MenB, there is a recommended interval of eight weeks between the first and second doses due at eight and 16 weeks respectively. Similarly, a delay is considered to be greater than two weeks after the eight weeks recommended.

5.5 Data analyses

Quantitative research designs signify that statistical processing is an appropriate method of analysis and Sarantakos (2013) describes three techniques: descriptive analysis, relational analysis and significance testing. The questions stated in section 5.2 indicate that all three techniques are relevant in this study. More detail concerning the methods of analysis are found in chapter six.

5.6 Ethical considerations and approvals

The selected design of secondary data analysis highlighted some specific ethical considerations, particularly anonymity and confidentiality. Anonymity concerns the use of identifiable information and Tripathy (2013) advises verifying with the appropriate approval board whether based on the data to be used, full approval is required. This was indeed checked with the Health Research Authority (HRA) and it was confirmed that infants' NHS numbers are considered to be patient identifiable information. Therefore, full ethical approval was sought via the Integrated Research Application System (IRAS). Additionally, the use of secondary data for this study without obtaining informed consent, required approval from the Confidentiality Advisory Group (CAG), and this was sought via the IRAS application.

Confidentiality was a specific consideration in terms of data storage. All information regarding the conduct of the study (applications, approvals and additional correspondence) and actual study data was electronic and accessible only by the researcher and two supervisors via password protected drives.

Further details regarding these ethical considerations are found in chapter six.

5.7 Conclusion

This chapter has described and justified the study's methodology and design, as well as reporting on some of the associated challenges; it has also defined the variables studied. The study's design and selected methodology are considered to be the most appropriate to address the aim of the research, to investigate the timeliness of vaccination in preterm infants at a regional level, and factors associated with timeliness. Details of the methods used are presented in the next chapter.

Chapter 6 Methods

Chapter five provided an overview and rationale for the selected study approach and design, and it also defined the study population and variables. The overarching aim of this study was to investigate vaccination timeliness in preterm infants and the methods used to do this are described in this chapter. This begins by defining the region and the sample, followed by how the data were collected and analysed. Finally, the ethical and approvals processes are described.

6.1 Study region and sample

The study took a population approach, using the Humber region, analysing primary vaccination data relating to preterm infants over a six-month period. The primary series includes the first vaccines offered to all infants at eight, 12 and 16 weeks of age. It was important to acknowledge that this region was not associated with poor coverage which may impact on the study's findings, and data revealed slightly higher coverage compared with England overall between 2017 and 2018 (NHS Digital, 2019). It was estimated that the identified six-month time frame would produce data relating to approximately 400 preterm infants who would be compared with full term controls also from the region, and due vaccination in the same time period (approximately 4,000-5,000 infants in total). The region hosted seven units providing care for preterm neonates, two of which were situated in the north, two in the south and three in the south west. Initially, a larger geographical area was identified as outlined by the Humber Coast and Vale area in Figure 6.1. This included the Humber and North Yorkshire region hosting six clinical commissioning groups (CCGs).

Figure 6.1 Humber Coast and Vale area

However, the COVID pandemic had an adverse impact on one of the organisation's ability to support the study; therefore, the North Yorkshire area was excluded and the Humber area only was studied. This is represented in Figure 6.1 as four CCGs (East Riding of Yorkshire, Hull, North Lincolnshire and North East Lincolnshire).

All infants (normal gestational age and preterm) born within the identified region were eligible for inclusion in the study, provided they were born on or after 6th November and up to and including 5th May 2018. This made them eligible for the first 8-week vaccinations between the dates of 1st January 2018 to 30th June 2018. These six months were selected because there were no changes to the UK primary schedule during this time,

and no problems with vaccination supply or delivery; it was important to avoid any disruption which may have had an impact on vaccine uptake.

6.2 Data sources and analysis

The study used secondary data sources; the Maternity Services Dataset (MSDS), Child Health Information Service or CHIS (which holds immunisation details for all infants), and the National Neonatal Research Database (NNRD). Details about each of these datasets and the rationale for using them is provided in chapter five.

The starting point was the MSDS, which identified all infants eligible for inclusion in the analysis, and for the Humber region, there were two MSDSs hosted by two organisations. Data for infants within the defined six-month time frame was requested from each of these organisations. Using the NHS number (from data already obtained from MSDS), additional data for infants born <35 weeks was requested from the National Neonatal Research Database (NNRD). This yielded information regarding the infants' health status and some parental demographic detail. Finally, and again using the NHS number as the common identifier, immunisation data was requested from the Child Health Information Systems (CHIS). There were three CHISs within the Humber region.

Once all requested data were received, a process of matching the data was undertaken, and this process is outlined in Figure 6.2. MSDS data were matched to NNRD data (where applicable) and then to immunisation data.

The processes of requesting and matching data involved using patient identifiable information. As the researcher, I was unable to have any access to this; therefore, this was done by data analysts at the lead site. Once completed, the matched study dataset was anonymised and sent to me for analysis. All data transfer was undertaken using nhs.net email accounts.

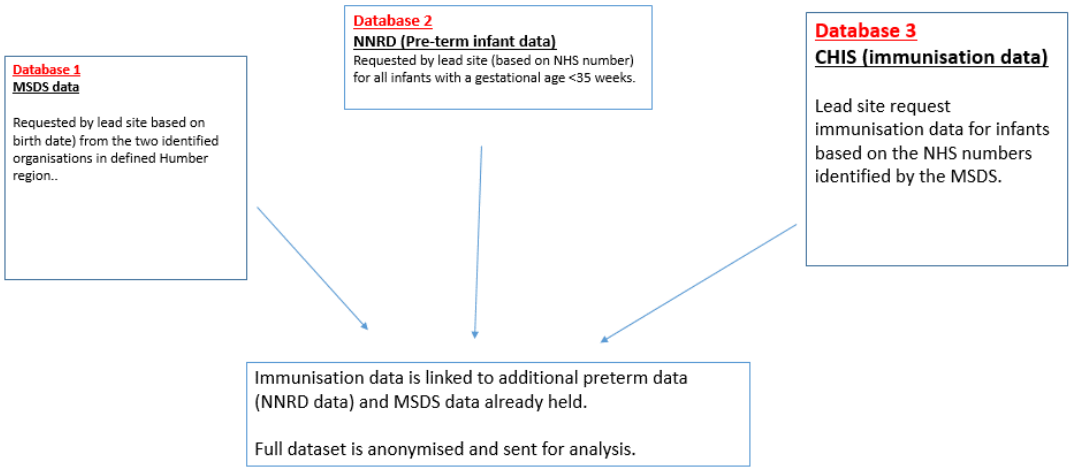


Figure 6.2 Overview of data management process

The anonymised data were checked and cleaned, and it became apparent that there were some missing data in places, and where a variable of interest was missing, it was not included in the analysis. Most notable, the dataset was missing immunisation data for some infants. This was checked with the data analysts and it was discovered that although these infants were born in the area (and had registered with the MSDS), they received their vaccines via an organisation outside of the study. Several values also had to be clarified and verified before the analysis could begin, so this meant checking with the data analysts at an individual infant/parent level. Identifying where values were deemed unusual was established by observing the shape and distribution of the data.

The data analysts received infant data in the form of dates for date of birth and immunisation events, and it was planned that I would then be able to calculate the timeliness of vaccination. However, it became apparent that infants' date of birth could serve as an identifier, therefore, the data analysts provided a dataset with gestational age

in days, and age (in days) of the first vaccination visit. Subsequent vaccination visits were also expressed as days between each visit. This calculation process was demonstrated by the analysts so I was confident that the data were accurate.

Data were initially described, and then some inferential analysis was undertaken, to specifically address the research aim. All analyses were undertaken using IBM, SPSS Version 26.0.0.

Descriptive statistics provide a helpful summary of numerical data and were used for this purpose in this study. This gave an overview of the key characteristics of the study population (infants and parents), and infants' vaccination data. The distribution of the data was also considered, using the mean as the measure of central tendency. The mean has many significant mathematical properties as well as being the most commonly used measure of central tendency. It was acknowledged that some of the data were not normally distributed, therefore in these cases, the standard deviation was also reported. This enabled a more complete picture of the data to be observed than reporting the mean alone.

Inferential analyses focused on associations between variables. Testing with Pearson's correlation coefficient was undertaken to explore the relationship between continuous variables, and the presence, direction and strength of the findings of these analyses are presented where relevant (number between -1 and +1). Tests of significance determine the level of probability (*p* value) that any findings are statistically significant; that is the extent to which the study's findings can be generalised. In this study, one-way ANOVA tests were used to establish the level of probability regarding differences between groups of infants and variables which were explored in relation to timeliness. Bootstrapping was used where there was evidence that statistical test assumptions were not met;

homogeneity of variance for all of the groups analysed could not be assumed. A *p* value of ≤0.05 was considered statistically significant.

6.3 Ethics and approvals

The nature of the project's design negated the need to obtain informed consent from all individuals whose data were included. For this project, full Health Research Authority and ethical approval were obtained via the Integrated Research Application System (IRAS). Additionally, the use of secondary data for this study without obtaining informed consent, required approval from the Confidentiality Advisory Group (CAG) (also gained via the IRAS application). In routine practice, prior to entering data into the MSDS, CHIS and the NNRD, parental consent is obtained where parents are informed of what data are being collected and why. Additionally, the NNRD is a national Research Ethics Committee approved database (Gale & Morris, 2016). There was also a need to acquire the necessary research and development permissions from the custodians of the datasets, and this was obtained from the hosts of the CHIS departments for the immunisation data (three organisations), the MSDS (two organisations), and the NNRD host organisation. Prior to undertaking the study, an application for ethical review and approval was also submitted to my organisation: The University of Hull, Faculty of Health Sciences. In total, permission was obtained from seven organisations.

The CAG guidelines regarding the management of patient identifiable data were strictly adhered to, and even though patient data were anonymised, confidentiality was a specific consideration in terms of data storage and transfer. Appendix 4 presents the approved data management plan. All electronic and paper versions of information regarding the conduct of the study (applications, approvals and additional correspondence) were kept on password protected drives or in secure cabinets, accessible only by me and two supervisors. Although this analysis has been completed, approval has been given for the anonymised dataset to be kept for a period of five years to allow it to be revisited and

even mined should the opportunity of future research arise. The original dataset with identifiers is still being held by the lead site for reference, but there is a determined date for this to be destroyed. Data transfer to the lead site for matching and anonymising was via nhs.net accounts. The lead site was also advised on the data management of this project by their Information Governance Team, to ensure that the legal obligations around data transmission and storage were fully adhered to.

Chapter 7 Results

7.1 Introduction

This chapter presents the findings of the analyses which were undertaken to answer the research question 'are vaccinations delayed in preterm infants?' More specifically:

- Is there a mean difference in vaccination age between preterm and full term infants?
- Is there a relationship between gestational age and age at vaccination?
- What are the factors associated with vaccination timeliness?

Using the data obtained from the MSDS, NNRD and CHIS, the chapter begins with a description of the data, and is followed by inferential analyses. Characteristics relating to the infants, parents and immunisations are described and analysed, to address the questions cited above.

7.2 Describing the data

This section considers characteristics associated with the infants in the study; this is followed by a description of the maternal and paternal data. Lastly, the immunisation data are described.

7.2.1 Infant data

Data for 4605 infants were retrieved from the MSDS, which revealed that 51.4% of the identified cohort were male, and 48.6% were female. Furthermore, 4591 births were recorded as live births, with 14 described as either antepartum stillbirth (n = 4), intrapartum stillbirth (n = 1), spontaneous abortion (n = 1) or stillbirth (n = 8).

A gestational age of less than 37 weeks (259 days) is counted as preterm and 428 infants (9.3%) fell into this category. Of these, 179 were born at less than 35 weeks, and additional information from the NNRD was extracted for these infants.

Gestational ages for infants ranged from 163 to 315 days, with a mean gestational age observed as 274 days (Figure 7.1).

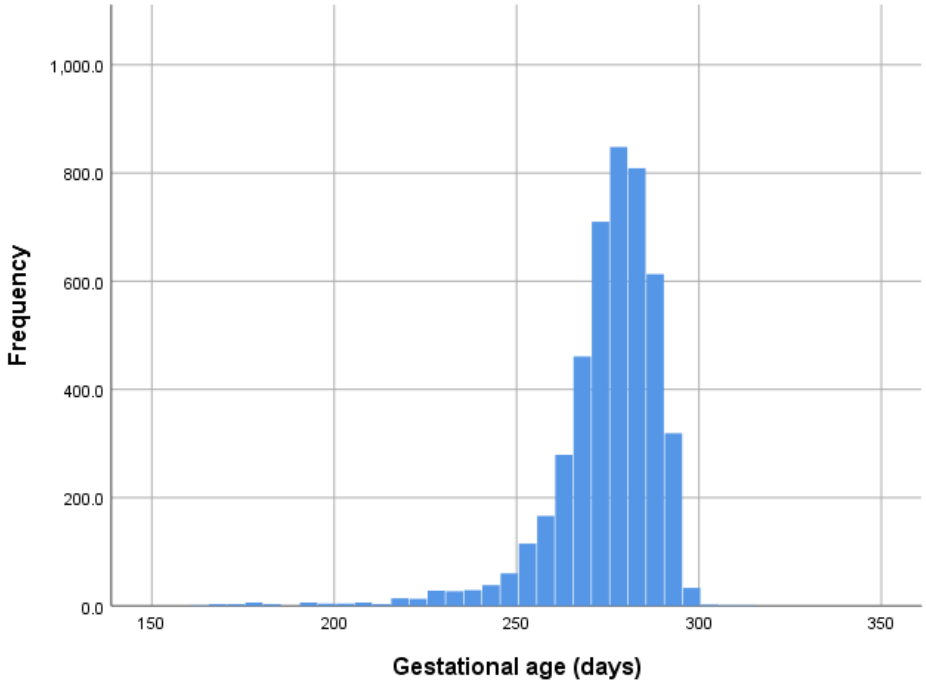


Figure 7.1 Gestational age of infants.

Using classifications of prematurity, the infants' gestational ages were also categorised. The vast majority of infants were born within a timeframe considered as a normal gestational age (90.7%), with 8% defined as moderate to late preterm, 0.8% as very preterm, and 0.5% as extremely preterm.

Birthweight was also recorded for all infants, and this ranged from 387g – 5820g, with a mean birthweight of 3344g (Figure 7.2).

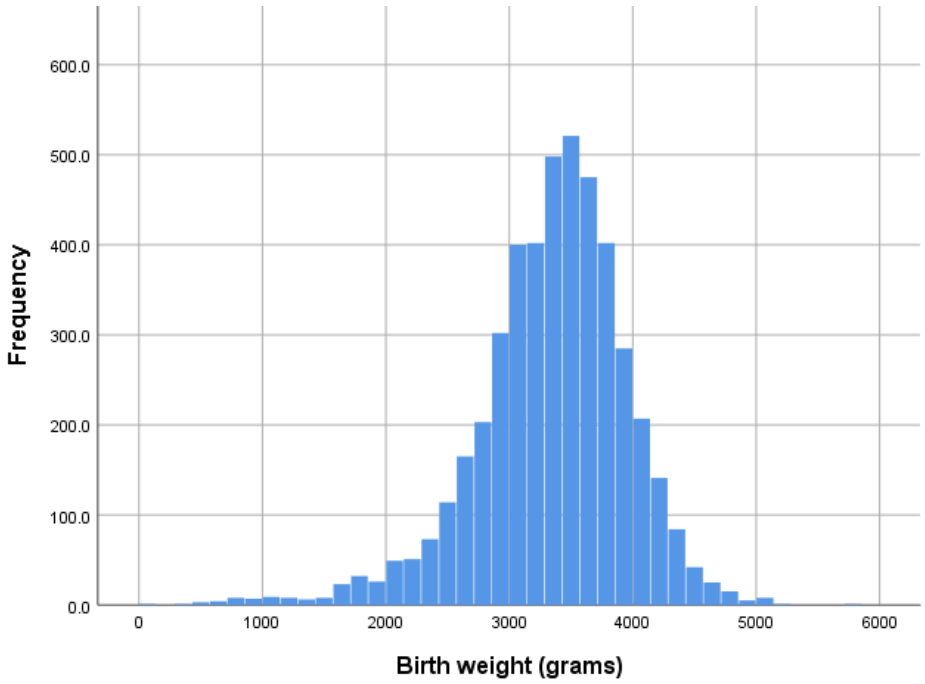


Figure 7.2 Infants' birthweights.

Using the three established categories of birthweights, infants were classified in the following way: 92.2% had a normal birthweight, 6.7% had a moderately low birthweight and finally, 1.1% had a birthweight recorded as very low.

The relationship between gestational age and birthweight was examined; this revealed a strong positive correlation between these two variables (r = 0.691, p = <0.001) which is represented in Figure 7.3 Scatterplot of gestational age and birthweight

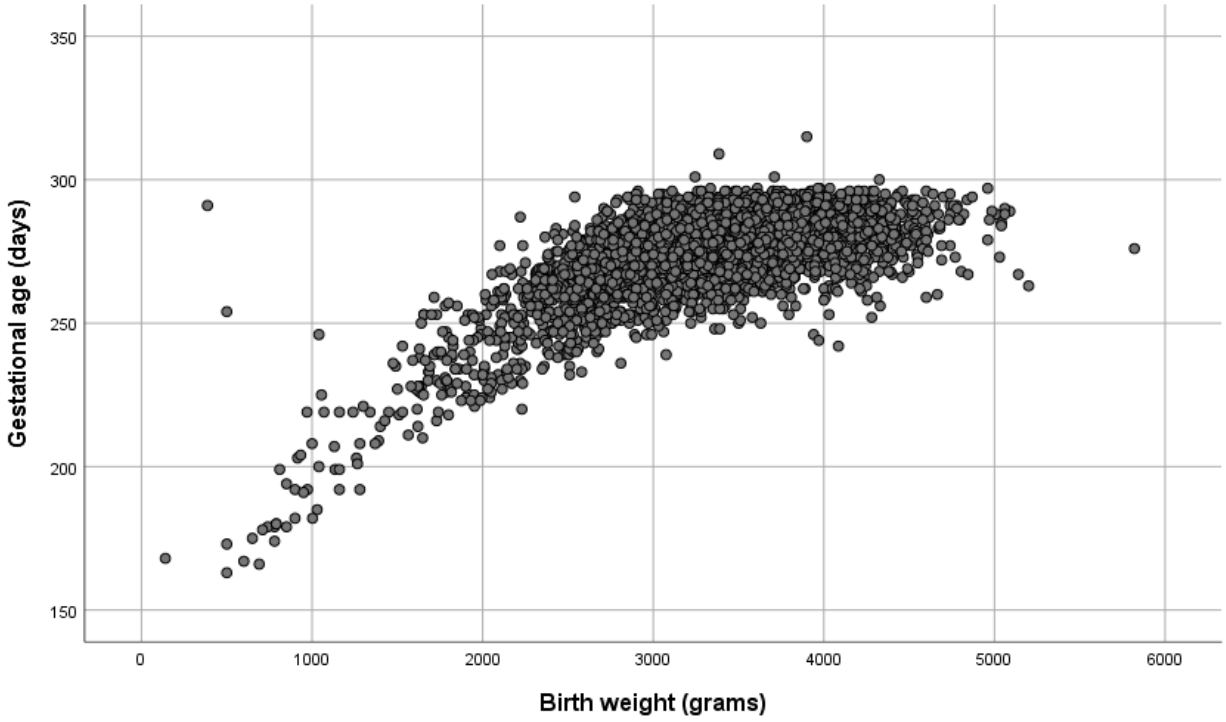


Figure 7.3 Scatterplot of gestational age and birthweight

Data were also retrieved for 173 infants born less than 35 weeks gestational age from the NNRD. This included the NNU the infant was admitted to, the primary reason for admission to the NNU, the length of stay on the NNU, the category of care required on admission, whether or not the infant was discharged on oxygen, and the diagnosis at discharge.

Table 7.1 shows the number of infants admitted to each unit, and the area in the region of the NNU has also been indicated.

Table 7.1 Admitting NNU

Admitting NNU	Area in the region	n
1	North	96
2	South	29
3	South	41
4	North	1
5	South West	2
6	South West	2
7	South West	7

Table 7.2 illustrates that prematurity was the greatest reason for admission, followed by respiratory disease; it is possible for admission to a NNU to be necessary for infants who are not premature.

Table 7.2 Reason for admission to the NNU

Reason for admission	n
Preterm	133
Respiratory disease	30
Hypoglycaemia	3
Social issues/foster care	1
Short observation/monitoring	1
Gastrointestinal tract disease	1
Continuing care	1
Readmission	2
Reason not recorded	1

The length of time that was spent on the NNU ranged from 1 day to 160 days, with the mean time spent on the unit being 31.2 days (Figure 7.4).

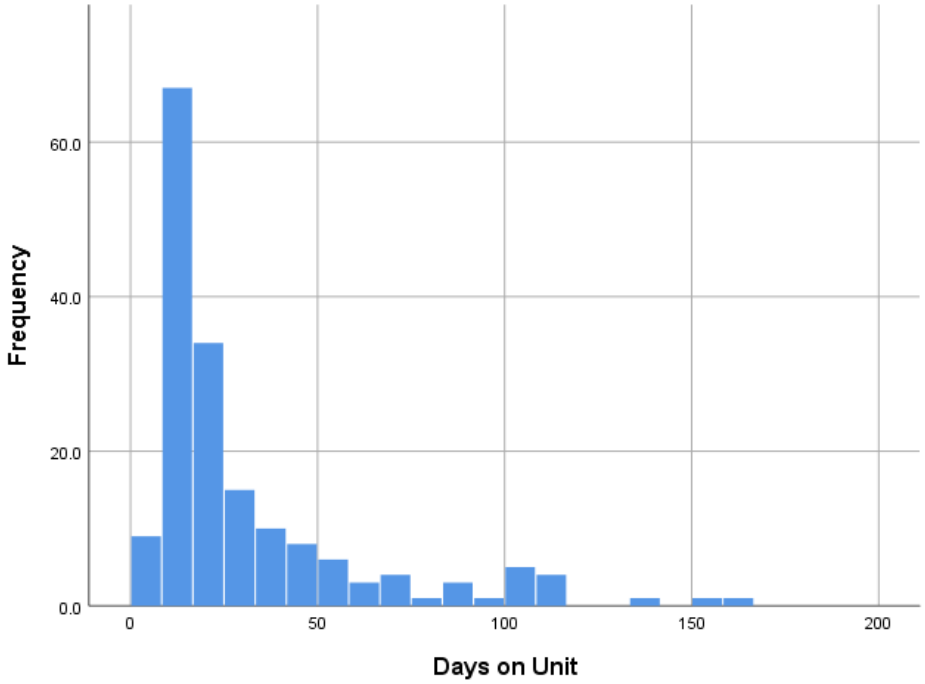


Figure 7.4 time (in days) spent on the NNU.

The category of care that was required for each infant on admission to the NNU is recorded in Table 7.3. This demonstrates that medical intensive care, medical high dependency care, and medical special care accounted for most of the admissions to the NNU.

Table 7.3 Category of care required on admission to the NNU

Category of care	n
Medical intensive care	61
Medical high dependency care	47
Medical special care	52
Continuing care	1
Transitional care	11

For those infants admitted to the NNU, data on whether they were discharged on oxygen was available for 166 of them. The number discharged on oxygen was 14 (8.4%) compared with 152 (91.6%) who were not.

Information on the diagnosis at discharge from the NNU was available for 165 infants. For many infants, multiple diagnoses were available, and these are summarised in Table 7.4:

Table 7.4 Diagnoses at discharge from the NNU

Diagnoses	n
Prematurity	148
Suspected sepsis	51
Respiratory distress	87
Twin pregnancy	11
Early infection risk	33
Hypoglycaemia	11

7.2.2 Parental data

Data for mothers were retrieved from both the MDSD and the NNRD, and for fathers, from the NNRD only. Data relating to maternal ages and ethnicity were available for all mothers. Data for paternal ages and ethnicities was not so complete. Additional maternal data included the number of previous pregnancies and occupation.

Mothers' ages at delivery ranged from 15 to 49 years, with the mean age being 28.5 years (Figure 7.5).

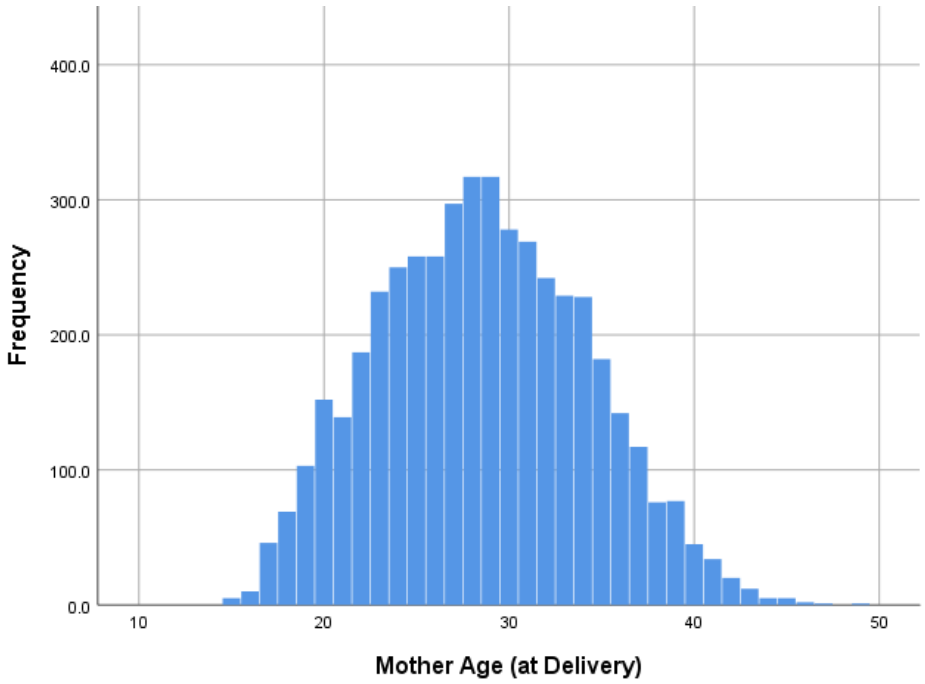


Figure 7.5 Maternal ages.

Maternal age by categories are presented in Table 7.5:

Table 7.5 Maternal age categories

Maternal age	Frequency
15 - 19	233
20 - 24	960
25 - 29	1447
30 - 34	1246
35 - 39	594
40 - 44	116
45 - 49	9

The ethnicity of mothers indicated that 89% (n = 4100) described themselves as White, whilst the remainder were described as Mixed 0.9% (n = 41), Asian 2.4% (n = 112), Black 0.9% (n = 40), and Other 6.8% (n = 213).

The number of previous pregnancies ranged from 0 to 18 (Figure 7.6), with the mode recorded as one previous pregnancy.

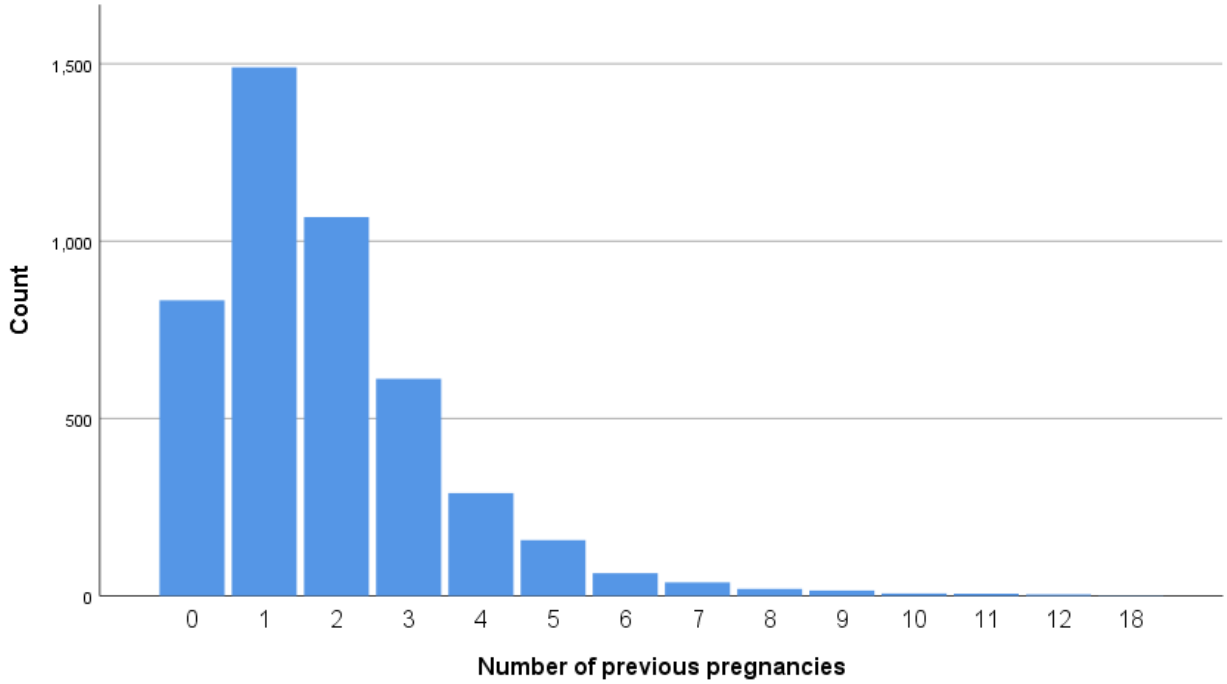


Figure 7.6 Number of previous pregnancies.

Occupations were classified according to the UK Standard Occupational Classification major groups (SOC) (ONS, 2020), which are described in Table 7.6.

Table 7.6 SOC Group classifications

SOC 2020 Major group	SOC 2020 Group title	% of mothers
1	Managers, Directors and Senior Officials	3
2	Professional Occupations	12
3	Associate Professional Occupations	9
4	Administrative and Secretarial Occupations	19
5	Skilled Trade Occupations	9
6	Caring, Leisure and other Service Occupations	21
7	Sales and Customer Service Occupations	9
8	Process, Plant and Machine Operatives	6
9	Elementary Occupations	10

Data were available for 66 mothers and Table 7.6 revealed that most mothers worked in administrative or secretarial, or caring, leisure or other service occupations.

Paternal data were available from the NNRD for age and ethnicity. Where recorded, fathers' ages ranged from 18 to 51 years, with a mean age of 32.0 years; this is displayed in Figure 7.7, where a bimodal distribution is evident. By categories, there were 39 (44%) fathers less than 30 years old, 41 between 31 and 40 years (46%), and 8 (9%) over 41 years.

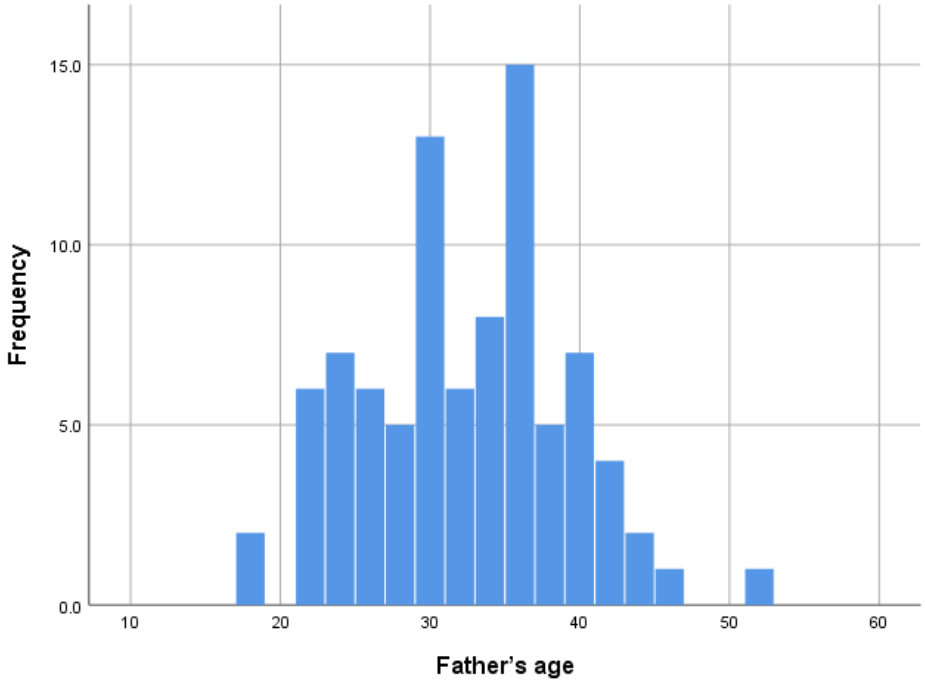


Figure 7.7 Paternal ages.

Ethnicity data were available for 113 fathers. The majority (n = 104) were described as White, whilst eight identified as Asian, and one as Black. No fathers were reported of Mixed ethnicity.

7.2.3 Immunisation data.

Immunisation data were extracted from the relevant CHIS, and full datasets were available for 4013 infants. This section describes the time in days from birth to immunisation for the first 8-week vaccinations (DTaP/IPV/Hib/HepB, PCV, MenB and Rotavirus). It then goes on to describe the time between vaccine visits; between the 8 and 12-week vaccines (DTaP/IPV/Hib/HepB and Rotavirus), time between 12 and 16-week vaccines (DTaP/IPV/Hib/HepB only), and time between 8 and 16-week vaccines (PCV and MenB). Table 7.7 illustrates which vaccines were scheduled and when:

Table 7.7 Vaccines and intervals between doses.

8-week vaccines	**12-week vaccines**	**16-week vaccines**
DTaP/IPV/Hib/HepB	DTaP/IPV/Hib/HepB	DTaP/IPV/Hib/HepB
PCV		PCV
MenB		MenB
Rotavirus	Rotavirus	

8-week vaccinations

The first vaccines are recommended at 8-weeks (56 days), although there are circumstances when vaccines may be given from 6 weeks (42 days). As discussed in chapter five, a delay is considered as greater than two weeks from the recommended date, so from 70 days. In some cases, vaccines were recorded as being administered prior to 42 days; it is reasonable to assume that in most cases, these are data entry errors and these have not been included in these analyses.

Table 7.8 summarises the mean and the range for the time to the first four vaccines given at 8-weeks:

Table 7.8 Mean time and range for first 8-week vaccines

	Mean (in days)	Range (in days)
DTaP/IPV/Hib/HepB	65.83	45 - 924
PCV	64.63	46 - 642
MenB	64.82	46 - 669
Rotavirus	63.89	45 - 994

Data were available for DTaP/IPV/Hib/HepB vaccination for 4008 infants. After excluding vaccines given before 42 days, this left data for 4000 infants. The range (in days) for this vaccine is 45 – 924, with the mean time to vaccination being 65.83 days. A total of 628 (15.7%) infants experienced a delay greater than 70 days in receiving this vaccine.

For PCV vaccination at 8-weeks, data were available for 3994 infants. After excluding cases where vaccination occurred less than 42 days, data for 3987 infants were reported. The range for infants receiving this vaccine was 46 – 642 days, with a mean age of 64.63 days. A delay of greater than 70 days was seen in 15.4% (n = 614) of the infants.

For MenB vaccination, data were recorded for 3999 infants. Exclusion of cases where the vaccine was given before 42 days, left data for 3993 infants. The range of receipt for this vaccine was 46 – 669 days, with the mean reported as 64.82 days. The number of infants with a delay of greater than 70 days for receipt of this vaccine was 616 (15.4%).

Finally, for Rotavirus vaccination, data were available for 3943 infants; following exclusion of cases where the vaccine was given earlier than 42 days, 3937 were identified for analysis. The range in days for this first vaccine was 45 – 994, with the mean recorded as 63.89 days. A delay greater than 70 days was seen in 14.6% (n = 574) of the infants.

12-week vaccinations

The 12-week vaccines scheduled are for a second dose of both DTaP/IPV/Hib/HepB and Rotavirus. Guidance recommends a 28-day interval between these first and second doses, but in some cases, it is possible to administer them after 21 days. Any vaccines given before 21 days are considered as data entry errors. As before, a delay is defined as two weeks, so infants who received their second dose at a time greater than 42 days are assumed as having experienced a delay. The mean and range for the time to these 12-week vaccines are summarised in Table 7.9:

Table 7.9 Mean time and range for second 12-week vaccines

	Mean (in days)	Range (in days)
DTaP/IPV/Hib/HepB	37.86	21 - 674
Rotavirus	33.98	21 - 134

For the second 12-week dose of DTaP/IPV/Hib/HepB, data were available for 3973 infants. After excluding any cases where the vaccine was given before 21 days, 3939 were included in the analyses. Time to this second vaccine ranged from 21 to 674 days, with the mean time recorded as 37.86 days. A delay of more than 42 days was seen in 690 (17.5%) infants.

Data were available for 3836 infants for the second Rotavirus vaccine also due at 12-weeks. After excluding cases where vaccine been recorded as given before 21 days, 3832 were analysed. The range for this was 21 – 134 days, and the mean was 33.98 days. A delay of greater than 42 days was seen for 18% (n = 690) of the infants.

16-week vaccinations

At this final vaccination visit in the primary course, three vaccines are scheduled; a third dose of DTaP/IPV/Hib/HepB, and second dose of both PCV and MenB. This means that as with time between doses one and two of DTaP/IPV/Hib/HepB, any third doses of this vaccine recorded as being given before 21 days are counted as errors. Additionally, as with the previous doses, time exceeding 42 days between the second and third DTaP/IPV/Hib/HepB, is considered a delay. For PCV and MenB, there is a recommended interval of 56 days between the first dose at 8-weeks, and the second dose at 16-weeks, so a delay is considered to be greater than 70 days (56 + 14 days). For both of these vaccines, there are published exceptions to the interval being less than 56 days; the interval can be 28 days if the first dose was administered late; therefore, vaccines given before 28 days were excluded. Table 7.10 summarises the mean and range for these 16-week vaccines:

Table 7.10 Mean time and range for 16-week vaccines

	Mean (in days)	Range (in days)
DTaP/IPV/Hib/HepB	39.22	21 – 630
PCV	74.17	28 – 658
MenB	76.46	28 – 674

For the third DTaP/IPV/Hib/HepB vaccine, data were available for 3905 infants, but following the exclusion of vaccines given before 21 days, 3891 remained for analysis. The range in days for this third vaccine was 21 – 630 days, and the mean was 39.22 days, and a delay of more than 42 days is recorded for 877 (22.5%) infants.

Administration of the PCV vaccine at the scheduled 16-week timepoint ranged from 28 to 658 days, and the mean time in days was 74.17; data were available for 3903 infants. A delay greater than 70 days was seen in 1217 (32.1%) infants for this vaccine.

For MenB, data were available for 3940 infants, which showed that at 16-weeks, the mean time in days was 76.46, with a range of 28 – 674 days. There was a delay of more than 70 days reported in 1233 (31.6%) infants.

7.3 Inferential analyses

This section presents the timeliness of vaccination whilst considering additional variables. Firstly, the gestational ages and birthweights of infants are studied for each vaccine at each scheduled time point. This is followed by examining the variables which are specific to infants admitted to a NNU (using NNRD data) to identify any significant factors which may affect vaccination timeliness. Finally, an exploration of how parental factors influenced vaccination timeliness for the scheduled 8-week vaccines.

7.3.1 Infant gestational ages, birthweights and 8-week vaccines

Correlations between the time intervals for each vaccine given at 8-weeks indicate that there is a strong relationship between the timing of all four vaccines. This is demonstrated in the correlation matrix (Table 7.11):

Table 7.11 Correlation matrix 8-week vaccines

		8-week DTaP/IPV/Hib/HepB	8-week PCV	8-week MenB	8-week Rotavirus
8-week DTaP/IPV/Hib/HepB	Pearson *r*	1	0.985	0.649	0.616
	Sig.		<0.001	<0.001	<0.001
	N	4008	3993	3997	3942
8-week PCV	Pearson *r*	0.985	1	0.867	0.618
	Sig.	<0.001		<0.001	<0.001
	N	3993	3994	3988	3931
8-week MenB	Pearson *r*	0.649	0.867	1	0.987
	Sig.	<0.001	<0.001		<0.001
	N	3997	3988	3999	3939
8-week Rotavirus	Pearson *r*	0.616	0.618	0.987	1
	Sig.	<0.001	<0.001	<0.001	
	N	3942	3931	3939	3943

This suggests some consistency in the timing of administration for all four 8-week scheduled vaccines. Subsequently, the time to each of the first 8-week vaccines for infants born within identified gestational age and birthweight categories are presented:

DTaP/IPV/Hib/HepB

Table 7.12 presents an overview of the mean and standard deviation (in days) of this vaccine for each gestational age category. It demonstrates that mean ages are higher in the extremely preterm and the moderate to late preterm categories, however, one-way ANOVA testing with bootstrapping revealed no significant differences between gestational age categories for this vaccine (F (3, 4004) = 0.210, p = 0.889).

Table 7.12 Gestational age and 8-week DTaP/IPV/Hib/HepB

GA category	N	Mean	SD
Extremely preterm	13	68.15	9.538
Very preterm	32	65.94	10.115
Moderate to late preterm	315	67.57	26.452
Normal gestational age	3640	65.67	33.912

The standard deviations show that the greatest dispersions of data are in the moderate to late and normal gestational age groups, and the shape of the distribution of data for these groups are illustrated in histograms (Figure 7.9 and Figure 7.8).

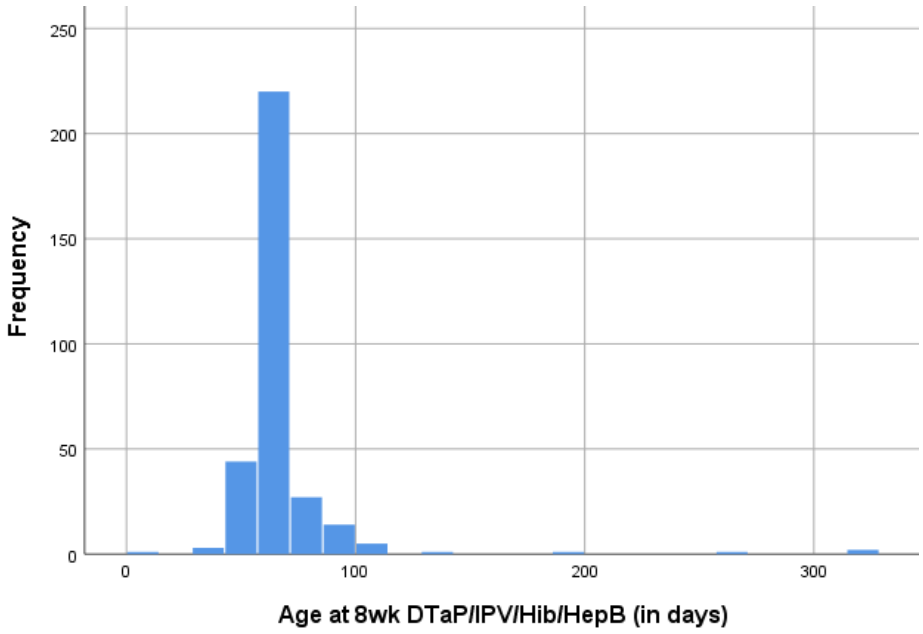


Figure 7.8 Moderate to late preterm category - 8-week DTaP/IPV/Hib/HepB

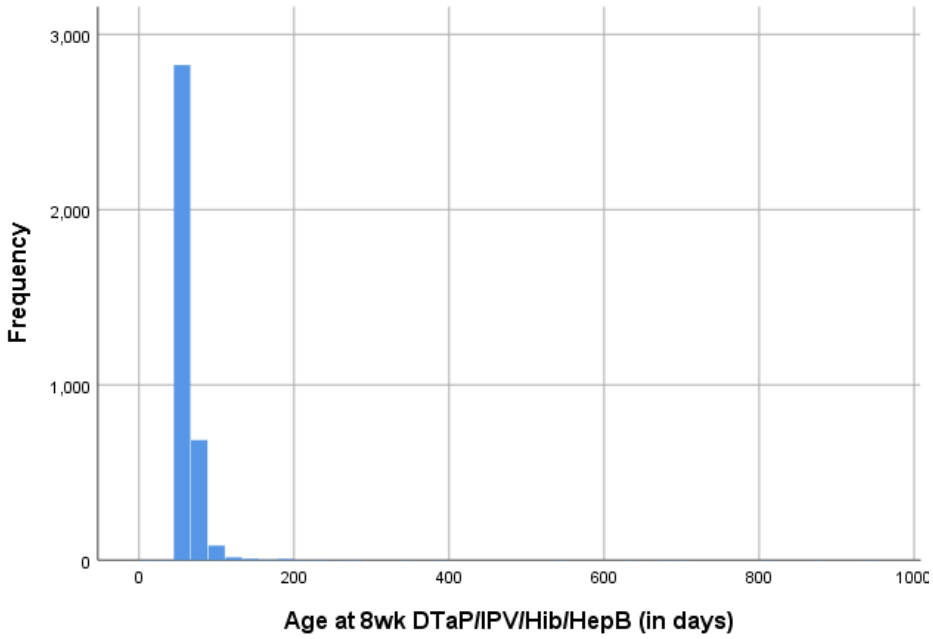


Figure 7.9 Normal gestational age category - 8-week DTaP/IPV/Hib/HepB

These histograms demonstrate a right-sided skew, and indicate some outliers; that some DTaP/IPV/Hib/HepB vaccines were given extremely late, and the range for administration of this vaccine is 42-942 days.

Using a similar approach, the timing of DTaP/IPV/Hib/HepB was analysed with birthweight categories (Table 7.13). Here, higher means are seen in the very low and moderately low birthweight categories, but higher standard deviations are observed in the moderately low and normal birthweight categories. However, there were also no statistically significant differences between birthweight groups as determined by one-way ANOVA testing (with bootstrapping): F (2, 4005) = 0.398, p = 0.672.

Table 7.13 Birthweight and 8-week DTaP/IPV/Hib/HepB

BW category	N	Mean	SD
Very LBW	38	67.05	9.076
Moderately LBW	272	67.40	26.491
Normal BW	3698	65.61	33.836

The shape of distribution for the moderately low and normal birthweight groups are presented in histograms, Figure 7.10 and Figure 7.11:

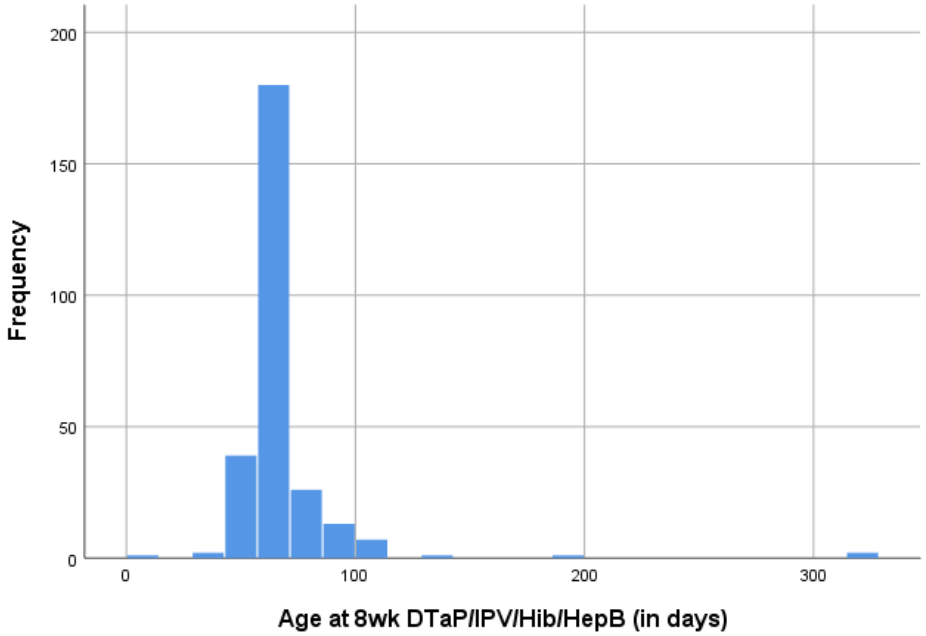


Figure 7.10 Moderately low birthweight category – 8-week DTaP/IPV/Hib/HepB

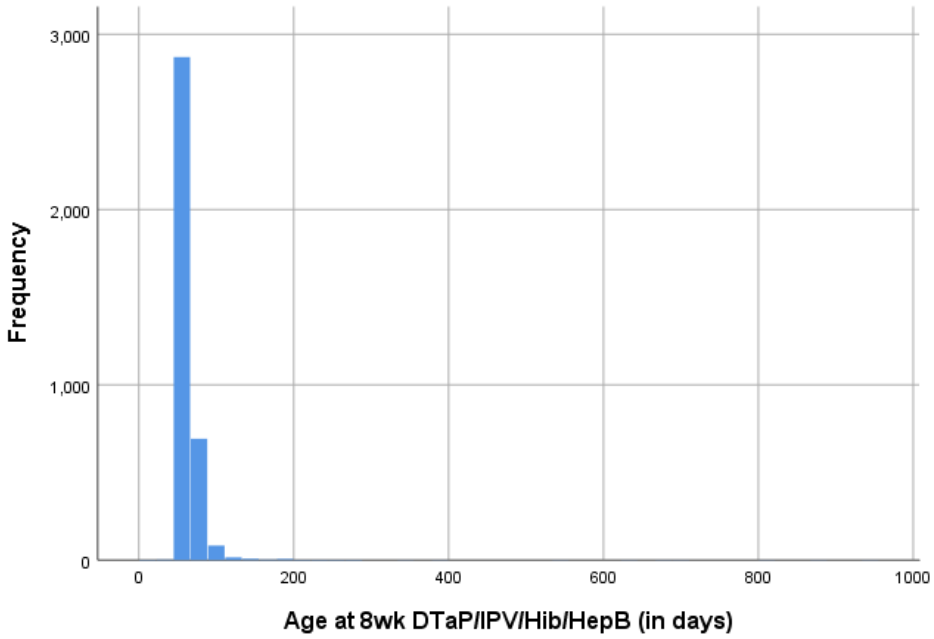


Figure 7.11 Normal birthweight category - 8-week DTaP/IPV/Hib/HepB

As with gestational age, these histograms are skewed to the right, and outliers are evident, indicating the extreme lateness in the administration of this vaccine for some infants.

PCV

Table 7.14 presents the mean and standard deviation of the first PCV dose by gestational age category. This demonstrates that the highest means are in the extremely preterm and the moderate to late preterm categories, and that the dispersion of data is greater in the moderate to late and normal gestational age groups (SD 27.012, 17.648). One-way ANOVA testing (with bootstrapping) revealed statistically significant results between at least two of the groups (F (3, 3990) = 2.624, p = 0.0490); therefore, a post-hoc Bonferroni adjustment was applied, and this identified that the significant difference was between the moderate to late and normal gestational age groups (p = 0.047).

Table 7.14 Gestational age and 8-week PCV

GA category	N	Mean	SD
Extremely preterm	13	68.15	9.538
Very preterm	32	66.38	10.064
Moderate to late preterm	315	67.66	27.012
Normal gestational age	3627	64.34	17.648

The shape of the distribution of data was the similar to what was observed for the DTaP/IPV/Hib/HepB vaccine in all gestational age categories, and for the moderate to late and normal gestational age groups, data were skewed to the right and there were extreme outliers. The range in days for the administration of this vaccine was 42-642.

For the first PCV dose and birthweight categories, the means and standard deviations for each group are displayed in Table 7.15, where the highest means are seen in the very low and moderately low birthweight categories. With bootstrapping, further one-way ANOVA testing revealed statistically significant differences between at least two groups (F (2, 3984) = 4.510, p = 0.011); therefore, post hoc Bonferroni adjustments were used; these revealed that the significant findings occurred between the moderately low and normal birthweight groups (p = 0.036).

Table 7.15 Birthweight and 8-week PCV

BW category	N	Mean	SD
Very LBW	38	67.42	8.982
Moderately LBW	269	67.71	26.138
Normal BW	3680	64.38	17.887

The greatest dispersion of data is in the moderately low birthweight group (SD 26.138), and the shape of this distribution is illustrated in Figure 7.12.

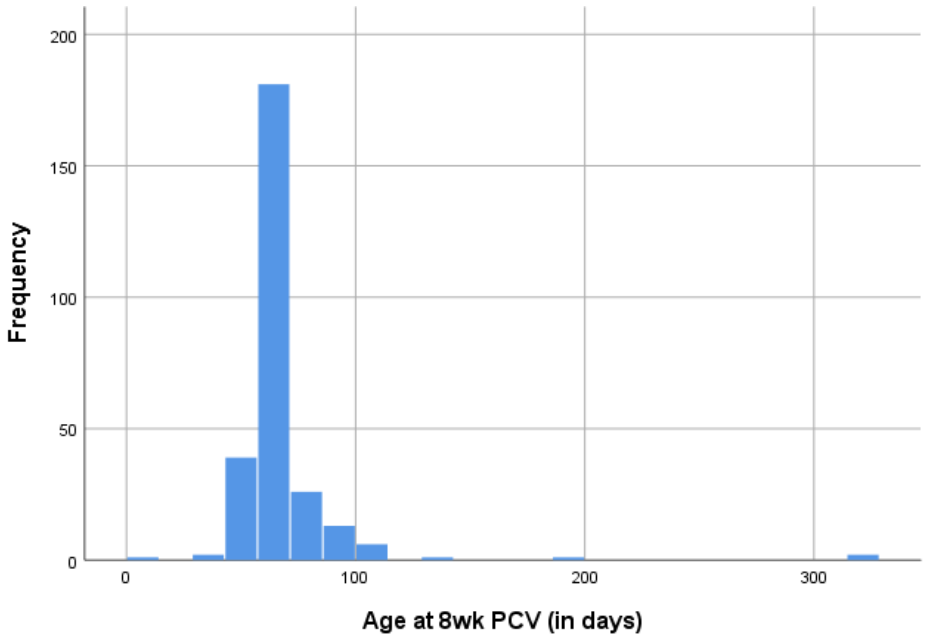


Figure 7.12 Moderately low birthweight category – 8-week PCV

MenB

Table 7.16 presents a summary of the mean and standard deviation for infants receiving their first MenB vaccine. The greatest means are seen in the extremely preterm and the moderate to late preterm categories, and the greatest dispersion of data in the moderate to late preterm group (SD 43.289). Additional one-way ANOVA testing with bootstrapping revealed a statistically significant difference between groups (F (3, 3989) = 6.300, p = <0.001); therefore, further a post hoc Bonferroni adjustment was undertaken. This revealed that the difference was between the moderate to late and normal gestational age groups (p = <0.001).

Table 7.16 Gestational age and 8-week MenB

GA category	N	Mean	SD
Extremely preterm	12	69.33	8.917
Very preterm	32	65.66	10.152
Moderate to late preterm	319	67.17	43.289
Normal gestational age	3636	64.35	17.677

The shape of the distribution of data for all gestational age categories was similar to what was observed for the previously reported DTaP/IPV/Hib/MenB and PCV vaccines. The data show a right sided skew, with extreme outliers in the moderate to late and normal gestational age groups. The range for the administration of this vaccine was 46-669 days.

The time to the first MenB vaccine across the identified birthweight categories is summarised in Table 7.17. This shows that the highest mean time in days to this first vaccination is in the moderately low birthweight group. With bootstrapping, ANOVA testing indicated that there was a statistically significant difference between at least two groups (F (2, 3990) = 8.546, p = <0.001). After the application of a Bonferroni adjustment,

it was revealed that the difference was present between the normal birthweight and moderately low birthweight groups (p = <0.001).

Table 7.17 Birthweight and 8-week MenB

BW category	N	Mean	SD
Very LBW	37	67.41	8.933
Moderately LBW	271	69.75	44.838
Normal BW	3685	64.43	17.878

The greatest standard deviation is observed in the moderately low birthweight category, and the shape of the distribution of data for this group indicates a right-sided skew and some extreme outliers (Figure 7.12).

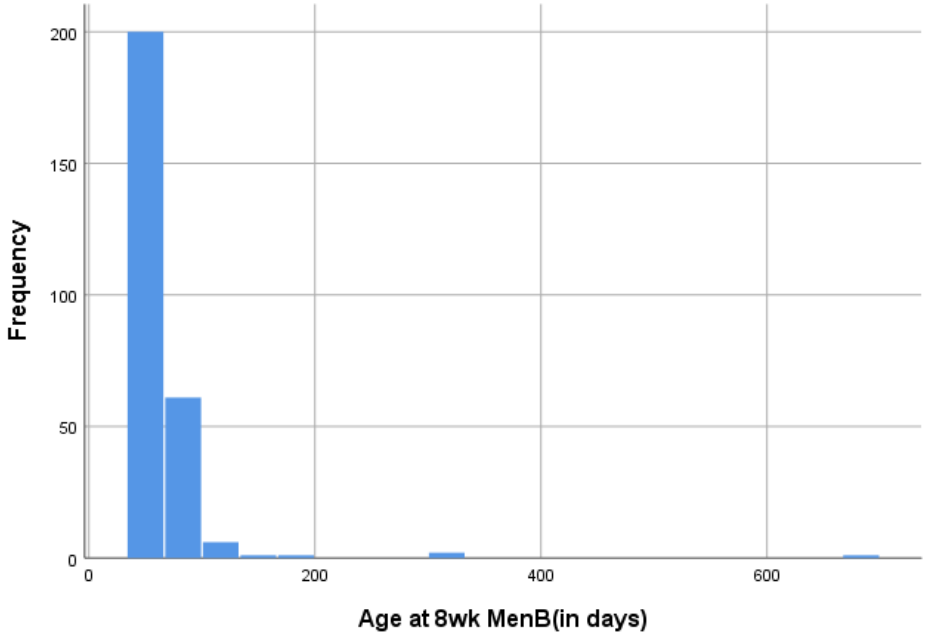


Figure 7.13 Moderately low birthweight category – 8-week MenB

Rotavirus

The mean and standard deviation for this first 8-week Rotavirus vaccine across the gestational age categories is presented in Table 7.18. The greatest mean is observed in the extremely preterm group, but one-way ANOVA testing (with bootstrapping) was undertaken, and identified no significant differences between any of the gestational age categories and time to the first vaccination.

Table 7.18 Gestational age and 8-week Rotavirus

GA category	N	Mean	SD
Extremely preterm	12	70.33	13.013
Very preterm	30	65.80	10.526
Moderate to late preterm	309	66.35	35.553
Normal gestational age	3586	63.64	18.319

The greatest dispersion of data is in the moderate to late preterm group (SD 35.553), and the range for the administration of this vaccine was 45-994 days.

An overview of the birthweight categories and 8-week Rotavirus vaccines in presented in Table 7.19:

Table 7.19 Birthweight and 8-week Rotavirus

BW category	N	Mean	SD
Very LBW	35	67.17	10.291
Moderately LBW	267	67.07	38.396
Normal BW	3641	63.56	18.254

This demonstrates a higher mean time in days to first Rotavirus vaccine for the very low birthweight and moderately low birthweight categories when compared with the normal birthweight group. The greatest dispersion in also in the moderately low birthweight group (SD 38.396). Following one-way ANOVA testing (with bootstrapping) a statistically significant difference between at least two of the categories was identified (F (2, 3940) = 4.236, p = 0.015). Further post-hoc analysis using a Bonferroni adjustment revealed that the difference occurred between the moderately low birthweight and the normal birthweight groups (p = 0.019).

As seen previously, the shape of the data indicate a skew to the right, and extreme outliers in the moderately low, and normal birthweight groups (Figure 7.14 and Figure 7.15).

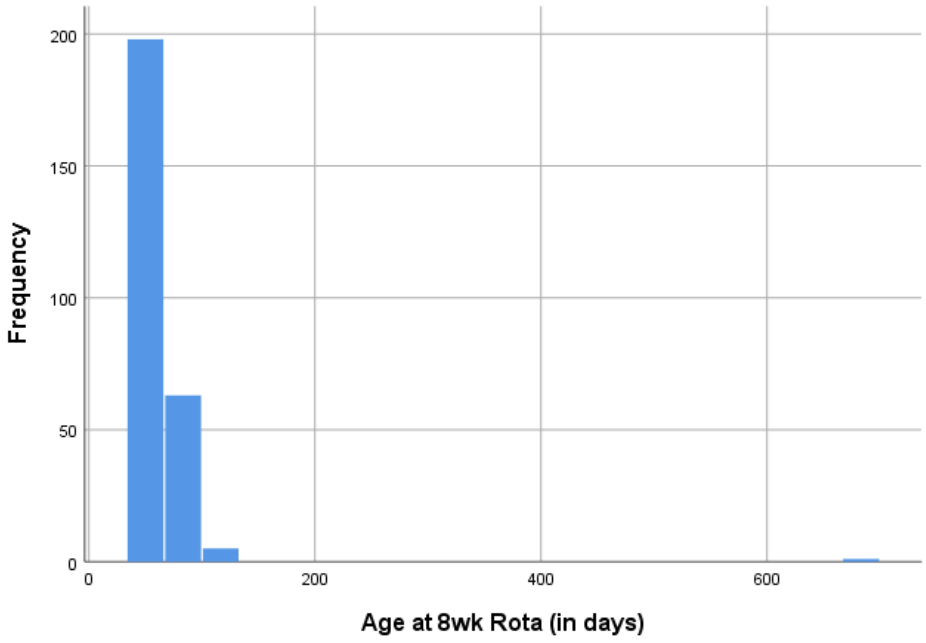


Figure 7.14 Moderately low birthweight – 8-week Rotavirus

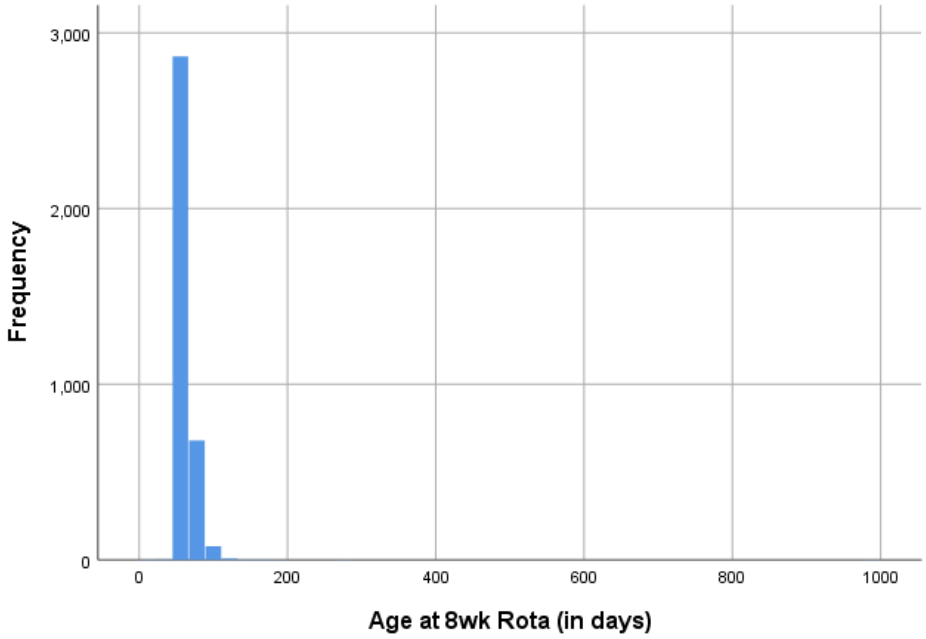


Figure 7.15 Normal birthweight – 8-week Rotavirus

7.3.2 Infant gestational ages, birthweights and 12-week vaccines

At the 12-week scheduled visit, infants are due a second dose of DTaP/IPV/Hib/HepB and Rotavirus vaccines. This section analyses the time between each of these two first 8-week vaccines and the second 12-week doses. There should 28 days between these vaccines, and a delay of two weeks means that any vaccines give later than 42 days are treated as delayed. As previously explained in certain situations, for DTaP/IPV/Hib/HepB and Rotavirus, it may be acceptable to give these vaccines after a three-week interval, but any vaccines given before this time are considered as errors.

The correlation matrix (Table 7.20) reveals strong correlation between the time of administration of these two vaccines.

Table 7.20 Correlation matrix 12-week vaccines

		12-week DTaP/IPV/Hib/HepB	12-week Rotavirus
12-week DTaP/IPV/Hib/HepB	Pearson *r*	1	0.959
	Sig.		<0.001
	N	3973	3826
12-week Rotavirus	Pearson *r*	0.959	1
	Sig.	<0.001	
	N	3826	3836

As with the previous section, infants born within identified gestational age and birthweight categories are presented, starting with gestational age for DTaP/IPV/Hib/HepB.

DTaP/IPV/Hib/HepB

The means and standard deviations for each of the gestational age groups are presented in Table 7.21. This demonstrates higher mean times in days between vaccines for the extremely preterm and the moderate to late preterm groups. With bootstrapping, one-way ANOVA testing identified a significant difference between the groups (F (3, 3935) = 5.560, p = 0.001). Following a post-hoc Bonferroni adjustment, the difference was identified between the moderate to late preterm and the normal gestational age groups (p = <0.001).

Table 7.21 Days since previous 8-week dose DTaP/IPV/Hib/HepB – Gestational age

GA category	N	Mean	SD
Extremely preterm	14	42.07	22.075
Very preterm	31	33.45	7.775
Moderate to late preterm	311	45.56	69.645
Normal gestational age	3583	37.21	30.748

The greatest dispersion is seen in the moderate to late preterm group (SD 69.645) and the shape of the data for this groups are illustrated in Figure 7.16. This shows a right-sided skew, and some extreme outliers. The range for the administration of this second DTaP/IPV/Hib/HepB was 21-674 days.

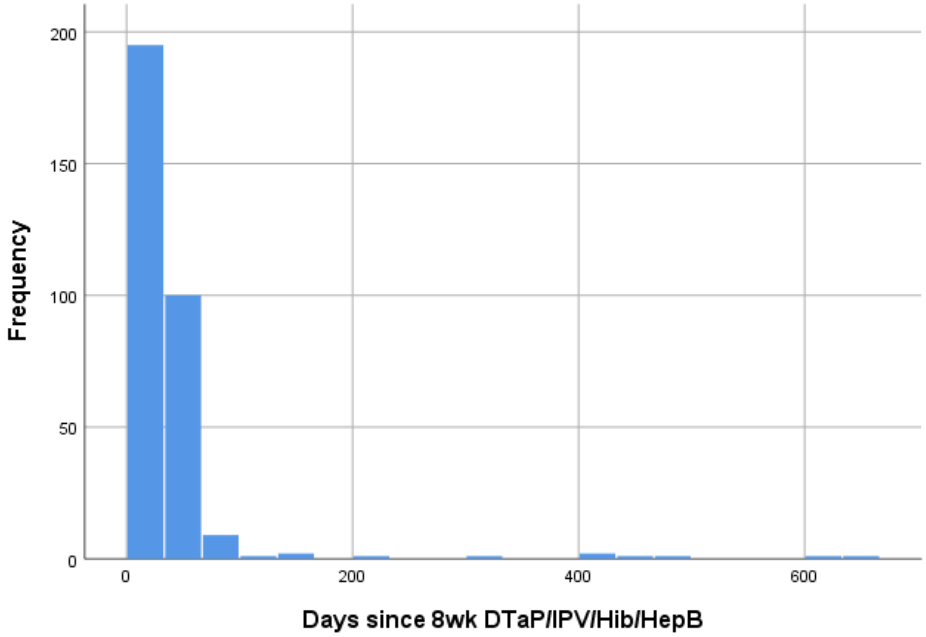


Figure 7.16 Moderate to late preterm – days since 8-week DTaP/IPV/Hib/HepB

A summary of the time to this vaccine with the birthweight categories is presented in Table 7.22. This demonstrates a higher mean age in days and greater dispersion of data (SD 70.773) for the moderately low birthweight group. ANOVA testing with bootstrapping revealed a statistically significant difference between the groups (F (2, 3936) = 8.980, p = <0.001), and further post hoc analyses (Bonferroni) revealed that these differences occurred between the moderately low and normal birthweight groups (p = <0.001).

Table 7.22 Days since previous 8-week dose DTaP/IPV/Hib/HepB – Birthweight

BW category	N	Mean	SD
Very LBW	38	36.45	15.188
Moderately LBW	265	46.72	70.773
Normal BW	3636	37.23	31.321

The shape of the distribution of data in all birthweight groups indicated a skew to the right, and extreme outliers were observed in the moderately low and normal birthweight groups.

Rotavirus

Table 7.23 demonstrates that greater mean differences exist between the extremely preterm groups compared with other gestational age categories for the second dose of Rotavirus vaccine. However, one-way ANOVA testing with bootstrapping was undertaken, and this found no significant differences between any of the groups (F (3, 3828) = 1.455, p = 0.225).

Table 7.23 Days since previous 8-week Rotavirus vaccine – gestational age

GA category	N	Mean	SD
Extremely preterm	12	40.50	22.089
Very preterm	29	33.41	8.588
Moderate to late preterm	300	33.81	11.389
Normal gestational age	3491	33.98	10.925

The standard deviation was also greater for the extremely preterm group. The distribution of data across the gestational age categories demonstrated a right-sided skew for all gestational age categories, with extreme outliers present in the extremely preterm,

moderate to late preterm and normal gestational age groups. The range in days for the administration of this vaccine was 21-134 days.

The time between Rotavirus vaccinations by birthweight categories is presented in Table 7.24, where the highest mean is seen in the very low birthweight group. Greater spread of data is seen in the very low and normal birthweight groups. One-way ANOVA testing (with bootstrapping) did not indicate any significant differences between the birthweight categories (F (2, 3829) = 0.731, p = 0.482).

Table 7.24 Days since previous 8-week Rotavirus vaccine – birthweight

BW category	N	Mean	SD
Very LBW	35	35.83	14.912
Moderately LBW	252	33.51	9.195
Normal BW	3549	33.97	11.106

The shape of the data illustrated that in all birthweight groups, the data are skewed to the right.

7.3.3 Infant gestational ages, birthweights and 16-week vaccines

Vaccines analysed in this section are the third dose of DTaP/IPV/Hib/HepB, and the second doses of PCV and MenB. There should be 28 days between the DTaP/IPV/Hib/HepB doses, and 56 days between PCV and MenB.

The correlation matrix (Table 7.25) once again indicates strong correlations between the time these three vaccines were administered.

Table 7.25 Correlation matrix 16-week vaccines

		16-week DTaP/IPV/Hib/HepB	16-week PCV	8-week MenB
16-week DTaP/IPV/Hib/HepB	Pearson *r*	1	0.848	0.835
	Sig.		<0.001	<0.001
	N	3905	3896	3895
16-week PCV	Pearson *r*	0.848	1	0.978
	Sig.	<0.001		<0.001
	N	3896	3909	3903
8-week MenB	Pearson *r*	0.835	0.978	1
	Sig.	<0.001	<0.001	
	N	3895	3903	3942

DTaP/IPV/Hib/HepB

Differences between the mean time (in days) for each category and standard deviations are illustrated in Table 7.26, which reports higher mean times for the normal and extremely preterm gestational age groups. The distribution of data is also greater in the normal gestational age group (SD 30.552). One-way ANOVA testing was undertaken and there were no significant differences between any of the gestational age categories (F (3, 3901) = 0.221, p = 0.882) in receiving this 16-week DTaP/IPV/Hib/HepB vaccine.

Table 7.26 Days since 12-week DTaP/IPV/Hib/HepB – gestational age

GA category	N	Mean	SD
Extremely preterm	13	40.92	18.355
Very preterm	32	36.31	17.575
Moderate to late preterm	299	38.15	21.527
Normal gestational age	3561	39.19	30.552

The distribution of data revealed marked right-sided skews for the very preterm, moderate to late preterm and normal gestational age groups. The range for the administration of this third DTaP/IPV/Hib/HepB vaccine was 21-630 days. Extreme outliers were observed in the moderate to late preterm and normal gestational age categories.

A similar picture emerged for the time between the second and third DTaP/IPV/Hib/HepB by birthweight category. The means and standard deviations are presented in Table 7.27, which demonstrates a lower mean in the very low birthweight group. The greatest dispersion of data are seen in the moderately low and normal birthweight groups (SD 30.435, 29.908).

One-way ANOVA testing did not identify any significant differences between the birthweight groups (F (2, 3902) = 0.103, p = 0.903).

Table 7.27 Days since 12-week DTaP/IPV/Hib/HepB – birthweight

BW category	N	Mean	SD
Very LBW	38	37.79	16.333
Moderately LBW	255	39.76	30.435
Normal BW	3612	39.06	29.908

The distribution of data also reflected what was observed in the gestational age groups; data were skewed to the right and extreme outliers were observed in the moderately low and normal birthweight categories.

PCV

Table 7.28 summarises the mean time and standard deviations in days between the first 8-week PCV vaccine, and the second dose scheduled for 16-weeks. This shows a greater mean in the extremely preterm category. The standard deviations are greater in the

moderate to late and normal gestational age groups. One-way ANOVA testing (with bootstrapping) does not reveal any significant differences between the gestational age categories and receipt of the second PCV vaccine (F (3, 3905) = 0.536, p = 0.658).

Table 7.28 Days since 8-week PCV – gestational age

GA category	N	Mean	SD
Extremely preterm	13	86.06	28.394
Very preterm	32	70.88	21.476
Moderate to late preterm	301	74.05	37.154
Normal gestational age	3563	74.05	37.129

The distribution of data for each category shows right-sided skews for the very preterm, moderate to late preterm and normal gestational age groups, and extreme outliers are observed in the two latter categories (Figure 7.17 and Figure 7.18). The range in days for the administration of this vaccine was 28-658 days.

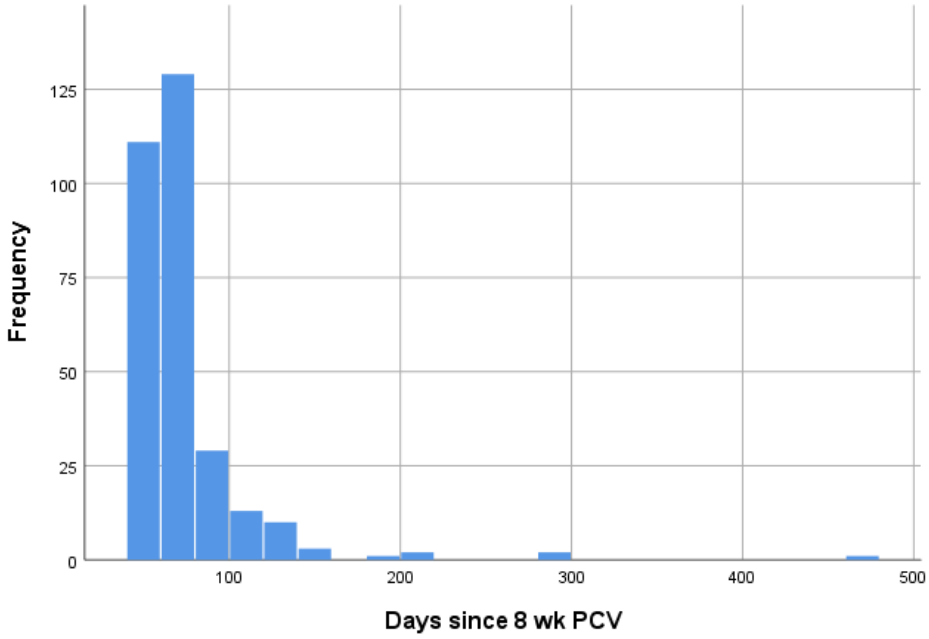


Figure 7.17 Moderate to late preterm category – days since 8-weeks PCV

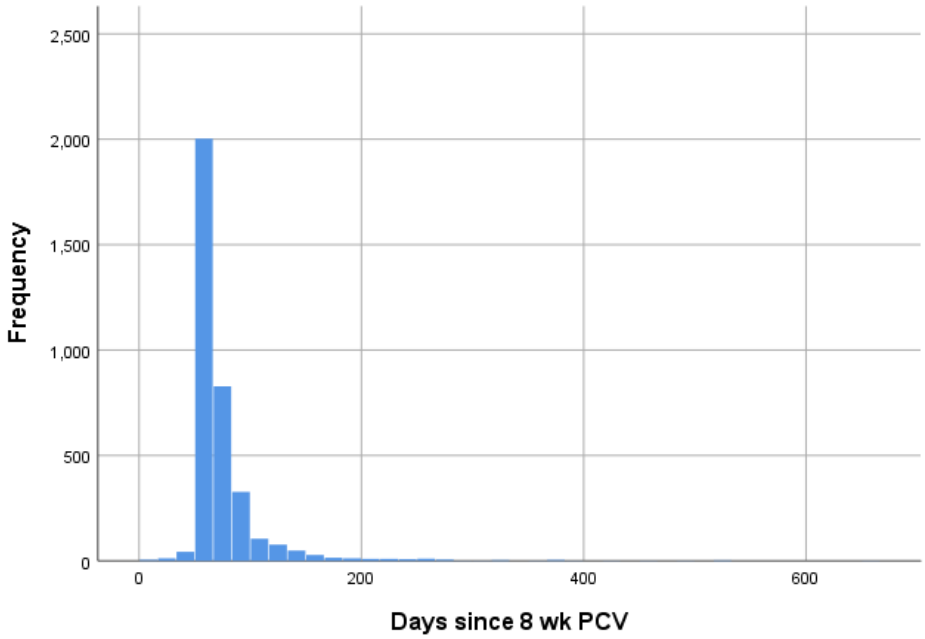


Figure 7.18 Normal gestational age category – days since 8-week PCV.

The mean and the standard deviation for time between PCV vaccines and birthweight are presented in Table 7.29. This shows that there are higher means for the very low and moderate low birthweight categories. Greater dispersion of data are observed in the moderately low and normal birthweight groups (SD 38.281, 37.023). One-way ANOVA testing with bootstrapping, did not reveal any significant differences between the groups (F (2, 3906) = 0.232, p = 0.793).

Table 7.29 Days since 8-week PCV – birth weight

BW category	N	Mean	SD
Very LBW	38	75.26	24.831
Moderately LBW	255	75.51	38.281
Normal BW	3616	73.95	37.023

The distribution of data in these categories revealed a skew to the right in all groups and extreme outliers in the moderate to low and normal birthweight categories.

MenB

The mean time and standard deviation in days between each 8-week and 16-week MenB vaccine by gestational age is summarised in Table 7.30, which shows a greater mean age in the extremely preterm group. The standard deviations are greater in the extremely preterm and moderate to late preterm groups. One-way ANOVA testing with bootstrapping reveals no significant differences between these groups (F (3, 3938) = 2.327, p = 0.073).

Table 7.30 Days since 8-week MenB – gestational age

GA category	N	Mean	SD
Extremely preterm	13	99.08	68.901
Very preterm	32	71.59	21.005
Moderate to late preterm	311	80.83	58.619
Normal gestational age	3586	76.00	43.627

The distribution of data across these gestational age categories showed that the data were skewed to the right in all groups, and extreme outliers were apparent in the extremely preterm, moderate to late preterm and normal gestational age groups. The range in days for the administration of this vaccine was 28-674.

Table 7.31 displays the time between MenB vaccines against the birthweight categories. This shows that the means (in days) are higher in the very low and moderately low birthweight categories, and the greatest standard deviation is in the moderately low birthweight category. One-way ANOVA testing with bootstrapping reveals no significant differences between the birthweight groups and time between MenB vaccines (F (2, 3939) = 1.485, p = 0.227).

Table 7.31 Days since 8-week MenB - birthweight

BW category	N	Mean	SD
Very LBW	38	80.08	44.808
Moderately LBW	263	80.79	55.934
Normal BW	3641	76.06	44.082

As with PCV, the distribution of data across each of the birthweight categories demonstrated that a right-sided skew and outliers are present in all birthweight categories.

7.3.4 Age at 8-week vaccinations and additional infant data

This section explores additional infant characteristics and time at 8-week vaccines, using data from the NNRD. Variables studied are the primary reason for admission to the NNU, the level of care required on admission to the NNU, the length of time the infant spent in the NNU, the admitting NNU, the diagnosis on discharge from the NNU, and whether discharged on oxygen.

Primary reason for admission to the NNU

The reasons for admission are displayed in Table 7.2, section 7.2.1. The main reason cited for admission was prematurity which accounted for 76.9% (n = 133) cases. The mean time in days to the first vaccines are displayed in Table 7.32. The highest mean is observed for the single infant admitted for social reasons, for all vaccines.

Table 7.32 Reason for admission and 8-week vaccines

DTaP/IPV/Hib/HepB				**PCV**			
Reason for admission	N	Mean	SD	Reason for admission	N	Mean	SD
Preterm	116	66.42	16.248	Preterm	116	66.10	15.923
Respiratory disease	22	65.59	12.227	Respiratory disease	22	66.23	12.177
Hypoglycaemia	36	65.00	10.817	Hypoglycaemia	3	65.00	10.817
Social issues	1	81.00		Social issues	1	81.00	
Short observation	1	66.00		Short observation	1	66.00	
GIT disease	1	61.00		GIT disease	1	61.00	
Readmission	2	66.50	4.950	Readmission	2	66.50	4.950
MenB				**Rotavirus**			
Preterm	115	71.83	58.349	Preterm	113	70.70	57.676
Respiratory disease	22	66.18	12.258	Respiratory disease	21	65.24	7.848
Hypoglycaemia	3	65.00	10.817	Hypoglycaemia	3	65.00	10.817
Social issues	1	81.00		Social issues	1	81.00	
Short observation	1	66.00		Short observation	1	66.00	
GIT disease	1	61.00		GIT disease	1	61.00	
Readmission	2	35.00	49.497	Readmission		1	

To investigate any significant differences between the reasons for admission, the categories were regrouped for analysis by one-way ANOVA testing (with bootstrapping). The new groups were categorised as in Table 7.33:

Table 7.33 Categories of reason for admission

Reason for admission (original)	Reason for admission (new)
Preterm	Preterm
Respiratory disease	Respiratory disease
Hypoglycaemia	Other disease
Social issues	Other reason
Short observation	Other reason
GIT disease	Other disease
Readmission	Other reason

No significant differences were observed between any of the categories for reason for admission, and any of the 8-week vaccines: DTaP/IPV/Hib/HepB – F (3, 142) = 0.124, p = 0.946, PCV – F (3, 142) 0.113, p = 0.952, MenB – F (3, 141) 0.218, p = 0.884 and Rotavirus – F (3, 137) 0.232, p = 0.874.

Level of care required on admission

The mean and standard deviation (in days) for the level of care required on admission is illustrated in Table 7.34. This shows that for DTaP/IPV/Hib/HepB and PCV, the mean is higher than for the other vaccines in the transitional care group. There is also a higher mean for MenB and Rotavirus vaccines in the medical high dependency group.

Table 7.34 Level of care required and 8-week vaccines

DTaP/IPV/Hib/HepB				**PCV**			
Level of care	N	Mean	SD		N	Mean	SD
Medical intensive care	52	67.56	11.592	Medical intensive care	52	67.83	11.528
Medical high dependency care	40	66.00	11.482	Medical high dependency care	40	65.08	9.983
Medical special care	43	63.98	8.940	Medical special care	43	63.98	8.940
Continuing care	1	54.00		Continuing care	1	54.00	
Transitional care	10	72.60	44.473	Transitional care	10	72.60	44.473
MenB				**Rotavirus**			
Medical intensive care	52	68.12	10.970	Medical intensive care	49	67.94	10.051
Medical high dependency care	40	80.72	95.937	Medical high dependency care	39	81.00	97.175
Medical special care	43	64.09	8.890	Medical special care	43	64.09	8.890
Continuing care				Continuing care	1	54.00	
Transitional care	10	66.30	50.091	Transitional care	9	51.56	19.417

Boxplots (Figure 7.19, Figure 7.20, Figure 7.21 and Figure 7.22) to display the distribution of the data show that extreme outliers have contributed to the higher means seen in Table 7.34. To do this the groups were revised; the categories of continuing care and transitional care were merged.

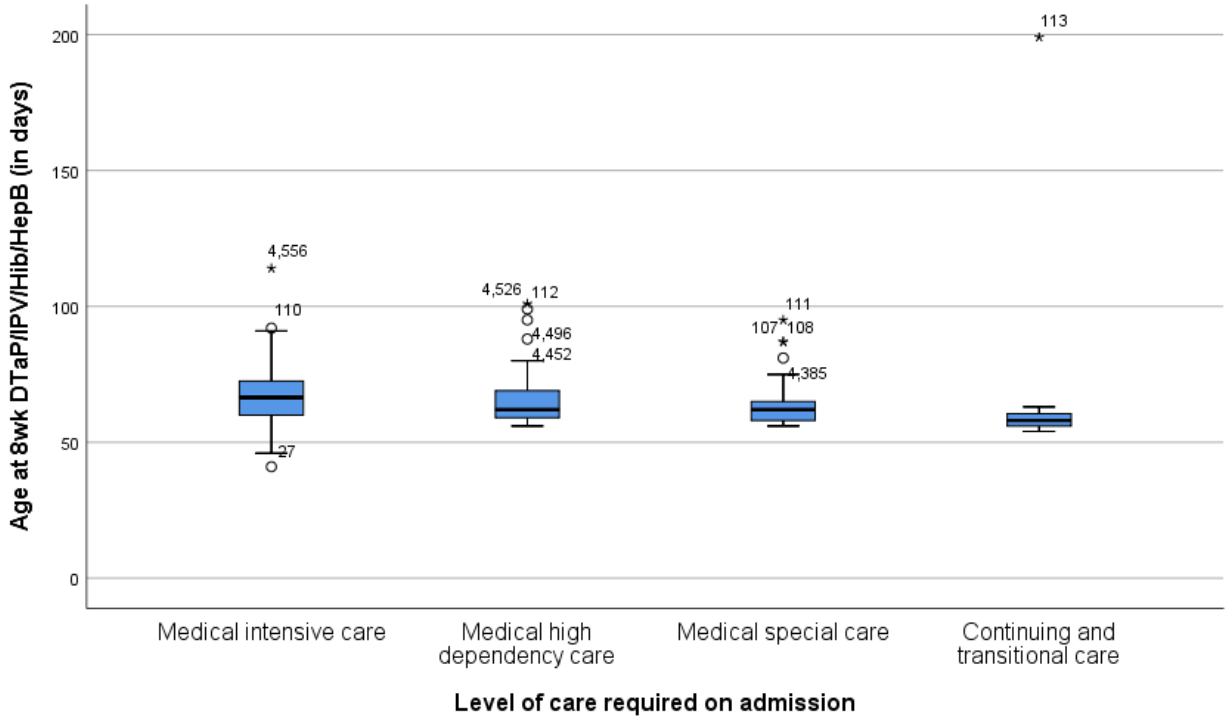


Figure 7.19 Level of care and DTaP/IPV/Hib/HepB

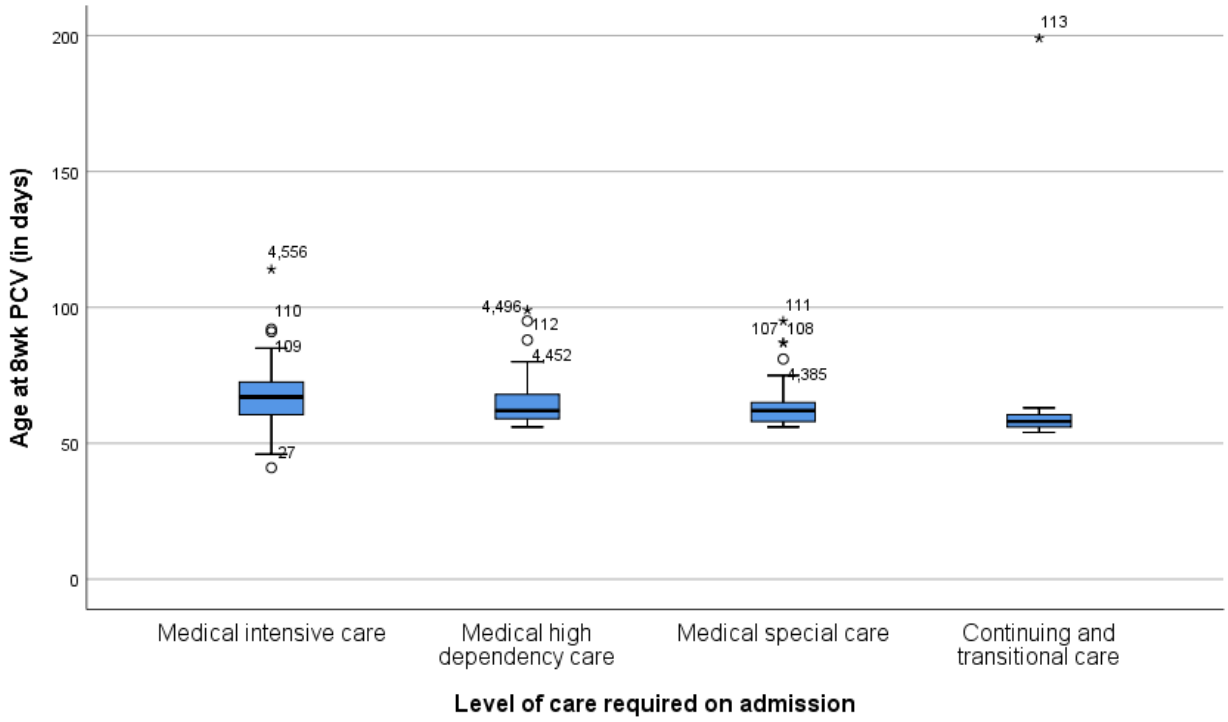


Figure 7.20 Level of care and PCV

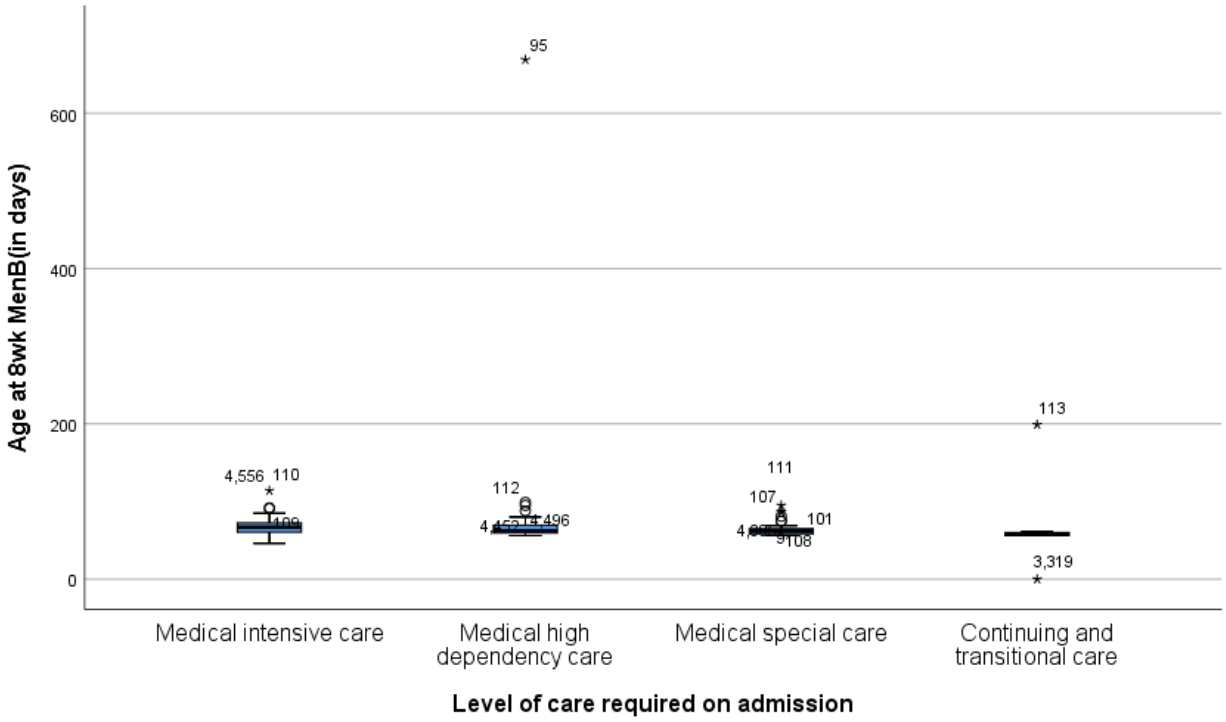


Figure 7.21 Level of care and MenB

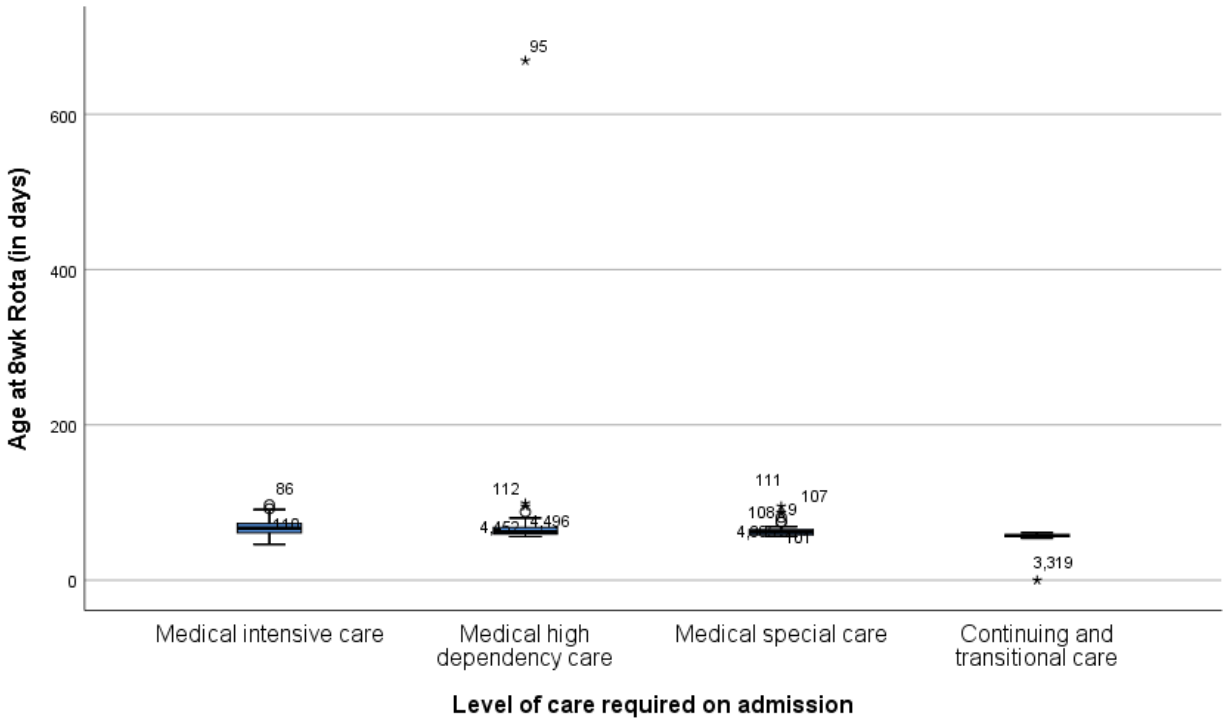


Figure 7.22 Level of care and Rotavirus

One-way ANOVA testing (with bootstrapping), did not reveal any significant differences between levels of care were seen for any of the 8-week vaccines: DTaP/IPV/Hib/HepB - *F* (3, 142) 0.780, *p* = 0.507, PCV – *F* (3, 142) 0.949, *p* = 0.419, MenB – *F* (3, 141) 0.771, *p* = 0.512 and Rotavirus – *F* (3, 137) 1.192, *p* = 0.315.

Days spent on the NNU and 8-week vaccines

Testing of gestational age, birthweight and time spent on the NNU revealed negative correlations; birthweight: Pearson's r = -0.695, p = <0.001, and gestational age – Pearson's r = -0.849, p = <0.001. The scatterplots (

Figure 7.23 and Figure 7.24) also demonstrate this negative correlation.

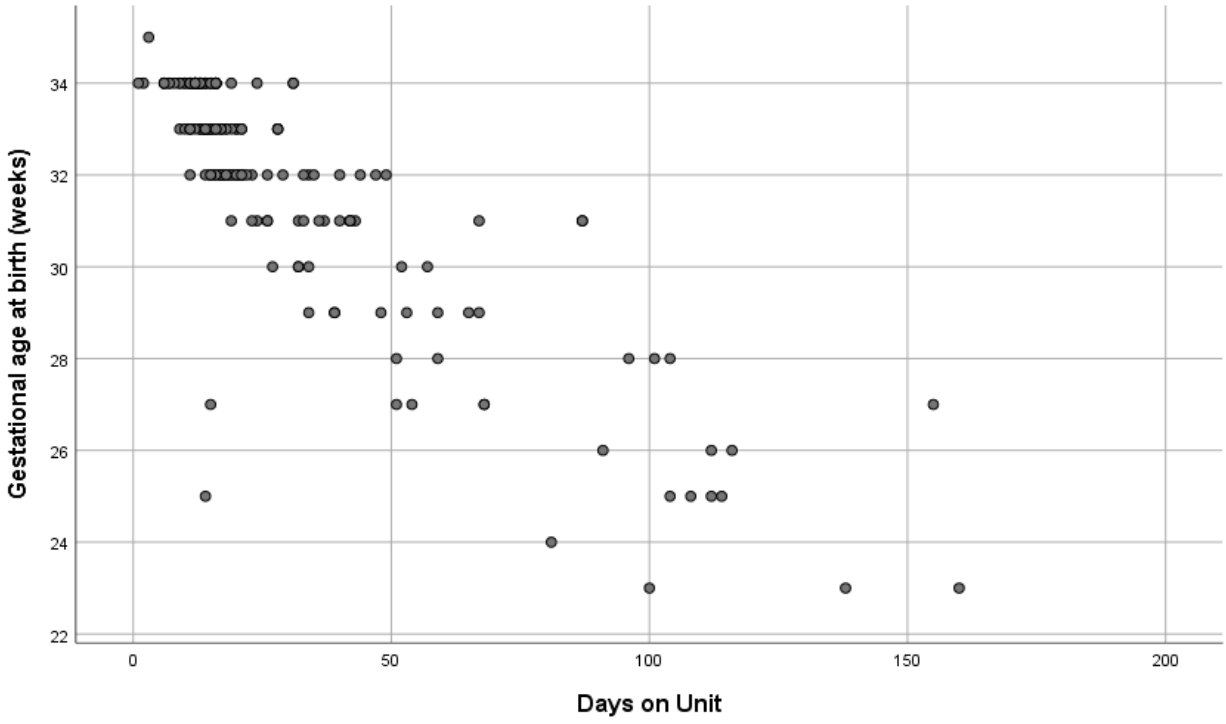


Figure 7.23 Scatterplot gestational age and time on the NNU

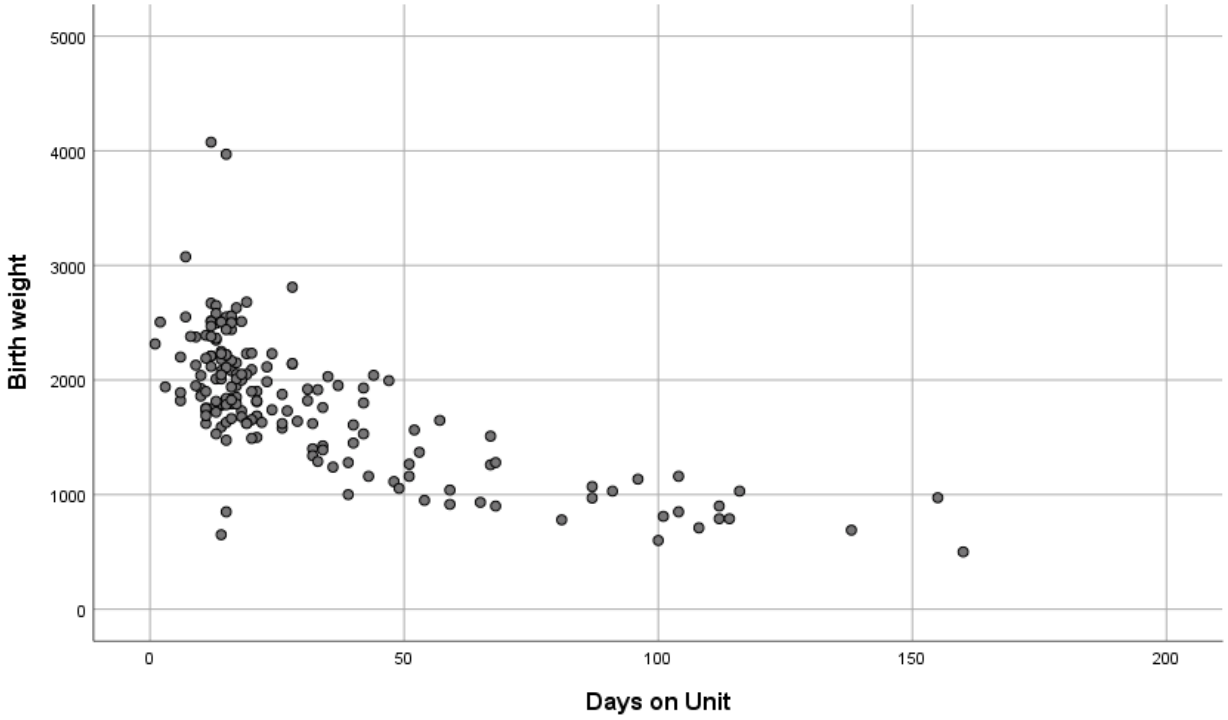


Figure 7.24 Scatterplot birthweight and time on the NNU

However, further testing exploring the relationship between time spent on the NNU and time of 8-week vaccines, did not reveal any significant correlations: DTaP/IPV/Hib/HepB – Pearson's r = 0.065 (p = 0.439), PCV – Pearson's r = 0.068 (p = 0.415), MenB – Pearson's r = -0.024 (p = 0.773) and Rotavirus – Pearson's r = -0.16 (p = 0.850).

Admitting NNU and time to first vaccine

Table 7.35 displays the mean and standard deviation for time to 8-week vaccines for the geographical areas into which the NNUs have been categorised (as illustrated in Table 7.1); to North, South and South West.

This shows the there is a higher mean in the North for DTaP/IPV/Hib/HepB and PCV, but a higher mean in the South for MenB and Rotavirus.

Table 7.35 Area of NNU and 8-week vaccines

DTaP/IPV/Hib/HepB				**PCV**			
NNU area	N	Mean	SD	NNU area	N	Mean	SD
North	88	68.02	17.889	North	88	68.18	17.861
South	57	63.89	9.892	South	57	63.25	8.534
South West	1	56.00	N/A	South West	1	56.00	N/A
MenB				**Rotavirus**			
North	88	68.02	17.889	North	83	66.31	10.564
South	56	74.07	81.810	South	57	73.72	81.119
South West	1	56.00	N/A	South West	1	56.00	N/A

Further regrouping of these areas was undertaken for one-way ANOVA analysis (with bootstrapping) and the areas of South and South West were merged. The distribution of data is displayed in Figure 7.25, Figure 7.26, Figure 7.27 and Figure 7.28. This identifies that the higher means are due to the extreme outliers seen for the DTaP/IPV/Hib/HepB and PCV (for the North) and MenB and Rotavirus (for the South).

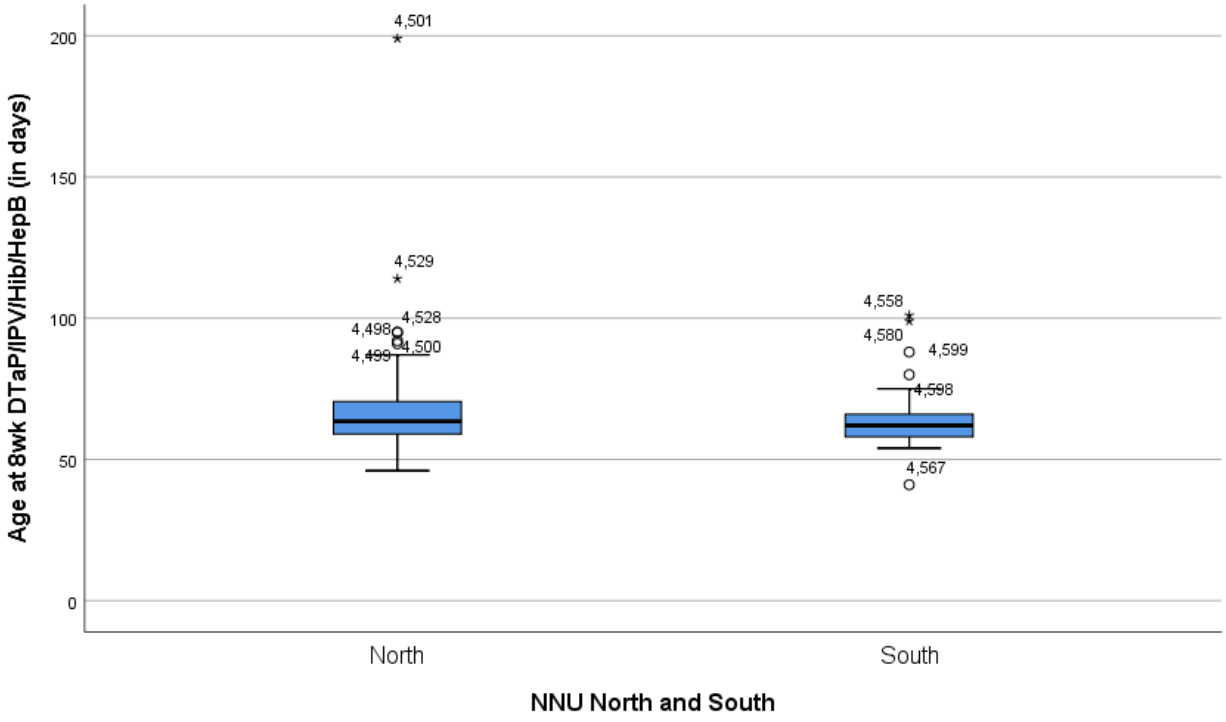


Figure 7.25 NNU area and 8-week DTaP/IPV/Hib/HepB

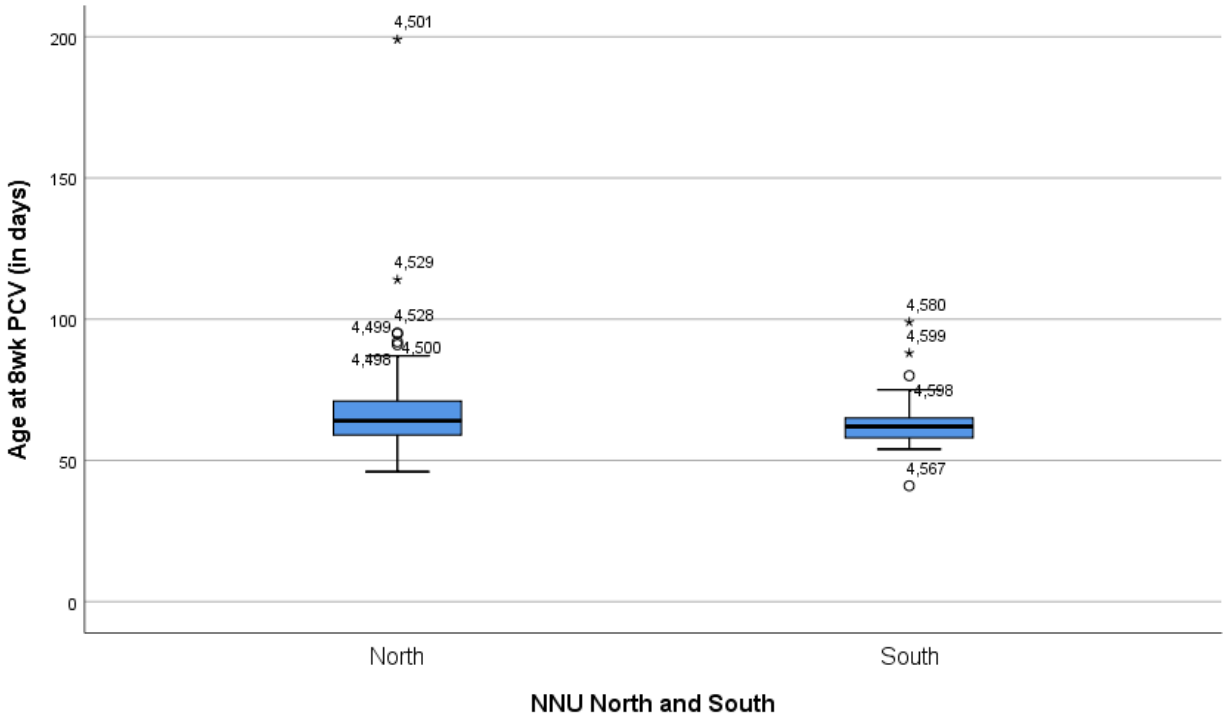


Figure 7.26 NNU area and 8-week PCV

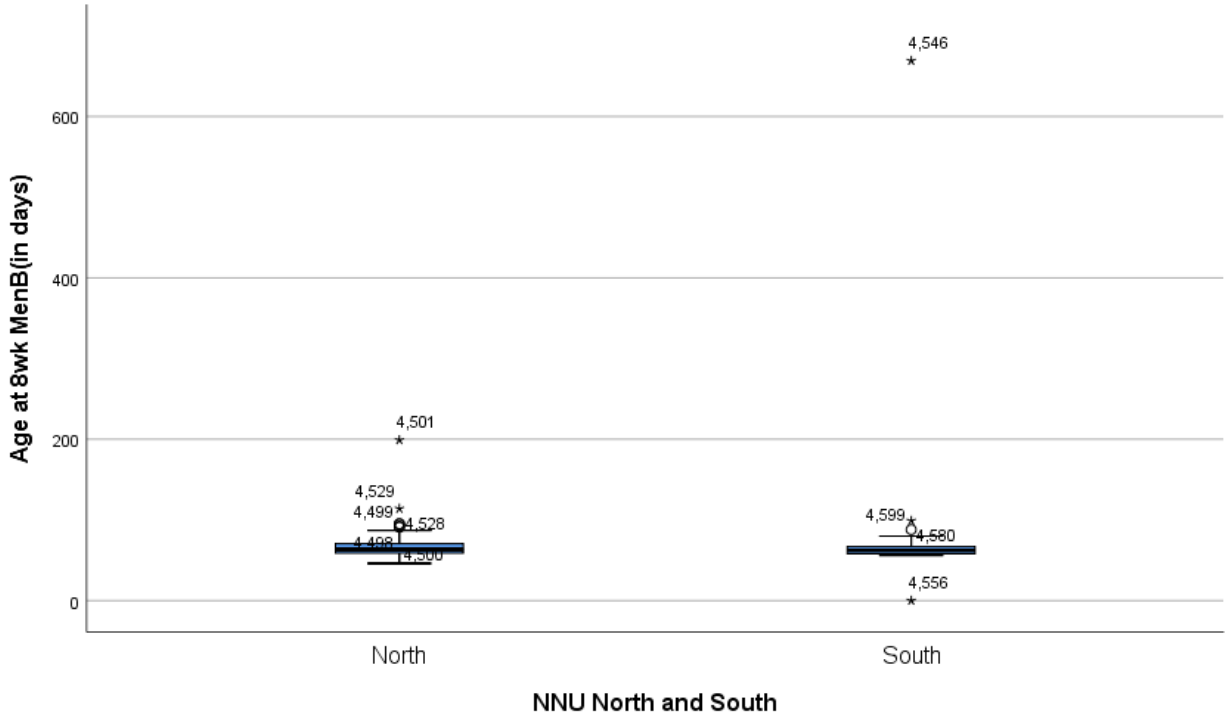


Figure 7.27 NNU area and 8-week MenB

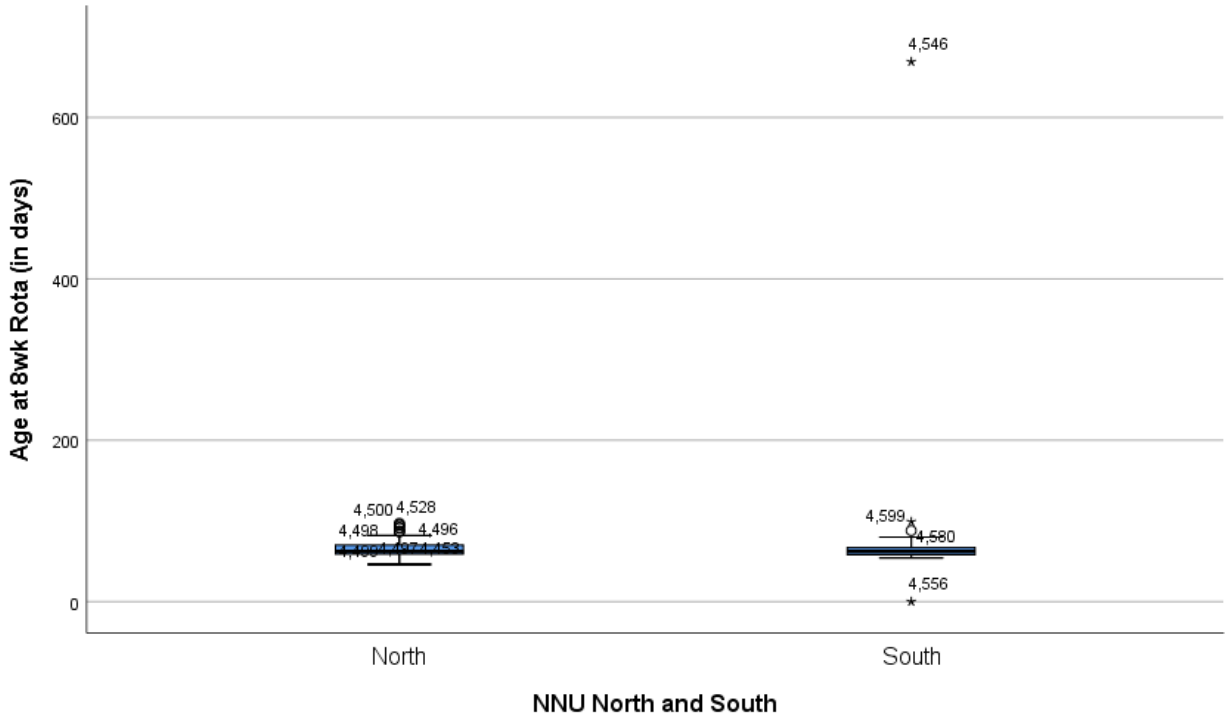


Figure 7.28 NNU area and 8-week Rotavirus

For DTaP/IPV/Hib/HepB (F (1, 144) = 2.742, p = 0.100), MenB (F (1, 143) = 0.410, p = 0.523) and Rotavirus, (F (1, 139) = 0.633, p = 0.428) there were no significant differences noted between the North and South. However, there was a statistically significant difference observed for PCV: F (1, 144) = 4.044, p = 0.046.

Infants discharged on oxygen and 8-week vaccines

When discharged from the NNU, 14 infants were still receiving oxygen therapy, compared with 152 who were not. The mean time in days to first 8-week vaccinations are displayed in Table 7.36. This demonstrates a higher mean for infants on oxygen therapy for 8-week DTaP/IPV/Hib/HepB and PCV vaccines compared with those not receiving therapy. For all infants receiving therapy, the highest mean is seen for MenB.

Table 7.36 Oxygen therapy at discharge and 8-week vaccines

DTaP/IPV/Hib/HepB				**PCV**			
O_2 therapy on discharge	N	Mean	SD	O_2 therapy on discharge	N	Mean	SD
Yes	11	68.64	11.057	Yes	11	68.64	11.057
No	131	65.94	15.698	No	131	65.76	15.387
MenB				**Rotavirus**			
Yes	10	70.10	10.472	Yes	11	68.64	11.057
No	131	70.69	54.840	No	127	69.68	54.417

One-way ANOVA testing did not reveal any significant differences between the two groups: DTaP/IPV/Hib/HepB - F (1, 140) = 0.311, p = 0.578, PCV – F (1, 140) = 0.366, p = 0.546, MenB – F (1, 139) = 0.001, p = 0.973 and Rotavirus – F (1, 136) = 0.004, p = 0.950.

Diagnosis on discharge and 8-week vaccines

Means for the most frequently occurring diagnoses on discharge are presented in Table 7.37, Table 7.38, Table 7.39 and Table 7.40. The mean time in days to vaccination for a diagnosis of prematurity and respiratory distress, is higher for all vaccines. Conversely, there is a lower mean time in days for infants who were diagnosed with early infection risk on discharge.

One-way ANOVA testing (with bootstrapping) revealed no significant differences in time to first vaccines for the diagnoses featured.

Table 7.37 DTaP/IPV/Hib/HepB and diagnoses at discharge

DTaP/IPV/Hib/HepB						
Diagnosis on discharge	N		Mean			
	Yes	No	Yes	No	*F*	*p*
Prematurity	126	14	67.02	61.93	1.351	0.247
Suspected sepsis	48	92	69.10	65.15	2.051	0.154
Respiratory distress	75	65	66.91	66.05	0.106	0.745
Early infection risk	24	116	65.79	66.66	0.061	0.806
Hypoglycaemia	10	130	66.80	66.48	-0.004	0.951

Table 7.38 PCV diagnoses at discharge

PCV						
Diagnosis on discharge	N		Mean			
	Yes	No	Yes	No	*F*	*p*
Prematurity	126	14	66.83	61.93	1.303	0.256
Suspected sepsis	48	92	69.40	64.75	2.961	0.088
Respiratory distress	75	65	66.60	66.05	0.045	0.831
Early infection risk	24	116	65.79	66.46	0.037	0.847
Hypoglycaemia	10	130	66.80	66.31	0.010	0.922

Table 7.39 MenB diagnoses at discharge

MenB						
Diagnosis on discharge	N		Mean			
	Yes	No	Yes	No	*F*	*p*
Prematurity	126	13	72.03	61.85	0.429	0.514
Suspected sepsis	48	91	69.71	71.80	0.048	0.827
Respiratory distress	74	65	75.43	66.12	1.057	0.306
Early infection risk	24	115	67.54	71.82	0.127	0.722
Hypoglycaemia	10	129	66.80	71.41	0.069	0.793

Table 7.40 Rotavirus diagnoses at discharge

Rotavirus						
Diagnosis on discharge	N		Mean			
	Yes	No	Yes	No	*F*	*p*
Prematurity	122	13	71.02	60.62	0.453	0.502
Suspected sepsis	45	90	69.00	70.52	0.025	0.875
Respiratory distress	72	63	75.32	63.95	1.561	0.214
Early infection risk	23	112	61.83	71.70	0.664	0.417
Hypoglycaemia	10	125	66.80	70.27	0.040	0.842

7.3.5 Age at 8-week vaccinations and parental characteristics

This section analyses age at each of the first 8-week vaccines with maternal characteristics of age, ethnicity and number of previous pregnancies, and paternal characteristics of age and ethnicity.

Maternal age and 8-week vaccines

Maternal ages were retrieved for all mothers, and the distribution of data for these are presented in Figure 7.5 and Table 7.5. Here, this is analysed against the four vaccines due at 8-weeks: DTaP/IPV/Hib/HepB, PCV, MenB and Rotavirus.

DTaP/IPV/Hib/HepB

Table 7.41 shows the mean and standard deviation of infant age at days for the first vaccine by maternal age group:

Table 7.41 Maternal age groups and 8-week DTaP/IPV/Hib/HepB

Age category	N	Mean	SD
15 - 19	203	69.58	54.410
20 - 24	846	66.87	41.950
25 - 29	1256	64.82	23.433
30 - 34	1076	65.34	32.109
35 - 39	522	66.00	31.899
40 - 44	98	63.22	8.815
45 - 49	7	61.86	8.989

This suggests that overall (exceptions are the 30-34 and 35-39 groups), as age increases, the mean and standard deviation decreases. One-way ANOVA testing (with bootstrapping) did not demonstrate any significant differences between the maternal age group categories (F (6, 4001) = 0.916, p = 0.482) and time to 8-week DTaP/IPV/Hib/HepB.

PCV

A summary of the means and standard deviation for each maternal age group and time in days to first PCV dose is presented in Table 7.42. As with the first DTaP/IPV/Hib/HepB dose, this also suggests a trend; that the mean and standard deviation decrease as the age groups increase.

Table 7.42 Maternal age groups and 8-week PCV

Age category	N	Mean	SD
15 - 19	202	65.37	13.791
20 - 24	843	64.59	14.580
25 - 29	1250	64.04	15.115
30 - 34	1074	64.50	17.844
35 - 39	520	65.84	31.813
40 - 44	98	63.22	8.815
45 - 49	7	61.86	8.989

Further one-way ANOVA testing with bootstrapping did not reveal any significant differences between age groups (F (6, 3987) = 0.749, p = 0.610).

MenB

The means and standard deviations (in days) for the maternal age groups are illustrated in Table 7.43. These show that the highest mean and standard deviation is in the 35-39 group, with the lowest mean in the 40-44 age category.

Table 7.43 Maternal age groups and 8-week MenB

Age category	N	Mean	SD
15 – 19	202	65.23	13.649
20 – 24	845	64.66	14.837
25 – 29	1257	64.35	16.029
30 – 34	1071	64.53	16.999
35 – 39	519	66.54	41.154
40 – 44	98	61.86	8.935
45 – 49	7	64.76	8.989

The application of one-way ANOVA testing with bootstrapping did not reveal any significant differences between the age groups and time of this first MenB vaccine (F (6, 3992) = 0.871, p = 0.515).

Rotavirus

Table 7.44 illustrates the mean and standard deviation for the first Rotavirus vaccine by maternal age. This demonstrates the greatest mean in the 15-19 and 30-34 age groups. No significant differences between the age groups were identified following one-way ANOVA testing (with bootstrapping): F (6, 3936) = 0.172, p = 0.984.

Table 7.44 Maternal age groups and 8-week Rotavirus

Age category	N	Mean	SD
15 – 19	200	64.74	10.837
20 - 24	822	63.59	8.795
25 - 29	1243	63.60	11.107
30 - 34	1058	64.16	30.115
35 - 39	504	63.77	28.281
40 - 44	98	63.71	9.779
45 - 49	7	61.86	8.989

The distribution of the data for maternal age groups were consistently skewed to the right, and there is a recurring pattern of the greatest standard deviation being in the 30-34 group – there is also a greater dispersion of data in the 15-19 group for first DTaP/IPV/Hib/HepB (SD 54.410).

Maternal ethnicity and 8-week vaccines

This section presents the mean age at the first 8-week vaccines (DTaP/IPV/Hib/HepB, PCV, MenB and Rotavirus) by maternal ethnicity.

Table 7.45

Table 7.46, Table 7.47 and Table 7.48 present the mean and standard deviation in days for these vaccines and shows the greatest means occur in the Black and Mixed groups. One-way ANOVA testing with bootstrapping for the groups reveals no significant differences between them.

Table 7.45 Maternal ethnicity and 8-week DTaP/IPV/Hib/HepB

Ethnicity	N	Mean	SD
White	3535	65.93	35.098
Mixed	36	69.00	25.743
Asian	104	65.08	12.578
Black	38	70.00	17.744
Other	295	62.86	7.943
F (4, 4003) = 0.835, p = 0.503			

Table 7.46 Maternal ethnicity and 8-week PCV

Ethnicity	N	Mean	SD
White	3521	64.58	19.229
Mixed	36	69.00	25.743
Asian	104	65.08	12.578
Black	38	70.74	21.011
Other	295	62.86	7.943
F (4, 3989) = 2.206, p = 0.066			

Table 7.47 Maternal ethnicity and 8-week MenB

Ethnicity	N	Mean	SD
White	3527	64.82	21.807
Mixed	35	67.34	18.142
Asian	104	65.49	14.746
Black	38	69.97	17.750
Other	295	62.83	7.939
F (4, 3994) = 1.395, p = 0.233			

Table 7.48 Maternal ethnicity and 8-week Rotavirus

Ethnicity	N	Mean	SD
White	3477	63.81	21.181
Mixed	34	65.24	13.376
Asian	103	65.22	13.288
Black	35	67.23	15.057
Other	294	63.03	8.281
F (4, 3938) = 0.527, p = 0.716			

Number of previous pregnancies and 8-week vaccines

Scatterplots and correlational analyses were undertaken to explore the relationship between the number of previous pregnancies, and infant age at first 8-week vaccines.

DTaP/IPV/Hib/HepB

Figure 7.29 appears to suggest a correlation; that as the number of previous pregnancies increases, the vaccination age in days decreases:

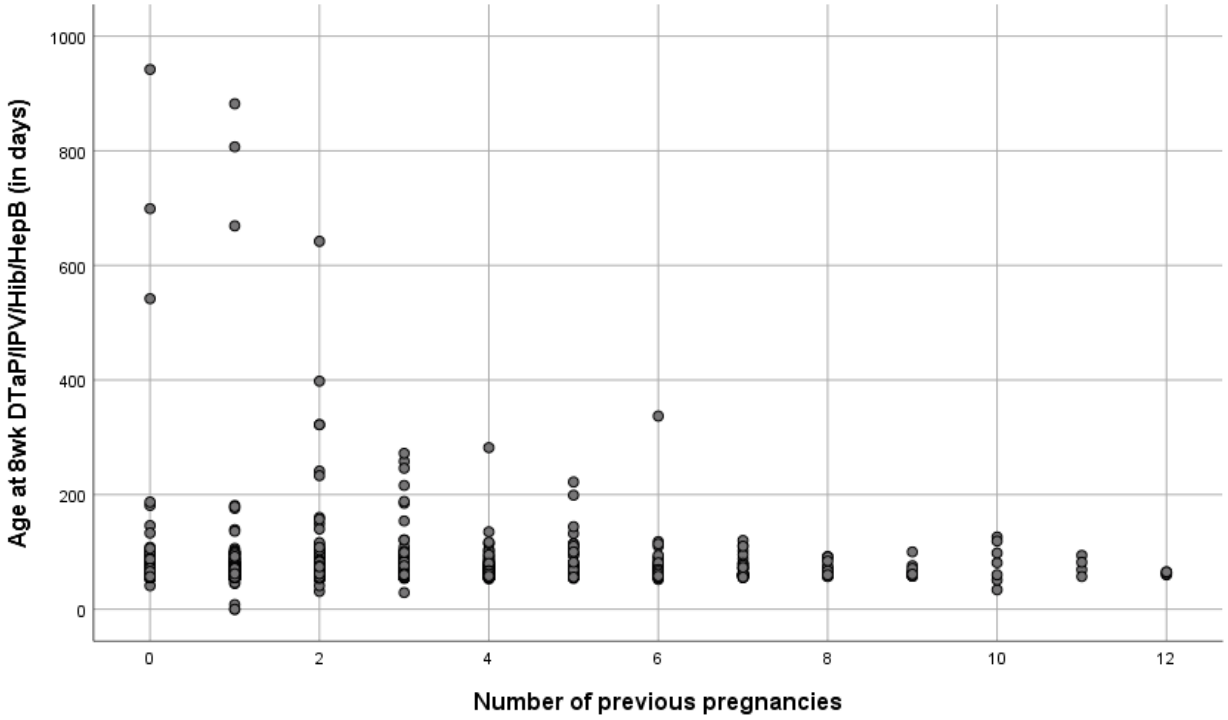


Figure 7.29 Number of previous pregnancies and 8-week DTaP/IPV/Hib/HepB

This relationship was tested further by using Pearson's correlation coefficient, however, this indicated a very weak correlation and was found not to be significant ($r = 0.028$, $p = 0.082$). Additional correlational testing (Table 7.49) and scatterplots (Figure 7.30, Figure 7.31, Figure 7.32) undertaken for the remaining 8-week vaccines (PCV, MenB and Rotavirus) did not suggest any correlations.

Table 7.49 Correlational tests for PCV, MenB and Rotavirus

	Pearson's *r*	*p*
PCV	0.097	<0.001
MenB	0.116	<0.001
Rotavirus	0.066	<0.001

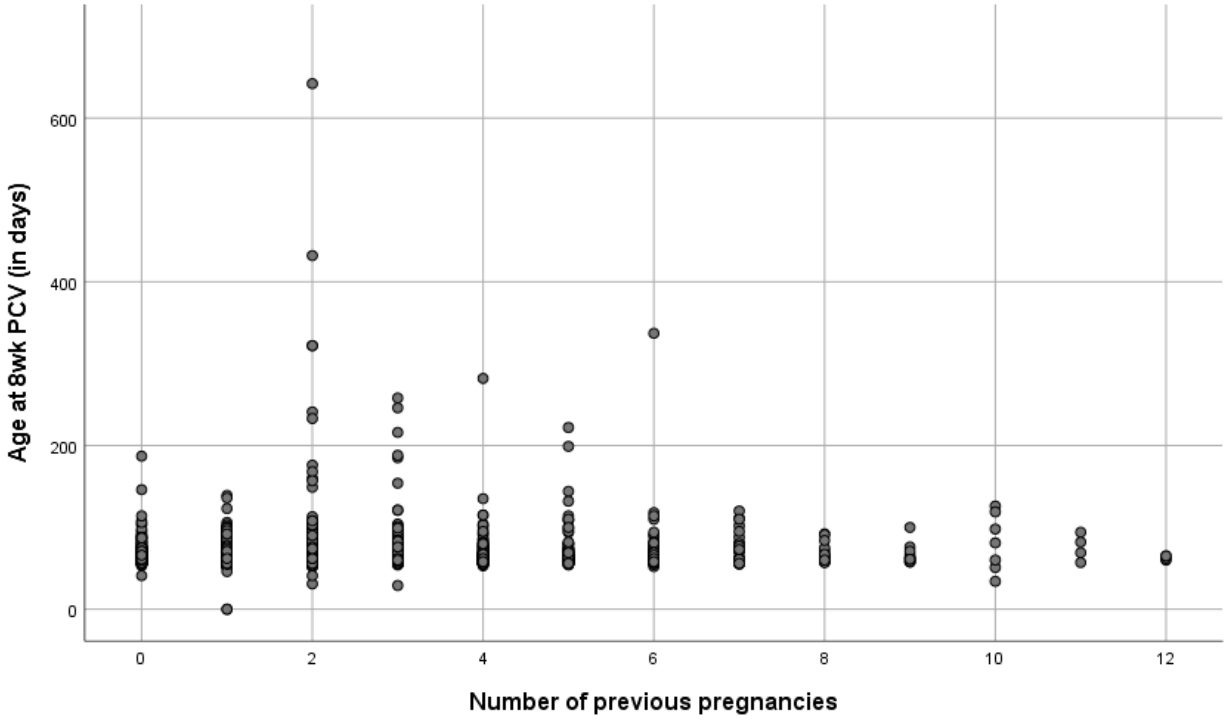


Figure 7.30 Number of previous pregnancies and 8-week PCV

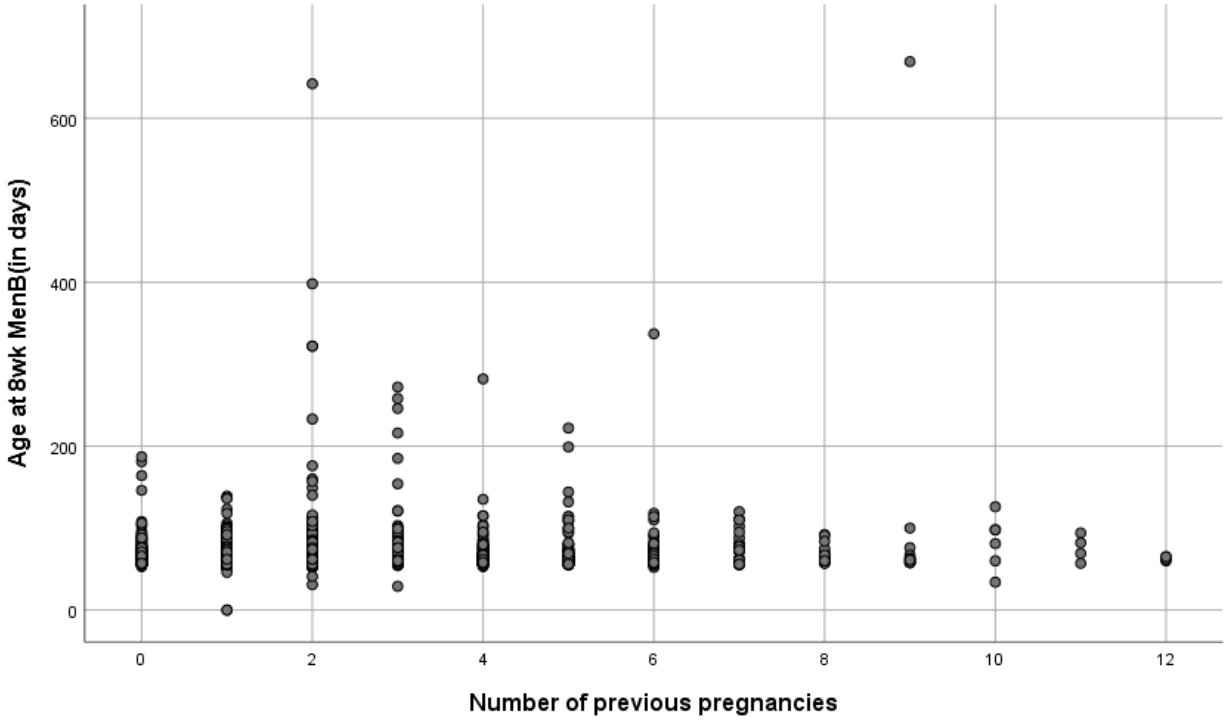


Figure 7.31 Number of previous pregnancies and 8-week MenB

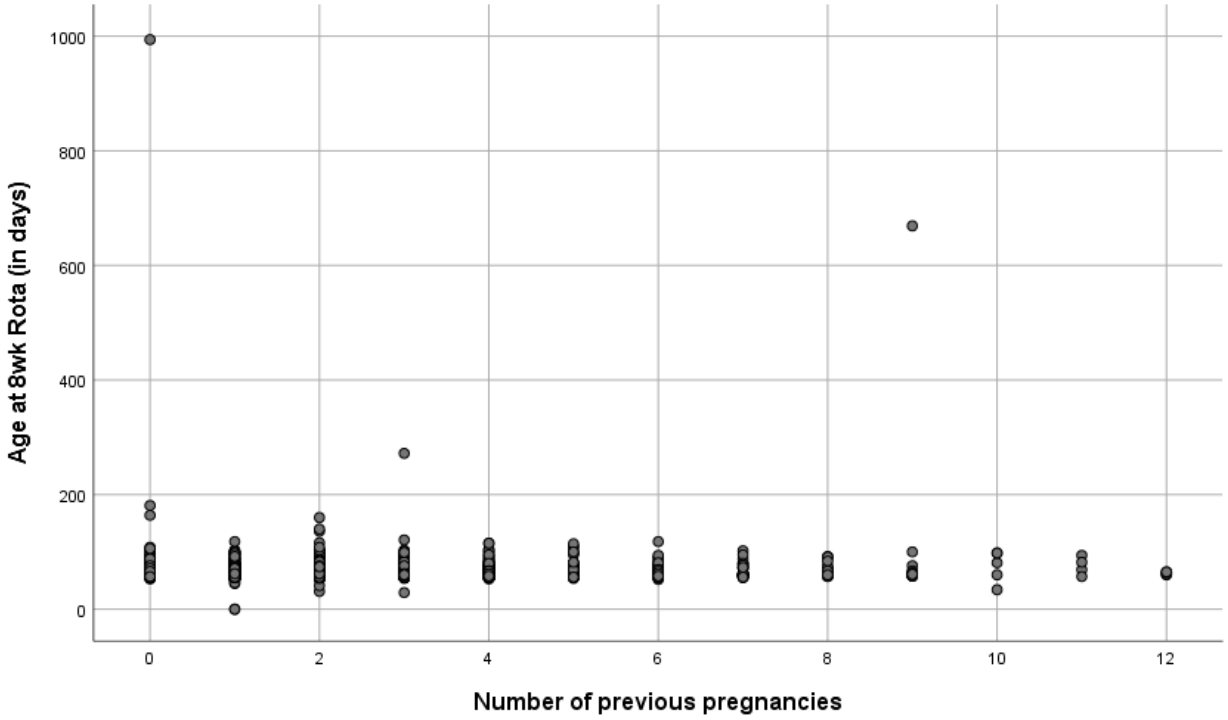


Figure 7.32 Number of previous pregnancies and 8-week Rotavirus

Mothers' occupation

DTaP/IPV/Hib/HepB

Table 7.50 illustrates the time of first DTaP/IPV/Hib vaccination with mothers' occupation. This shows that the highest means for this vaccine are in groups 6 and 8.

Table 7.50 Maternal occupations and 8-week DTaP/IPV/Hib/HepB

SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	Managers, Directors, Senior Officials	2	64.00	7.071
2	Professional Occupations	5	62.20	11.389
3	Associate Professional Occupations	6	62.50	11.077
4	Administrative, Secretarial Occupations	9	62.56	9.029
5	Skilled Trade Occupations	6	60.17	2.787
6	Caring Leisure and other Service Occupations	13	77.46	7.369
7	Sales, Customer Service Occupations	6	61.50	7.369
8	Process, Plant, Machine Operative	3	79.00	19.079
9	Elementary Occupations	7	67.43	13.464

The distribution of data for these occupation groups are shown in Figure 7.33, which also demonstrates that outliers are present in SOC groups 3, 4, 6 and 7.

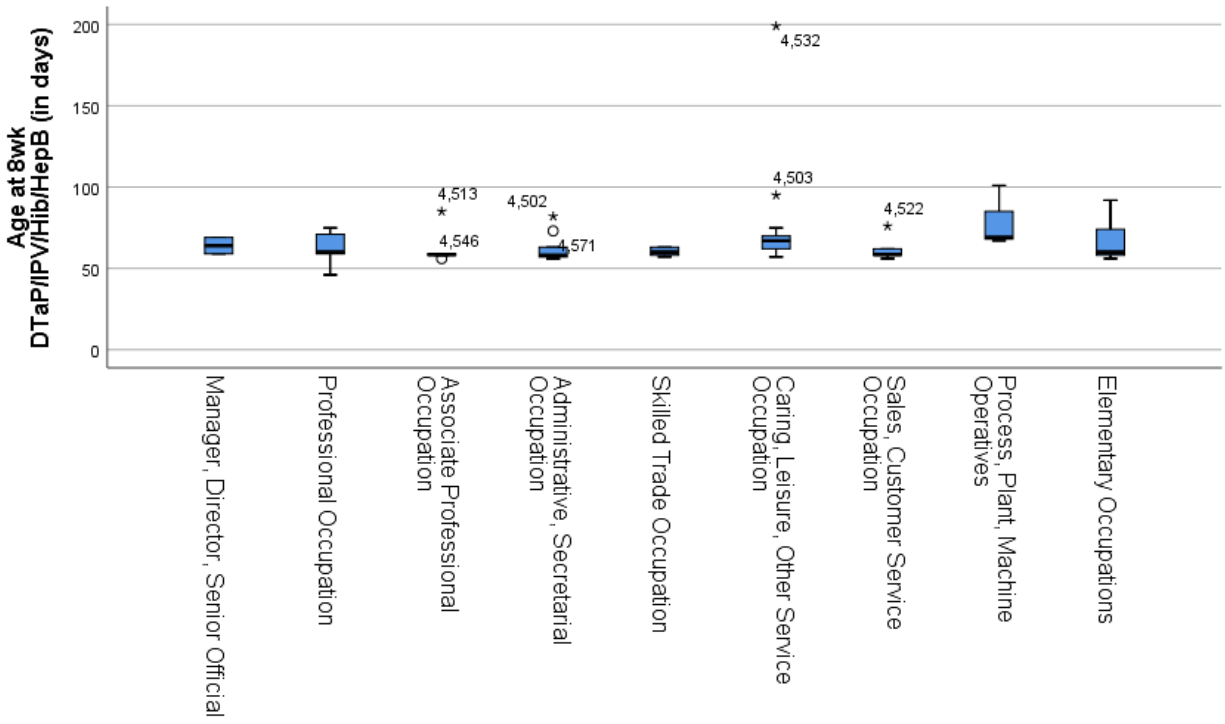


Figure 7.33 Boxplot of maternal occupation and 8-week DTaP/IPV/Hib/HepB

To perform one-way ANOVA testing, the SOC groups were merged (as demonstrated in Table 7.51), to create three new groups: 1 – Managerial and Professional, 2 – Administrative, Skilled and Caring and Leisure, and 3 – Sales, Operatives and Elementary.

Table 7.51 Merged SOC groups and 8-week DTaP/IPV/Hib/HepB

	SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	1	Managers, Directors, Senior Officials	13	62.62	9.946
	2	Professional Occupations			
	3	Associate Professional Occupations			
2	4	Administrative, Secretarial Occupations	28	68.96	26.94
	5	Skilled Trade Occupations			
	6	Caring, Leisure and other Service Occupations			
3	7	Sales, Customer Service Occupations	16	67.38	13.416
	8	Process, Plant, Machine Operative			
	9	Elementary Occupations			

However, this did not reveal any significant differences between these groups: F (2, 54) = 0.414, p = 0.663.

PCV

The mean time and standard deviation of the first PCV dose is shown in Table 7.52. This highlights a higher mean time until this first vaccine in group 6, Caring Leisure and other Service Occupations.

Table 7.52 Maternal occupations and 8-week PCV

SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	Managers, Directors, Senior Officials	2	64.00	7.071
2	Professional Occupations	5	62.20	11.389
3	Associate Professional Occupations	6	62.50	11.077
4	Administrative, Secretarial Occupations	9	62.56	9.029
5	Skilled Trade Occupations	6	60.17	2.787
6	Caring Leisure and other Service Occupations	13	77.46	37.795
7	Sales, Customer Service Occupations	6	63.83	8.208
8	Process, Plant, Machine Operative	3	66.67	2.517
9	Elementary Occupations	7	67.43	13.464

Figure 7.34 demonstrates the distribution of data for the first PCV dose with mothers' occupations, and outliers are observed in groups 3, 4 and 6.

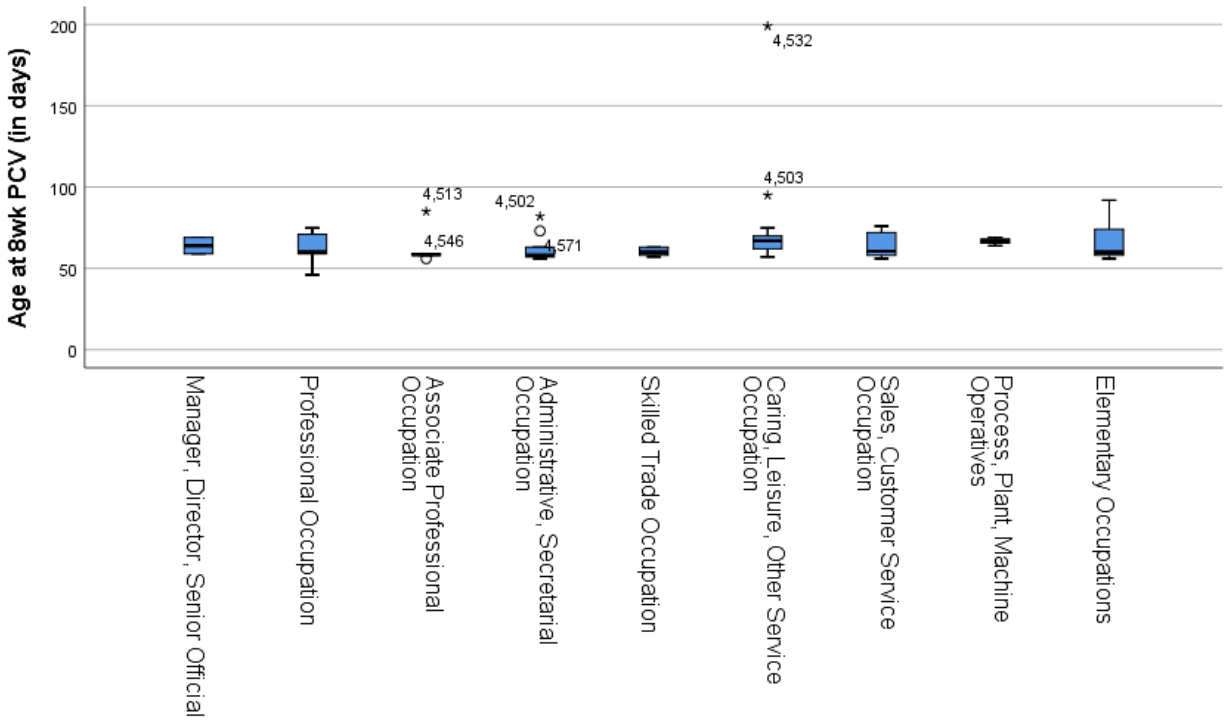


Figure 7.34 Boxplot of maternal occupation and 8-week PCV

The merged SOC groups were subjected to one-way ANOVA testing (Table 7.53). However, no significant differences were found between the groups (F (2, 54) = 0.448, p = 0.641).

Table 7.53 Merged SOC groups and 8-week PCV

	SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	1	Managers, Directors, Senior Officials	13	62.62	9.946
	2	Professional Occupations			
	3	Associate Professional Occupations			
2	4	Administrative, Secretarial Occupations	28	68.96	26.946
	5	Skilled Trade Occupations			
	6	Caring, Leisure and other Service Occupations			
3	7	Sales, Customer Service Occupations	16	65.94	9.936
	8	Process, Plant, Machine Operative			
	9	Elementary Occupations			

MenB

For the first MenB vaccine, the mean and standard deviation (in days) by mothers' occupation is shown in Table 7.54. This demonstrates a much higher mean in the Professional Occupations group, (group 2).

Table 7.54 Maternal occupations and 8-week MenB

SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	Managers, Directors, Senior Officials	2	64.00	7.071
2	Professional Occupations	5	184.40	271.153
3	Associate Professional Occupations	6	62.17	11.250
4	Administrative, Secretarial Occupations	9	55.56	22.705
5	Skilled Trade Occupations	6	60.17	2.787
6	Caring Leisure and other Service Occupations	13	77.46	37.795
7	Sales, Customer Service Occupations	6	61.50	7.369
8	Process, Plant, Machine Operative	3	66.67	2.517
9	Elementary Occupations	7	69.57	12.067

The distribution of data for this is presented in Figure 7.35. Whilst outliers are visible in groups 2, 3, 4, 6 and 7, it is an extreme outlier related to case 4498, which has contributed to the high mean value reported in group 2.

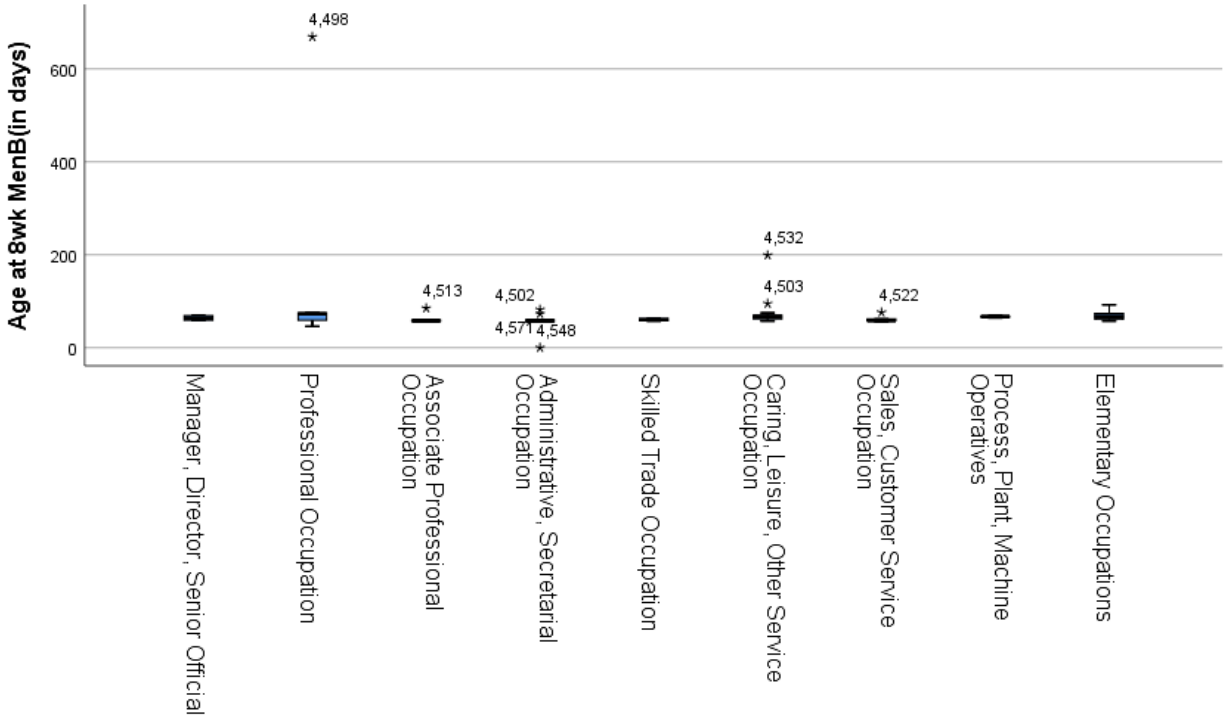


Figure 7.35 Boxplot of maternal occupation and 8-week MenB

Using the merged SOC groups (Table 7.55), one-way ANOVA testing (with bootstrapping) was undertaken, but this did not produce any significant results: F (2, 54) = 1.370, p = 0.263.

Table 7.55 Merged SOC groups and 8-week MenB

	SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	1	Managers, Directors, Senior Officials	13	109.46	168.427
	2	Professional Occupations			
	3	Associate Professional Occupations			
2	4	Administrative, Secretarial Occupations	28	66.71	28.928
	5	Skilled Trade Occupations			
	6	Caring, Leisure and other Service Occupations			
3	7	Sales, Customer Service Occupations	16	66.00	9.557
	8	Process, Plant, Machine Operative			
	9	Elementary Occupations			

Rotavirus

The mean time and standard deviation for mothers' occupation and first Rotavirus vaccine are reported in Table 7.56. Again, a much higher mean of 184.40 is seen in group 2.

Table 7.56 Maternal occupations and 8-week Rotavirus

SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	Managers, Directors, Senior Officials	2	78	26.870
2	Professional Occupations	5	184.40	271.153
3	Associate Professional Occupations	5	57.60	1.342
4	Administrative, Secretarial Occupations	9	55.56	22.705
5	Skilled Trade Occupations	6	60.17	2.787
6	Caring Leisure and other Service Occupations	12	67.33	10.174
7	Sales, Customer Service Occupations	6	61.50	7.369
8	Process, Plant, Machine Operative	3	66.67	2.517
9	Elementary Occupations	6	69.50	13.217

The boxplot (Figure 7.36) shows that the extreme outlier (case 4498) has affected the mean reported in Table 7.56.

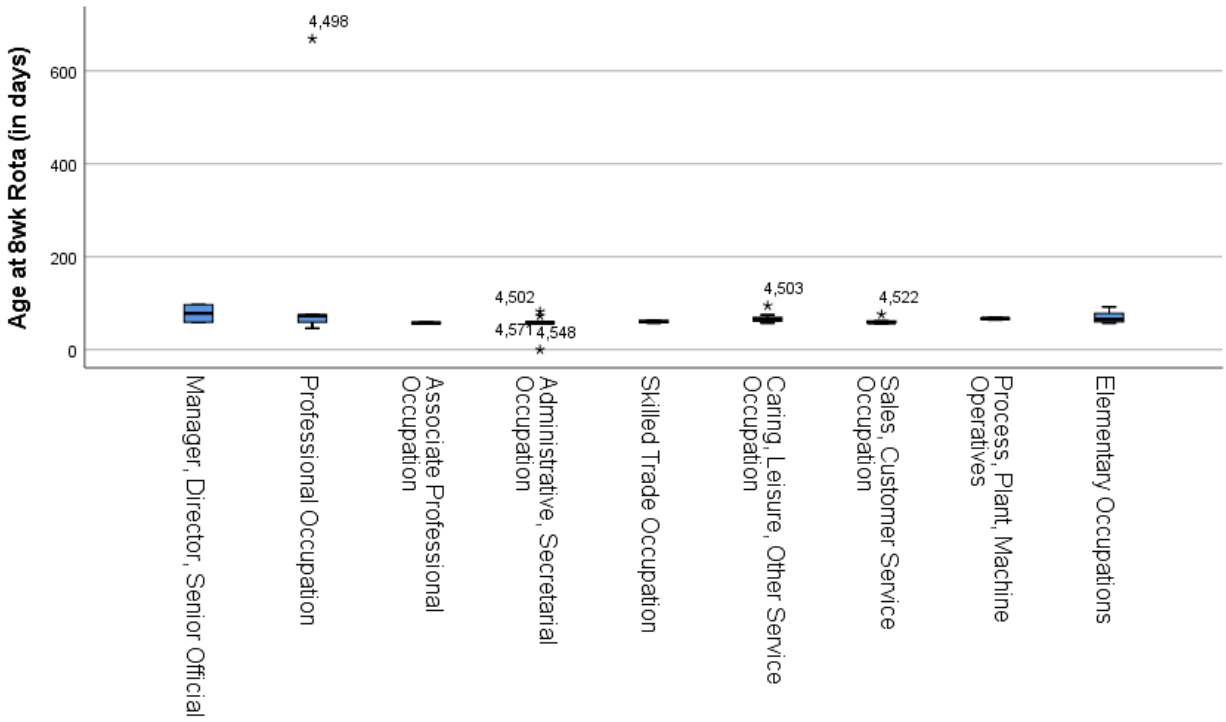


Figure 7.36 Boxplot of maternal occupation and 8-week Rotavirus

The merged SOC groups (Table 7.57), underwent one-way ANOVA testing, but produced no significant results: F (2, 51) = 1.776, p = 0.180.

Table 7.57 Merged SOC groups and 8-week Rotavirus

	SOC Major Groups	SOC 2020 Group Title	N	Mean	SD
1	1	Managers, Directors, Senior Officials	12	113.83	175.318
	2	Professional Occupations			
	3	Associate Professional Occupations			
2	4	Administrative, Secretarial Occupations	27	61.81	15.237
	5	Skilled Trade Occupations			
	6	Caring, Leisure and other Service Occupations			
3	7	Sales, Customer Service Occupations	15	65.73	9.830
	8	Process, Plant, Machine Operative			
	9	Elementary Occupations			

Fathers' age and 8-week vaccines

Paternal ages were obtained from the NNRD for 88 fathers. Ages ranges from 18 to 51 years and are displayed in Figure 7.7 in section 7.2.2. These ages are grouped, and the mean and standard deviation for each age group for each 8-week vaccine is displayed in Table 7.58.

Table 7.58 Fathers' age groups and 8-week vaccines

DTaP/IPV/Hib/HepB				**PCV**			
Age group	N	Mean	SD	Age group	N	Mean	SD
15 - 20	1	75.00		15 - 20	1	75.00	
21 - 30	31	63.61	9.106	21 - 30	31	64.04	9.165
31 - 40	36	65.67	9.934	31 - 40	36	65.67	9.934
41 - 50	6	72.67	12.801	41 - 50	6	72.67	12.801
51 - 60	1	57.00		51 - 60	1	57.00	
MenB				**Rotavirus**			
15 - 20	1	75.00		15 - 20	1	75.00	
21 - 30	31	64.55	8.144	21 - 30	30	64.37	8.219
31 - 40	36	65.67	9.934	31 - 40	36	67.22	11.647
41 - 50	6	72.67	12.801	41 - 50	4	70.25	14.569
51 - 60	1	57.00		51 - 60	1	57.00	

Whilst there are differences in the means across the age groups, Table 7.58 demonstrates a consistent mean for each age individual group regardless of vaccine. The highest means are seen in the 15-20 and 41-50 groups.

To illustrate the distribution of these data and perform ANOVA testing, age groups were re-categorised as follows:

- 15 – 20 merged with 21-30 to become 15-30
- 31 – 30 remained the same
- 41-50 and 51-60 merged to become 41-60.

The distribution of the data for each vaccine by age group is displayed in Figure 7.38, Figure 7.39, Figure 7.40 and Figure 7.41. For all vaccines, this shows similar medians for all groups, although a greater inter-quartile range for the 41-60 group. Outliers are associated with groups 15-30 and 31-40 for all vaccines, but for 41-60, Rotavirus only.

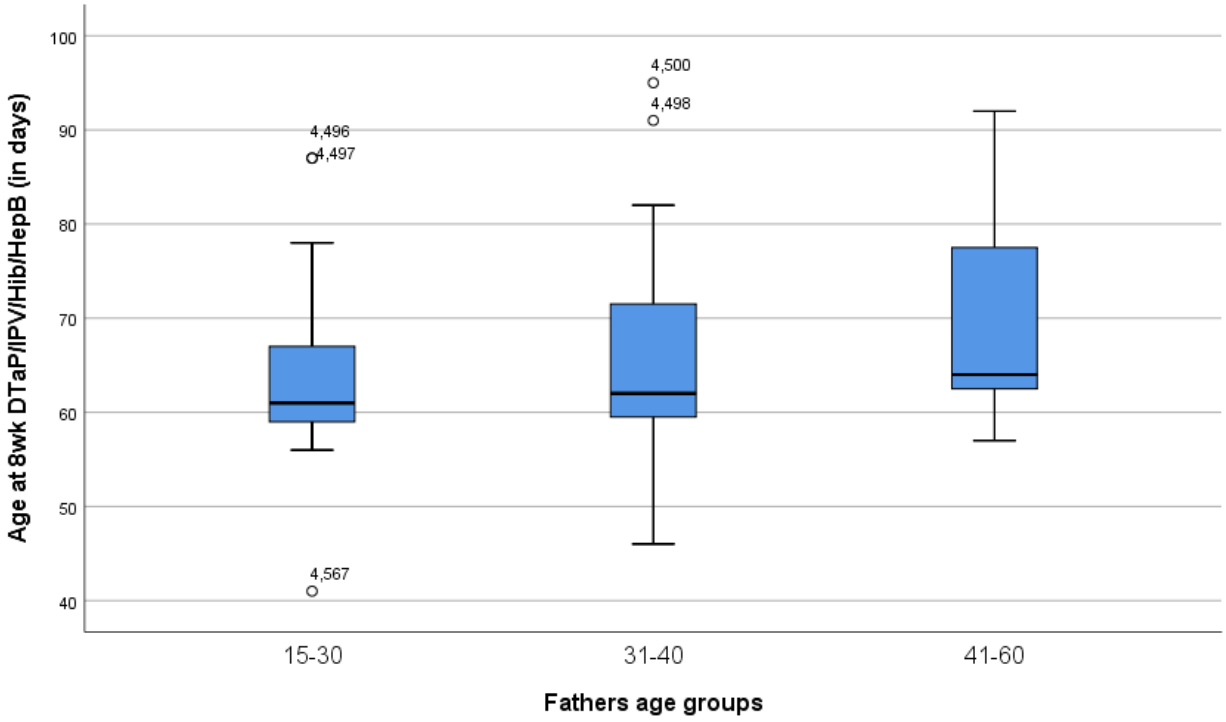


Figure 7.37 Boxplot fathers' ages and 8-week DTaP/IPV/Hib/HepB

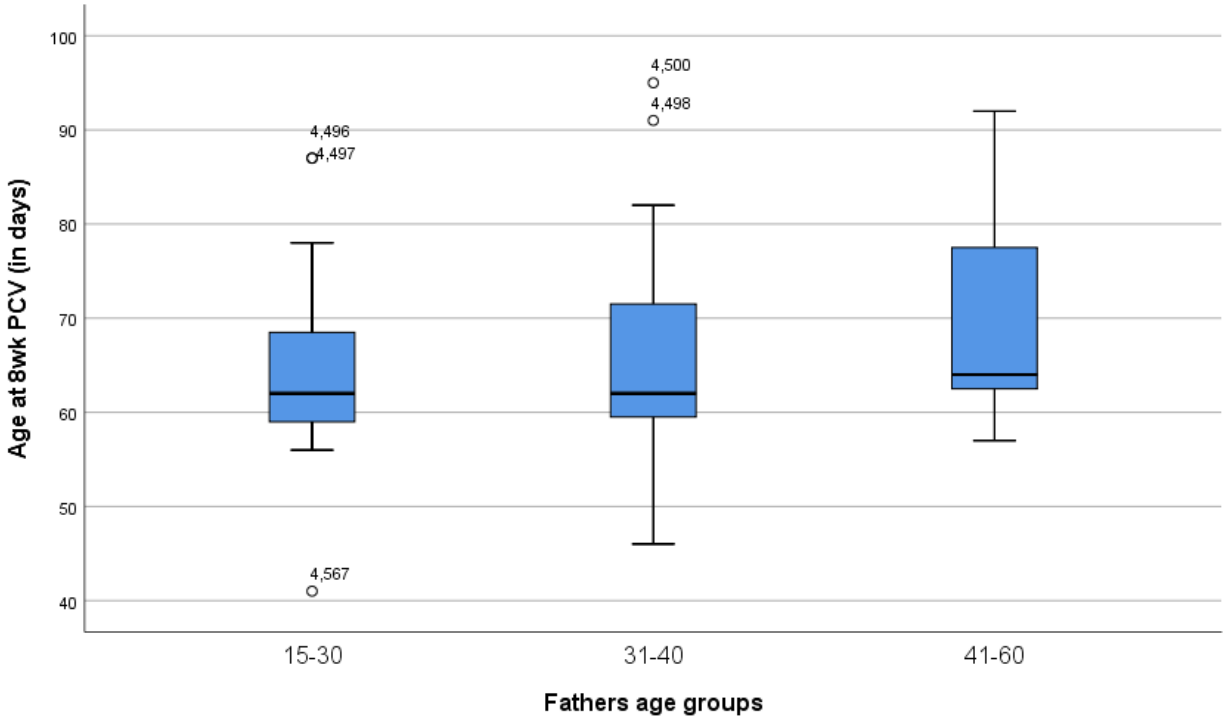


Figure 7.38 Boxplot fathers' ages and 8-week PCV

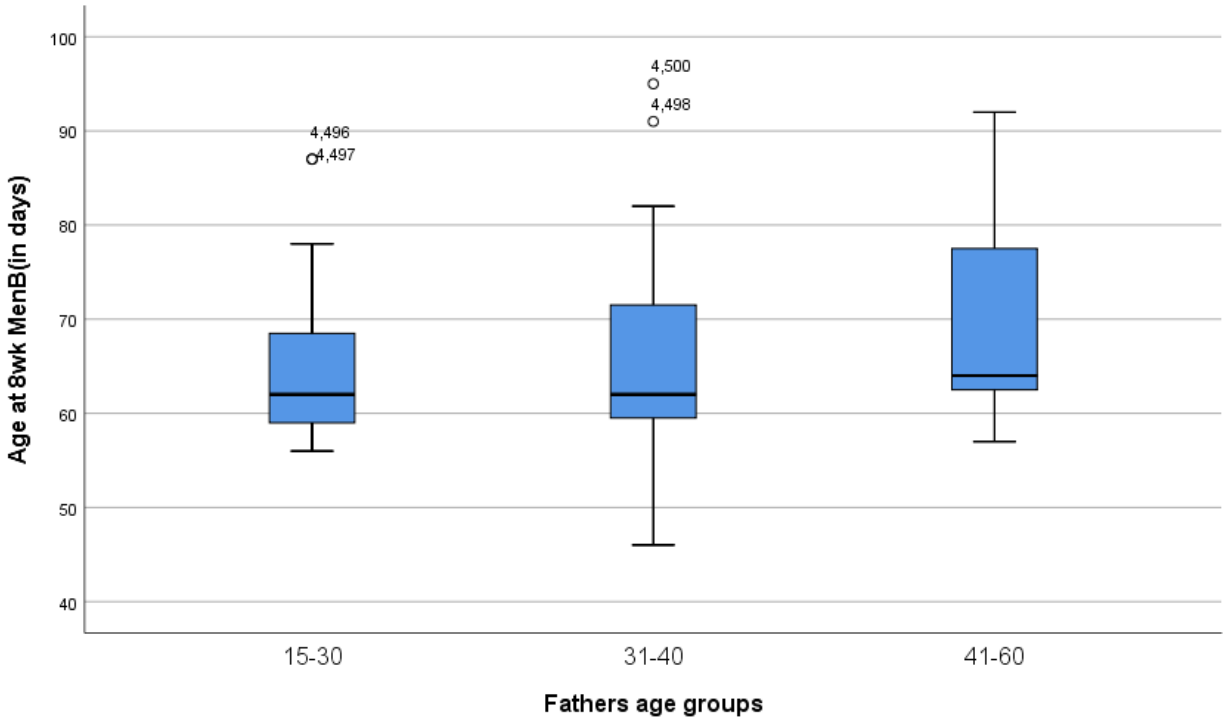


Figure 7.39 Boxplot fathers' ages and 8-week MenB

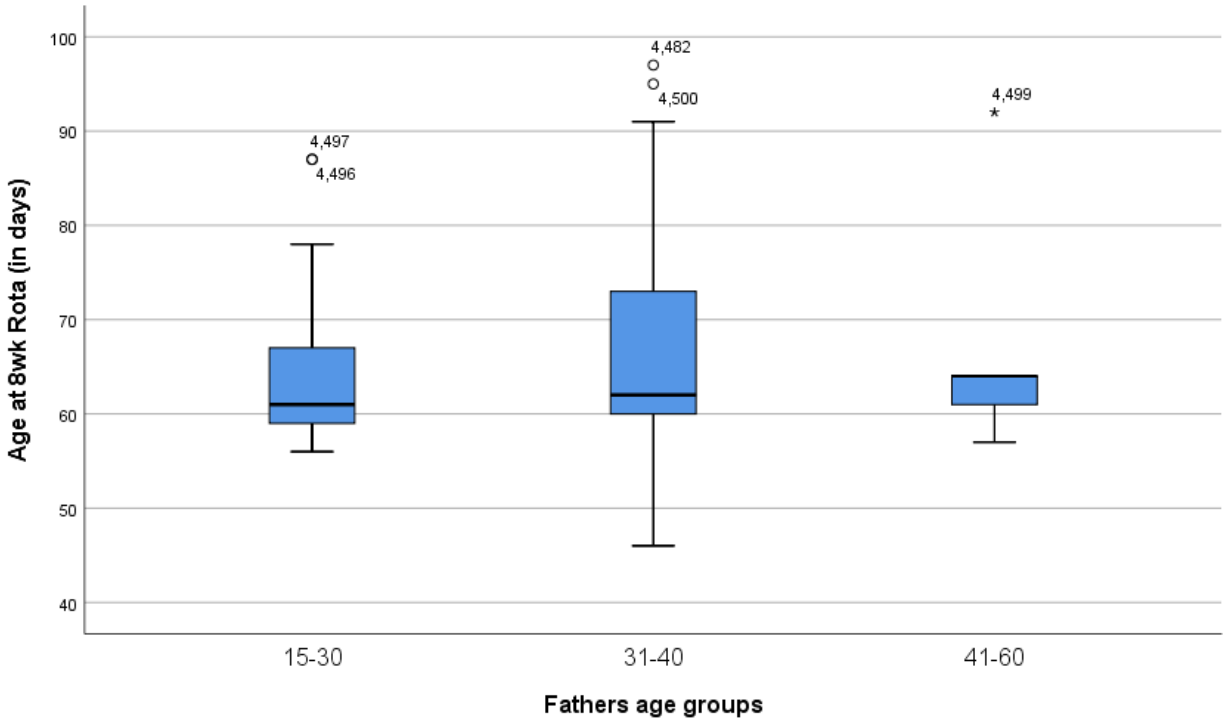


Figure 7.40 Boxplot fathers' ages and 8-week Rotavirus

One-way ANOVA testing (with bootstrapping) revealed no significant differences between any of the groups: DTaP/IPV/Hib/HepB - F (2, 72) = 1.243 p = 0.295, PCV - F (2, 72) = 1.056 p = 0.353, MenB - F (2, 72) = 0.974 p = 0.383 and Rotavirus - F (2, 69) = 0.528 p = 0.592.

Fathers ethnicity and 8-week vaccines

Ethnicity data were available for 113 fathers, and the mean and standard deviation for each 8-week vaccine by ethnic group are displayed in Table 7.59. This shows a greater mean in days in the White group for all vaccines; also in this group, for MenB and Rotavirus, the standard deviation is greater.

Table 7.59 Fathers' ethnicity and 8-week vaccines

DTaP/IPV/Hib/HepB				**PCV**			
Ethnicity	N	Mean	SD	Ethnicity	N	Mean	SD
White	87	67.20	17.366	White	87	67.36	17.345
Asian	7	61.14	8.513	Asian	7	61.14	8.513
Black	1	58.00		Black	1	58.00	
MenB				**Rotavirus**			
White	87	74.48	66.728	White	84	73.60	66.552
Asian	7	61.14	8.513	Asian	7	61.14	8.513
Black	1	58.00		Black	1	58.00	

These ethnic categories were regrouped to White (n = 104) and non-White (n = 9) for analysis. The distribution of data for these two groups for each vaccine are shown in Figure 7.41, Figure 7.42, Figure 7.43 and Figure 7.44.

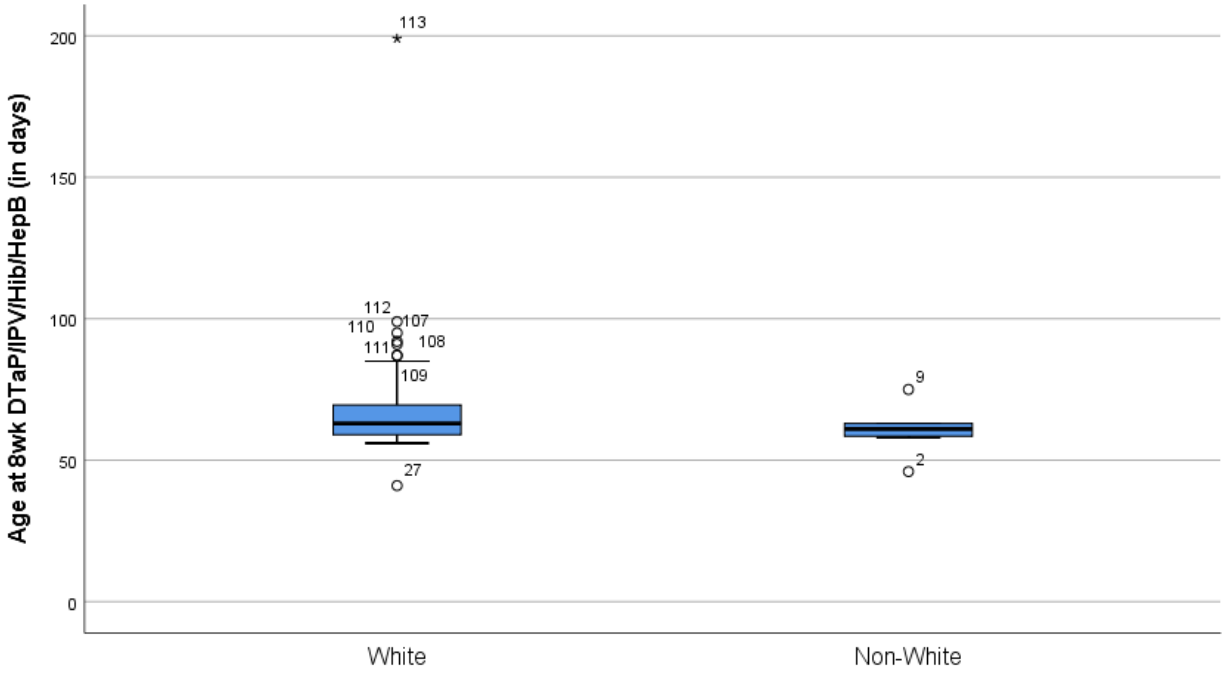


Figure 7.41 Boxplot fathers' ethnicity and 8-week DTaP/IPV/Hib/HepB

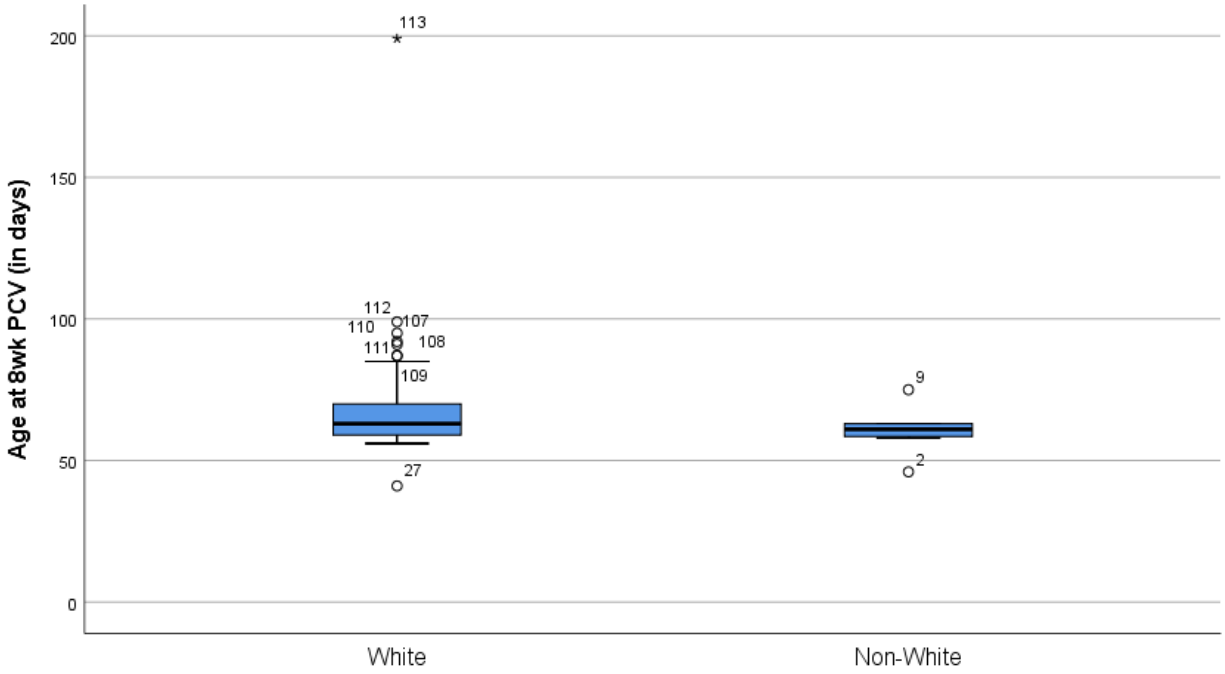


Figure 7.42 Boxplot fathers' ethnicity and 8-week PCV

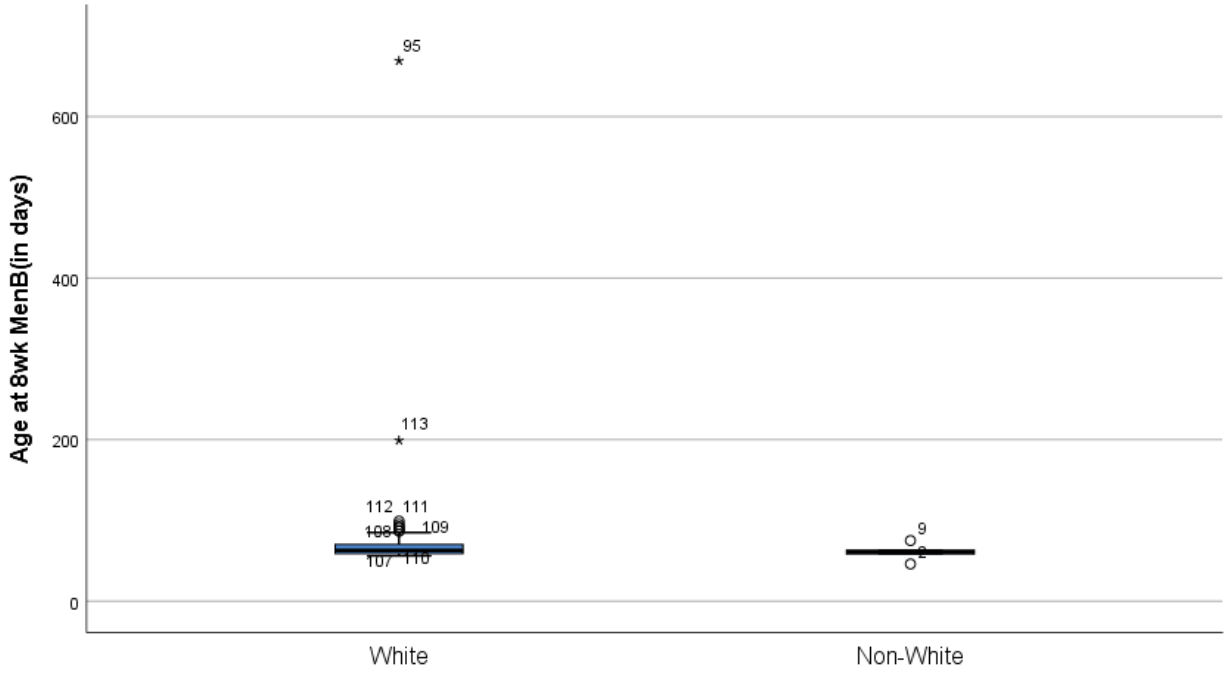


Figure 7.43 Boxplot fathers' ethnicity and 8-week MenB

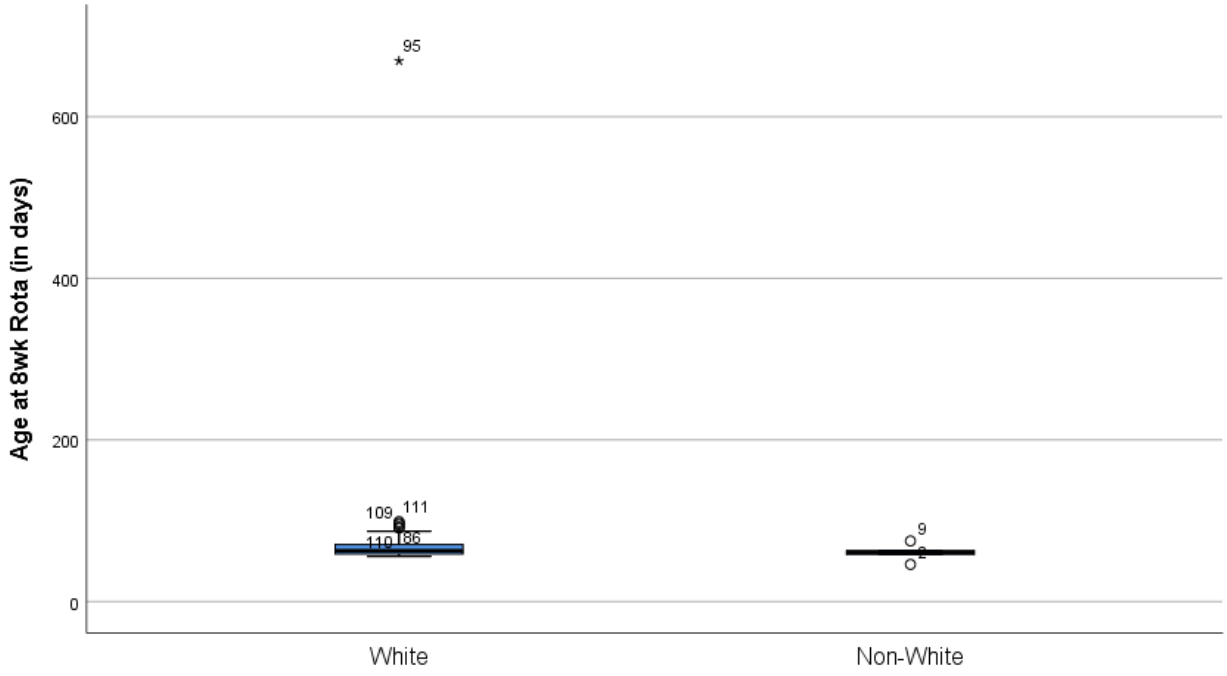


Figure 7.44 Boxplot fathers' ethnicity and 8-week Rotavirus

One-way ANOVA testing (with bootstrapping), resulted in no significant differences between the groups: DTaP/IPV/Hib/HepB - F (1, 93) = 1.073, p = 0.303, PCV – (1, 93) = F 1.130, p = 0.291, MenB - F (1, 93) = 0.335, p = 0.564 and Rotavirus F (1, 90) = 0.295, p = 0.589.

7.4 Conclusion

This chapter aimed to answer the research question 'Are vaccinations delayed in preterm infants?'. These analyses and subsequent results have revealed the following in respect of the questions cited:

7.4.1 Is there a difference in vaccination age between preterm and full term infants?

For the 8-week vaccines, there was no significant difference in the time of vaccination between full term and preterm infants for DTaP/IPV/Hib/HepB and Rotavirus. However, differences were found for PCV and MenB; more specifically, these vaccines were given significantly later in infants categorised with a moderate to late gestational age, compared with infants of normal gestational age.

Birthweight was also analysed for the 8-week vaccines, as whilst there were no significant findings for DTaP/IPV/Hib/HepB vaccination at this time, there were for all other vaccines. For PCV, MenB and Rotavirus, infants in the moderately low birthweight category, all experienced receiving their vaccines significantly later than infants in the normal birthweight group. Interestingly, with the exception of the 8-week Rotavirus vaccine in extremely preterm infants, none of the mean times in days exceeded the 70-day definition of a delay (section 5.4.5) for these first 8-week vaccines.

The time between 8-week and 12-week doses of DTaP/IPV/Hib/HepB and Rotavirus were analysed; no significant differences were noted for Rotavirus for either gestational age or birthweight, but there were significant findings for DTaP/IPV/Hib/HepB. Infants classed as either moderate to late preterm or moderately low birthweight, all received this vaccine significantly later than their full term or normal birthweight counterparts. Once again, considering the study definition of a delay for these 12-week vaccines (42 days), mean time in excess of this was seen in moderate to late, extremely preterm and moderately low birthweight infants for DTaP/IPV/Hib/HepB.

For the scheduled 16-week vaccines, there were no significant differences found between gestational age, or birthweight groups for any of the vaccines (DTaP/IPV/Hib/HepB, PCV, MenB). However, according to the definition of a delay (70 days) for the second doses of PCV and MenB, the mean times in all gestational age and birthweight groups were exceeded.

Despite not always meeting the definition of a delay as described in this study, the finding that infants with a moderate to late gestational age and moderately low birthweight experience the greatest delays is important to consider. Whilst this may appear clinically inconsequential it does highlight a consistent pattern of later vaccination in these infants.

The size of the delay seen for some of the vaccines in some infants was considerable. Although this finding was not exclusive to preterm infants, it is concerning nonetheless and worthy of further exploration.

7.4.2 Is there a relationship between gestational age and age at vaccination?

This question aimed to investigate the notion that greater prematurity may lead to later vaccination. However, whilst some of the findings did indicate later vaccination for some vaccines in one of the gestational age groups (moderate to late preterm) when compared with infants of normal gestational age, this was not seen in all categories of prematurity.

Similarly, no inverse relationship was observed for birthweight. Whilst compared with infants with a normal birthweight, some vaccines were given significantly later, this was only seen in infants in the moderately low birthweight category.

7.4.3 What are the factors associated with vaccination timeliness?

The time of first 8-week vaccination was analysed with additional infant data obtained for infants admitted to the NNU. The primary reason for admission, level of care required on admission, days spent in the NNU and diagnosis on discharge were not found to be significant factors in vaccination timeliness. Which NNU infants were admitted to was

also studied – this revealed that infants admitted to an NNU in the North of the region, received their 8-week PCV vaccine significantly later than those admitted to a NNU in the South. Being discharged whilst still receiving oxygen therapy did not influence vaccination timeliness one way or another.

Parental characteristics and timing of 8-week vaccines were also analysed. Maternal age, ethnicity, occupation and number of past pregnancies were no influential factors in vaccine timeliness; neither were paternal age or ethnicity.

Chapter eight explores the meaning and relevance of these findings in depth, referring to current policy and practice. It also considers previous research on the topic, outlines possibilities for future research, and recommendations for practice are made.

Chapter 8 Discussion

8.1 Introduction

The main findings of the study have revealed that some vaccines are delayed for preterm infants, but only for those classified as moderate to late preterm or those with a moderately low birthweight. No correlation was seen between gestational age or birthweight and age at vaccination, and none of the additional infant or parental factors studied had an impact on vaccination timeliness.

This chapter considers these findings and explores them within the current practice and policy context, considering their relation to previous relevant research. The limitations of the study are discussed, and recommendations for practice and further research are made.

8.1.1 The study population

The characteristics of the infants and parents in the study are first explored and compared with those of infants and parents more widely; this is to ensure that any findings are generalised appropriately.

When the gestational age categories are considered, of the 428 study infants who were born prematurely, 370 were born between 23-37 weeks, 36 between 28-32 weeks and 22 were born at less than 28 weeks. When equated with data for England from 2018 (Office for National Statistics (ONS), 2020a), the rates of preterm birth compare as follows: the rate of moderate to late preterm birth in the study cohort is 8.03%, higher than the England rate of 6.64%. In the very preterm category, England's rate for 2018 is 0.78%; the same as the rate for the study cohort, 0.78%. The rates for infants born extremely prematurely are also similar (0.46% for England, and 0.47% for the study cohort). A total of 68 births were recorded as post-term or greater than 42 weeks. The rate of post-term birth in the study cohort is 1.48%, and this is lower than 2.04%, the rate in England across 2018 (ONS, 2020a). Considering birthweight, when compared with data from England across 2018

(ONS, 2020a) the rates of low birthweight in the study cohort are higher. In the moderately low birthweight category, the rate for the study cohort is 1.08%, and for England this figure is 0.94%. Rates for England in the very low birthweight division are 6%, and for the study cohort 6.7%. Many of the study data are similar to national data, but rates of moderate to late preterm births and infants born with a moderately low birthweight are higher in the study cohort. This may be explained by the region from which the study data were taken. This hosts two local authorities which fall in the most deprived 10% nationally (Ministry of Housing, Communities and Local Government, 2019), and there is evidence linking deprivation and lower birthweights and earlier gestational ages (Dibben et al., 2006; Taylor-Robinson et al., 2011). There is a complex set of interrelated influences associated with low birthweight and prematurity which includes maternal age and lifestyle in the antenatal period (Morris, 2018).

The most common reasons for infants in the study to be admitted to the NNU was for prematurity (77%), followed by respiratory disease (22.5%). Preterm infants can be born with additional needs which require immediate support; these needs and the level of support required increases as gestational age decreases (Lissauer et al., 2020). Respiratory disease, specifically, respiratory distress syndrome is a major cause of morbidity and mortality in preterm infants, necessitating specialist care (Lissauer et al., 2020). Therefore, it is unsurprising that the data indicate these two reasons as the most common for admission to the NNU. Although ‘prematurity’ may be an ambiguous term here, it can most frequently be associated with respiratory disease as well as other problems related to prematurity. Most significantly, the study’s findings reported a strong positive correlation between prematurity and birthweight. Whilst birthweight was not recorded as a reason for admission, this is a reliable indication that the term ‘prematurity’ encompasses infants who also have a lower birthweight.

Rowe et al. (2021) recently undertook a national population-based study exploring neonatal admissions and mortality, and the category of care required on admission was studied. Although there was some variation between centres with higher cases, most infants were admitted requiring special care, followed by high-dependency care, and lastly, intensive care. This does not reflect data from this study, where most infants were admitted to a NNU accessed intensive care (37%), followed by special care (31%) and then high-dependency care (28%). This difference may be due to the small number of units in the current study; Rowe et al.'s (2021) study specifically looked at NNU admissions for infants born in any of the 123 alongside midwifery units in the UK, indicating the involvement of many more NNUs.

A negative correlation between the length of time spent on the NNU and infants' gestational age and birthweight was identified in the current study. Previous studies exploring influences on length of stay in the NNU have reported that gestational age and birthweight are reliable indicators for length of stay (Lee et al., 2016; Seaton et al., 2019), with the lowest gestational ages and birthweights equating to the lengthiest stays.

The most frequently reported diagnosis at discharge in the study was prematurity (89.7%), followed by respiratory distress (52.8%) and suspected sepsis (31%). The ambiguity associated with the term prematurity has already been discussed, but again, it is suggested that respiratory disease is a significant factor here (Lissauer et al., 2020). Rowe et al. (2021) reported that the two most common diagnoses on discharge were respiratory problems and suspected infection.

Parental data studied included maternal age, ethnicity, occupation and number of previous pregnancies, and paternal age and ethnicity. Maternal age ranged from 15 to 49 years, and when categorised into age groups, the 25 to 34-year group closely reflects national data from 2018 where 60% is reported (vs 58% from study cohort). However, the study cohort

has a higher number of mothers less than 25 years old (17% vs 26%) and a lower number of mothers over 35 years (15% vs 23%). As already discussed, the study was undertaken in an area of high deprivation where age at conception is known to be lower (ONS, 2020b).

Maternal ethnicity data from the study revealed that the vast majority identified as White (89%), while the remainder identified as Mixed (0.9%), Asian (2.4%) or Black (0.9%). The data for England and Wales data from the same year, refer to infant ethnicity; whilst it cannot be assumed that this is the same as mothers' ethnicity, it is still considered to be a useful comparison. When this is considered, the data are very different, with 71% reporting as White, 8.6% as Asian, and 4.1% as Black; there are no data for Mixed ethnicity. This indicates a much higher proportion of White mothers, and a lower proportion of Asian and Black mothers in the study cohort, compared with the infant ethnicity nationally (ONS, 2020a).

Maternal occupation was retrieved for 66 mothers and revealed that most of the mothers had an administrative or secretarial (19%), or caring, leisure or other service occupation (21%). Only 3% of mothers had an occupation which was in the manager, director or senior official group. The Department for Education (2020) report that certain occupations are more strongly represented by certain genders, and the data for maternal occupation in the study reflect this. The number of previous pregnancies for the mothers in the study also echoed the national picture, with most mothers having had just one previous pregnancy (ONS, 2020a).

Considering fathers' ages, study data were comparable to data from the same year in England and Wales (ONS, 2020a) with 49.5% (vs study data 44%) less than 30 years, 42% between 31-40 years (vs study data 46%) and 8.7% over 41 years old (vs study data 9%).

Paternal ethnicity was available for 113 fathers in the study. This revealed that 92% identified as White, 7% as Asian and less than 1% as Black. As already discussed, this can only be compared with infant ethnicity, but as with maternal ethnicity, the study cohort had a higher proportion of White fathers, and lower proportion of Asian and Black fathers than the national data for the same year (ONS, 2020a).

The characteristics of the parents in the study region indicate that maternal age and ethnicity, and paternal ethnicity differ to the wider population, meaning that any generalisations would need to be reached with caution.

8.1.2 Immunisation data

The size of the delay seen in some infants in the study cohort is considerable (section 7.2.3). For example, although the mean time to the first DTaP/IPV/Hib/HepB was 65 days, this was 942 days for one infant (born at a normal gestational age). Remaining unvaccinated for any length of time, for any infant, leaves them vulnerable to the relative infections. This infection risk is increased for preterm infants (Lissauer & Carroll, 2018) and it could be argued that any delay, regardless of size, is a greater problem for these infants. However, the substantial delays observed in some infants is concerning and is acknowledged; it is suggested that further research is needed to investigate this extreme delay.

The timing of the first 8-week vaccines demonstrated a significant delay for some infants and some vaccines. Infants in the moderate to late preterm group and the moderately low birthweight group received their PCV and MenB vaccines later, when compared with infants of normal gestational age and birthweight. A delay was also noted for infants receiving their first Rotavirus vaccine, although this was only significant in the moderately low birthweight group compared with normal birthweight infants. Delays for the first scheduled vaccines have been reported in previous studies for infants with lower

birthweights and gestational ages (Roper & Day, 1988; Magoon et al., 1995; Slack & Thwaites, 2000; Woestenberg et al., 2014; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021). A significant delay for first scheduled vaccines was also reported for infants with lower gestational ages by Fortmann et al. (2021). It is important to note that the vaccines considered in these earlier studies differed slightly, possibly owing to what was scheduled in that specific country and available vaccines at the time the study was undertaken. All studies included DTP or DTaP which is a constituent of the DTaP/IPV/Hib/HepB vaccine which features in the current study, where curiously, this was not significantly delayed at 8-weeks. Only two studies included PCV (Bary-Weisberg & Stein-Zamir, 2021; Fortmann et al., 2021) and none included MenB; this is also likely due to the uniqueness of the vaccine schedules in different countries and the vaccines available at the time the studies were undertaken. The UK was the first to introduce MenB into the schedule in 2015, and it is not widely used in all countries (European Centre of Disease Prevention and Control, 2021). Similarly, none of the studies where a delay at first vaccination was reported featured Rotavirus, and again, this may be because the vaccine was only introduced in the UK in 2013 and does not feature in any of the countries where the studies were set.

DTaP/IPV/Hib/HepB is commonly referred to as the 6 in 1 vaccine, offering protection against six diseases in one vaccine. Also offered at the first visit are PCV, MenB and Rotavirus vaccines, which altogether, are given as three intramuscular injections and an oral vaccine. A common reason associated with a delay (for all infants) is concern about the vaccines, often discussed in terms of risk (Díaz Crescitelli et al., 2020; McGregor & Goldman, 2021). An element of this has been expressed specifically as concern over the number of antigens in the vaccines and number of injections offered at a single visit (Gellin et al., 2000; Kerrigan et al., 2020). It is possible that parents in the current study, preferred to accept one vaccine (DTaP/IPV/Hib/HepB) offering broader protection

against more diseases, and opted to delay others. Green et al. (2021) explored the transition from the NNU to the home environment and reported that mothers acknowledged that their preterm infants were identified as 'abnormal', and 'different' to expected norms; this could denote an acceptance of different approaches to standard treatments, including immunisation. This also has resonance with the definition of acceptance described by Thomson et al. (2016). In their determinants of vaccine uptake, factors associated with concerns about the vaccines are included, and in this sense, there is a reluctance to accept all the scheduled vaccines. Furthermore, decision making is a key part of consent, which is required for vaccination. Parents have found that post-discharge from the NNU, their decision-making was impaired, which connected directly to being in the NNU where most of the decisions were made by health care professionals (Boykova, 2016). This could transpire as uncertainty leading to a delay in accepting any vaccines that are offered. Green et al. (2021) stressed how perfectly situated community nurses are to support parents post-discharge from the NNU, but also highlighted a knowledge shortfall through lack of specific training on the needs of preterm infants. Reluctance on the part of vaccinators to administer multiple vaccinations to infants at the same visit is documented (Tabana et al., 2016), and Bertini et al. (2021) studied muscle thickness in preterm infants compared with full term infants. This included the quadriceps femoris region, an area where intramuscular vaccines are administered, and it was concluded that preterm infants had lower muscle acquisition relative to full term infants. Therefore, it is also possible that those administering the vaccines may be more averse to give three injections at one visit, especially in situations where the infants may be smaller than their full term counterparts at eight weeks of age.

This implies that there are not only deficits in professional knowledge and training, but that subsequently, parents may also require more information and support with decision-making. These findings can be supported by Thomson et al's. (2016) determinants of

awareness and activation. Parental awareness of the vaccines and diseases are central to understanding and subsequent decision-making, and these are both activities which may be supported by activation – that is the actions of health professionals and services to provide cues to action, even if this is only to seek further information.

The delays for the first MenB, and PCV vaccines reported in the current study were only observed in the moderate to late preterm group (32-37 weeks), and for MenB and PCV, and Rotavirus in the moderately low birthweight (1500g-2499g) groups. The same delays were not seen in the lower gestational age groups and birthweight groups, which does not concur with previous studies which have reported a greater vaccination age with the lowest gestational ages and birth birthweights (Magoon et al., 1995; McKechnie & Finlay, 1999; Slack & Thwaites, 2000; Langkamp et al., 2001; Batra et al., 2009; Woestenberg et al., 2014; Ochoa et al., 2015; Rouers et al., 2019; Bary-Weisberg & Stein-Zamir, 2021).

Although these are infants classed as preterm or low birthweight, they are not at the extreme end of these measures, and they might not have been admitted for any supplementary care. However, for those who were admitted, they may well have been discharged by eight weeks of age, meaning that the delay seen, more closely parallels practices and decision making in the community setting. Breivold et al. (2019) looked specifically at the experiences of mothers of moderate to late preterm infants, post-discharge from the NNU. They report that mothers felt as though they coped better when things were 'going well' with their infants, yet this sense of optimism could be quickly replaced by stress over concerns about their infant's health. It is quite possible for all infants, regardless of prematurity, to experience common local and systemic reactions following their vaccinations, and this could result in prolonged hesitancy in concerned parents, leading to a delay in vaccination. Living in constant fear was a key finding in the review by Adama et al. (2016), who undertook a meta-synthesis of parents' experiences

post-discharge from the NNU. They described this fear as directly related to the infants' fragility and condition. The current study did not see any significant delays in vaccination for the more premature infants (those in the very preterm and extremely preterm groups), and those with lowest birthweights (less than 1500g). It is feasible that these infants are still in hospital at the time the vaccines are due, and are under greater observation, where the scheduled immunisations have become part of their routine care. This once again resonates with the findings of the study by Boykova (2016), that to some extent, whilst still admitted to the NNU, parental consent and decision-making reflects a process which may be heavily influenced by health professionals. The concept of omission bias which is described in Thomson et al's. (2016) determinant of acceptance may explain this delay. Parents may not want to accept a seemingly risky intervention if their infant's health is stable or even improving, and this decision could also be influenced by the reduction in clinical monitoring post-discharge from the NNU. Increased provision for parents around the time vaccines are due is recommended; this may be to support vaccine choices, but also to support parents at the time of, and post-vaccination.

These findings provide a convincing indication that an area requiring attention is the community setting, where infants classed as moderate to late preterm or moderately low birthweight are experiencing a delay in some of their 8-week vaccines.

At 12-weeks, a significant delay for infants in the moderate to late preterm and moderately low birthweight groups was seen for the second DTaP/IPV/Hib/HepB, but not for the second Rotavirus. The difference between the timing of these vaccines may be due to the guidelines which apply to the administration of the Rotavirus vaccine; it is recommended that both doses are administered by 16 weeks of age due to the increased risk of intussusception if given any later (PHE, 2015). This vaccine is also given orally, so it may be more acceptable than an intramuscular injection. No significant delays were observed

for the 16-week vaccines studied, but this was relative to the previous doses of DTaP/IPV/Hib/HepB, PCV and MenB. The delays seen for some of the 8-week and 12-week vaccines were not repeated for any of the vaccines due as final doses in the primary series. This finding has some resonance with those reported by Magoon et al. (1995) and Rouers et al. (2019), who only observed delays for the first scheduled vaccines, and found that subsequent doses were not delayed.

This finding could indicate increasing confidence and decision-making as the infant matures, and in the knowledge that infants have tolerated previous vaccine doses. It could be assumed that primary health care providers are more assured in promoting and administering the vaccines knowing that the infant has already safely received at least one dose; equally, this may also be true of parents giving consent, who might be assured by the fact that this would not be the first time their child is to be vaccinated. Related to the determinant of acceptance, Thomson et al. (2016) describe how previous vaccine acceptance is a strong predictor of uptake.

8.1.3 Other infant characteristics

For the infants who had been admitted to a NNU, further analysis was undertaken. There were no significant delays in the timing of any of the first 8-week vaccines when the reason for admission, level of care and days spent on the NNU were considered. Reason for admission and level of care was not explored in any of the previous studies, although the length of stay on the unit was. Davis et al. (1999), Crawford et al. (2009), Woestenberg et al. (2014) and Fortmann et al. (2021) found that infants were more likely to be up to date or vaccinated on time with a longer hospital stay, while Slack and Thwaites (2000), Laforgia et al. (2018) and Rouers et al. (2019) found the opposite, that a lengthier stay equated to less timely vaccination. Denziot et al. (2011) and Woestenberg et al. (2014) also reported that starting the scheduled vaccinations on the NNU improved future coverage. In the current study, it was not possible to determine exactly where the

immunisation series had been started, although it could be assumed that it would have been more likely for infants with longer stays (8 weeks and longer) to have started their immunisations whilst still inpatients, and these are likely to be infants with the lower gestational ages and birthweights.

No significant delays were seen whether or not the infant had been discharged on oxygen, which is at odds with findings of two previous studies; Tooke and Louw (2019) and Fortmann et al. (2021) found that infants discharged whilst receiving oxygen therapy experienced delays in vaccination, and it is speculated that this may be due to clinicians' reluctance to administer a further 'inflammatory stimulus' (Fortmann et al., 2021). The current study found that diagnosis on discharge also had no significant influence on timing. One of the common diagnoses at discharge was respiratory distress syndrome, which develops into bronchopulmonary dysplasia in most infants (Lissauer et al., 2020), and Davis et al. (1999) also reported that a diagnosis of bronchopulmonary dysplasia was not associated with vaccination status. It could be that infants with any of these diagnoses or in receipt of oxygen therapy fell within the lowest birthweight and earliest gestational age groups. Because of this, they may have still been inpatients at the time the first doses were due, facilitating timely vaccination.

Infants in one of the areas (North) in the study observed a significant delay in receipt of the first 8-week PCV vaccine, but it is not possible to speculate a particular reason for this.

8.1.4 Parental characteristics

This study found that parental age and mothers' occupation and number of previous pregnancies had no bearing on vaccination timeliness. Previous studies have considered parental factors associated with timeliness and reported mixed results. Langkamp et al. (2001), Woestenberg et al. (2014) and Rouers et al. (2019) found that lower

socioeconomic or educational status in mothers was associated with lower vaccination rates in infants born with lower birthweights or at lower gestational ages. Whereas Magoon et al. (1995) reported that the level of parental education did not have any bearing on vaccination status. Whilst socioeconomic and educational status are not the same as occupation, it is suggested that there is a connection between them.

Similarly, this study did not find an association with parental ethnicity and vaccination timeliness; whilst this echoes the findings of Hofstetter et al. (2019), it does not concur with the reported results in the studies by Batra et al. (2009) and Bary-Weisberg and Stein-Zamir (2021).

Poorer vaccination uptake and timeliness in populations with lower socioeconomic status and in minority ethnic groups has been explored in studies for infants of all gestational ages and birthweights and ethnicity has been considered to be an important factor on perceptions of the importance of vaccinations and decision-making in those from Black and Asian backgrounds (Forster et al., 2017).

There were also inconsistencies between the findings regarding the number of previous pregnancies. The current study did not find any association between this and timeliness, but previous studies have reported that not being first-born (Bary-Weisberg & Stein-Zamir, 2021) or having a greater number of siblings (Tozzi et al., 2014), had a negative impact on vaccination timeliness, and this has also been found in infants of all gestational ages and birthweights (Homel and Edwards, 2018).

Although not significant findings in this study, the factors relating to parental characteristics analysed are identified as being associated with health inequalities. In their strategy to reduce inequalities in vaccine uptake in all children, Public Health England

identify dimensions of inequality which include socio-economic status, ethnic origin, family size and parental age (PHE, 2021).

Generally, vaccine coverage for the childhood vaccination programme in the UK observed a slow decline from 2014 (Sisson, 2019). The reasons for this are not entirely clear, although anti-vaccine efforts are not thought to be responsible (Edelstein et al., 2020). Prior to the COVID pandemic, uptake was high, and whilst COVID restrictions had an initial impact on coverage, this appears to have stabilised, and more recent data indicate an increase in coverage (NHS Digital, 2021). Public confidence in the childhood vaccination programme is high (Campbell et al., 2017) suggesting that the decline may be more associated with accessing immunisation services. In its guidance aimed to reduce differences in vaccination uptake, NICE (2009) recommended greater flexibility in the availability of services, home visits and a tailored individual approach to communicating and information sharing. The endorsement of home visits and a tailored approach are significant when the findings of this study are considered. This study's findings suggest that the preterm infants at risk of a delay in receiving their vaccines, are likely to be at home in the sole care of their parents, and in this setting, an individual approach could facilitate greater information exchange and support in decision-making. The literature review revealed that vaccine coverage and timeliness were increased with more well-child contacts, and this aligns with the recommendation to verify immunisation status at every interaction (NICE, 2009). Moreover, Make Every Contact Count (MECC) is a behaviour change approach aimed at supporting people to make positive health changes (Health Education England, 2021). This emphasises the value of interactions between health professionals and parents, and the opportunities such contacts offer. Contact opportunities at this stage point towards the role the health visitors may play in supporting parents of preterm infants. This is a further approach which could help in identifying those preterm infants who are at risk of, or who already have a vaccination delay. This is

strongly supported by Thomson et al. (2016) who describe access and affordability as being central determinants on uptake. However, this is not a simple suggestion as this approach relies on the contacts occurring. There is evidence that home visits can positively impact on immunisations (Early Intervention Foundation, 2015), yet investment in this area has stalled, and provision has been affected (Institute of Health Visiting, 2019) impacting on all contacts, whether in the home or the clinic setting. It is difficult to foresee an end to funding in this area meaning that some alternative practical suggestions should be considered. Heightened awareness regarding the importance of vaccination in preterm infants may be achieved initially by ensuring that parents receive the information regarding vaccination which has been specifically designed for parents of preterm infants (NHS, 2019). This should be offered prior to discharge from the NNU, and referred to at the new birth visit and is an opportunity to emphasise the importance of timely vaccination in these infants. Where possible, it may also be beneficial to develop a 'flagging' system which generates a prompt for health visitors to initiate contact with parents just as the first vaccination visit is approaching. This may be a crucial point in time to address any concerns parents have, although it is acknowledged that this could be resource intensive.

As previously noted, health professionals having the right knowledge, and access to resources to support uptake and parental choices is essential, and NICE (2009) highlight that regular approved training is accessed to facilitate this. However, two recent studies have identified a knowledge deficit regarding immunisations among neonatal staff and stressed the importance of training to address this (Stetson et al., 2019; Macintosh et al., 2020). Immunisation training is a mandatory requirement for all staff involved (PHE, 2018), and extending this to ensure that all staff based on NNUs are equally skilled and informed is important. The guidance asserts that those involved with a role in vaccination, whether promoting them or administering them should undertake the training (PHE,

2018). However, it could be argued that being more explicit and naming specific professionals in specific settings such as the neonatal or maternity unit, would be beneficial. Even if the infant is to be discharged before the vaccines are due, staff still have a part in reminding parents and promoting vaccination prior to discharge; this is perhaps even more important for preterm infants. The determinant of activation (Thomson et al., 2016) is relevant here, but of paramount importance, are the skills and knowledge of staff. Thomson et al. (2016) mention staff in the awareness determinant, but only in terms of their own vaccination choices. Health professionals are seen as the most trusted source of vaccine information (Campbell et al., 2017) so it is incredibly important that they are fully informed and able to provide the latest evidence-based facts which support parental decisions.

According to the Local Government Association (2021), current strategies to increase uptake vary according to area and the issue causing the low uptake. These aim to address vaccine hesitancy, fragmentation regarding the provision of vaccination services, and how GP practices manage and deliver their vaccination services. Whilst these methods are not specifically aimed at increasing uptake in preterm infants, it could be argued that generic approaches may benefit all infants. However, further work at a GP practice level which identifies preterm infants, and uses methods specifically designed to increase timely uptake is recommended. Proactive strategies may include personalised correspondence and the offer of opportunities to discuss particular concerns. This places a responsibility on GP practices keeping accurate records and staff involved being knowledgeable about their own coverage data, so that those at risk of under-immunisation (whether or not this includes preterm infants) are identified. These efforts are described by Thomson et al's. (2016) determinant of access, affordability and activation. Convenience, expense and individualised prompts are all identified as key factors influencing uptake.

8.2 Study's strengths, limitations and future directions

This study features some important strengths. It identified a legitimate area of study and examined a large dataset to address the research question; this required the application of methods which were both methodical and meticulous. Furthermore, the originality of the research is acknowledged; this is a significant study which makes an original contribution to knowledge, as this is the first time that this question has been addressed at a population level in the UK.

There are some limitations to this study; specifically, there were some challenges associated with the secondary data analysis design. First, there were doubts about the accuracy of some of the data. The immunisation data included some vaccines which appear to have been given earlier than scheduled. It is possible to administer some of the 8-week vaccines before 56 days; PHE (2019b) say that in certain circumstances it may be possible to give from six weeks. However, some of the vaccines were reported as given on the day of birth, or at two or three weeks of age. It was not possible to revisit the original source of the data to check these, so it was unclear whether these entries were clinical errors, or administrative errors.

Second, there were some problems with the completeness of the data; some immunisation data were missing, and this was due to infants being born and entered onto the MSDS in one region, but living in an area which fell in a different CHIS boundary for vaccination purposes. However, the challenge of encompassing all potential organisations in an attempt to ensure data completeness would have incurred additional time and expense. Finally, the variables studied were influenced by the available data in the defined datasets. Whilst some valuable insights have been gained from the data studied, this restricted the analysis.

The choice of study design has been justified in chapter 5 and some related challenges have been discussed in this chapter. However, it is important to consider the wider difficulties that were associated with undertaking this study. Collaboration with the lead site was needed so that data storage and management requirements could be met. Yet, establishing this collaboration coupled with the number of organisations concerned, made the approvals process more complex and the result was that the study took much longer to complete than anticipated. Whilst I was eager to progress, I was constrained by the organisations involved, and these issues were exacerbated by the COVID pandemic. I lost the support of one organisation because of this, and the acquisition of data was further delayed from the other organisations involved. Even so, this enabled the development of new skills and enabled an insight into the required approval processes. This also had a profound effect on me personally, as I grew in resilience and tenacity.

The UK immunisation schedule has changed during the course of the study and will continue to do so. Therefore, further studies exploring the association between prematurity and vaccination timeliness may be needed to continue to assess this phenomenon. In addition, further work to assess the impact of the COVID pandemic on vaccination timeliness in preterm infants could provide valuable understanding into its impact on vaccine hesitancy and the determinants of vaccine uptake.

This study has taken a quantitative approach and investigated vaccination timeliness in preterm infants, and some of the factors associated with this. Whilst the theory of the determinants of vaccine uptake (Thomson et al., 2016) has helped to explain the findings, further research which takes a qualitative approach, to fully understand parental and health professional perspectives would provide a greater understanding of these determinants in preterm infants.

8.3 Conclusion

The findings of this study have reported a delay in some 8-week vaccines for infants born with a moderate to late gestational age and a moderately low birthweight. The same delays were not observed in infants with greater prematurity and lower birthweights. This suggests that the delay observed primarily concerns practices in the community.

Health professionals in contact with families of preterm infants are in a position to be able to promote vaccines and support parents making vaccine choices. All opportunities to discuss vaccines in a manner which is personalised is encouraged – it is also suggested that contacts should be prioritised and increased to support families around this crucial time. Immunisation training for health professionals is stressed as vital in the provision of support, and it is advocated that staff are mindful of vaccine uptake in their areas which could enable the identification of strategies to address any coverage deficits.

It is acknowledged that decreased funding and resource shortages continue to pose significant challenges to the delivery of services; but with the exception of increased contacts, the suggested actions are advised in existing policy.

Chapter 9 Conclusion and recommendations

This study sought to investigate vaccination timeliness in preterm infants. The background chapter identified the importance of vaccines in the prevention of infectious diseases, and highlighted the vulnerability of preterm infants. The idea of preterm infants experiencing a delay in receiving their vaccines was introduced and the need to investigate this further was emphasised. Identifying a delay in vaccinating preterm infants is important so that appropriate strategies can be designed to address any shortfalls and ultimately, ensure that these infants are offered maximum protection against vaccine preventable diseases.

An exploration of the determinants of vaccine uptake was identified as the theoretical perspective for the subsequent investigation. Initially, the literature review presented in chapter four supported the idea of a delay in preterm infants receiving their vaccines, and this was examined further using a quantitative approach with a secondary data analysis design.

The results of the study were presented in chapter seven and compared with findings from earlier research, there were some similarities and differences; a delay was found for some vaccines, but these were only observed in infants with a moderate to late gestational age or moderately low birthweight. This contrasts with previous studies where a delay was reported in preterm infants of all gestational ages and birthweights. Furthermore, some of the prior research also saw a negative correlation between vaccination timeliness and birthweight and gestational age, a finding which was not replicated in this study. This study did not find an association between timeliness and any other infant or parental characteristics; again, this contradicts some of the previously published studies which have reported parental ethnicity, maternal educational level and socioeconomic status, and number of children as influential factors in vaccination timeliness.

As previously noted, this study found that vaccination delays occurred in infants with a moderate to late gestational age or moderately low birthweight. This finding suggests that the delay is occurring in the community setting, as these infants are more likely to have been discharged (if admitted) from the NNU, and in the sole care of their parents. This emphasises the role of health professionals in promoting vaccines and supporting parents with their vaccine choices.

Whilst this research may suggest a trend in vaccination practices in preterm infants, they are not definitive. Greater knowledge of practice and policy in individual communities and NNUs could add to a greater, more informative interpretation of the findings.

9.1 Recommendations for practice

The role of the health professional is seen as crucial in supporting parental choices and subsequent coverage. This applies to all staff in contact with families from birth up until the time of the first vaccines, who are ideally positioned to promote or administer them. Staff in the clinical setting (maternity or NNU) or in the community should stress the importance of preterm infants receiving their vaccines on time. The leaflet discussed in chapter eight (NHS, 2019) could support this.

Omission bias appears to be central to vaccine acceptance, and greater support for parents of preterm infants at all stages of the vaccination process is crucial. This equates to support with decision-making as well as increased contact after vaccination if needed. Increased opportunities for such contacts (including the home setting) with information which is adapted to suit individual needs is seen as an important facilitator of timely vaccination. Again, the use of the leaflet designed for parents of preterm infants (NHS, 2019) could be used to open up a dialogue which may happen in person. Alternatively, the leaflet could be sent to parents with an accompanying note offering an opportunity for further discussion if required.

Health professionals with a role in vaccination regardless of their work setting should be appropriately trained according to the recommended standards and have an awareness of coverage in preterm infants in their own practice area. This will enable the development of area specific approaches to address any shortfalls.

It is acknowledged that decreased funding and resource shortages continue to pose significant challenges to the delivery of services; but with the exception of increased contacts, the suggested actions should be work already ongoing.

9.2 Recommendations for research

There are some suggestions for future research which have emerged from this study. Further qualitative exploration of parental and staff perceptions of vaccinating preterm infants in the community setting may provide a better understanding of influences on uptake; any findings from such research could inform existing training. A contemporary awareness of coverage in preterm infants is essential, and ongoing research which scrutinises this would account for any changes to the schedule, as well as monitor the impact of any wider influences on vaccine uptake. Finally, the study data identified some extreme delays in vaccination. Research which specifically explores this concerning occurrence may lead to further strategies to address it.

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Appendix 1 Summary of studies

Authors	Country	Study design	Sample size	Data collection	Data analysis	Findings	Comments
Bary-Weisberg & Stein-Zamir (2021)	Israel	Retrospective cohort analysis	181,543	Israeli immunisation registry	Multiple regression analyses	LBW = delay Delay greater in smallest infants	National cohort study
Batra et al. (2009)	US	Retrospective cohort analysis	7785	Data from computer database (another study)		Greater prematurity = greater delay	Immunisation data on all in first year of life
Crawford et al. (2009)	Australia	Retrospective immunisation audit	100	Hospital records	Logistic regression	Delay which increases with age	Other data also collected

		& questionnaire (Neonatologists)					
Davis et al. (1999)	US	Cohort & case/control analyses	11580	Data part of VSD project	Logistic regression	Prematurity not an indicator for delay but VLBW lag behind	Used regional data
Denziot et al. (2011)	France	Observational study	602	NICU database	x^2-test Mann-Whitney	At 5- & 24-months immunisations are delayed. First vaccine in NICU before discharge linked with better coverage later	Single NNU
Fortmann et al. (2021)	Germany	Observational study	8,401	German Neonatal Network	Univariate analysis Logistic/linear regression	A significant proportion of EGLANs were not vaccinated on time	Studied extremely low gestational age infants (EGLANS)

Hofstetter et al. (2019)	US	Retrospective cohort study	10,367	Electronic health records Washington State Immunisation System	Chi square test, multivariate logistic regression	At 19 and 36 months more than 50% preterm infants under-vaccinated.	Set in the US state of Washington
Laforgia et al. (2018)	Italy	Cross sectional study	159	Hospital database and regional Immunisation Register	Correlation coefficient Logistic regression	Delay associated with LBW, lower GA however, up to date by 24 months. Vaccination age increases as GA and BW lower and length of hospitalisation is higher	Vaccines given in hospital and community setting

Langkamp et al. (2001)	US	Logistic regression analysis	8285 VLBW infants	Data from National maternal & Infant health survey	Logistic regression analysis	VLBW receive first 3 doses of DTP and first 2 polio later than NBW infants. Still at 12 and 36 months these children are less likely to be up to date with their immunisations	Not exclusively in the NNU and unable to differentiate where
Magoon et al. (1995)	US	Survey design	153	Questionnaires	Logistic regression & other stats tests	Delayed post discharge but getting better	Focus on 'high-risk' infants
McKechnie & Finlay (1999)	UK	Retrospective study	110 PT and 220 controls	NICU records	Chi squared test	Fewer PT infants received vaccines on time over 12m period. Earlier immunisations more likely to be given on time	Single NNU
Nestander et al. (2018)	US	Retrospective cohort study	135,964	Military Healthcare System database	Chi square	Immunisation completion decreases in: LBW, VLBW or ELBW.	Focus on completion of

					Logistic regression	<32 weeks GA Infants with chronic lung disease Male infants Inconsistent health care visits	immunisation rather than delay
Ochoa et al. (2015)	Peru	Prospective cohort study	222	Followed up with parents	Fisher's exact test Mann-Whitney	Significant delays in VLBW infants	Authors state set in developing country
Pinquier et al. (2009)	France	Prospective study	87	Perinatal network	Chi square T test	Delays observed in preterm infants	Infants <33 weeks in a region in France
Roper and Day (1988)	UK	Data comparison	LBW n=395	Child health records	Descriptive	LBW = delay Delay not evident in later vaccinations	Guideline in place

			controls n=3426				
Rouers et al. (2019)	Netherlands	Part of a larger prospective cohort study	276	Parental questionnaire, medical records	Multivariate logistic regression	Lower GA and BW = delay Low SES and longer hospitalisation negatively influenced timeliness	Used parental surveys and medical notes
Ruiz et al. (1991)	US		'High risk' infants n=38 'low risk' infants n=30 and 'normal'	Questionnaire to parents	Chi squared test	57% of high-risk infants not vaccinated with pertussis by 1yr of age	Focus on pertussis

			infants n=59				
Slack and Thwaites (2000)	UK	Case/control	212 first vaccines 205 last vaccines	Hospital notes, parents and central computer	Pearson correlation & Kruskal-Wallis non-parametric test	Vaccination delayed in preterm infants especially once discharged from NICU	Also rates measured post discharge
Tillmann et al. (2001)	Switzerland	Retrospective case/control study	60	Vaccination records	x^2-test Mann-Whitney *U*-tests	PT vaccinated later than term	Immunisation data from parents
Tozzi et al. (2014)	Italy	Part of a larger prospective cohort	1102	Vaccination certificates checked at follow	Kaplan Meier method	Delay common and related to vaccine type (HEXA & Men C ok but others = lower rate)	Unclear whether or not infants were in the NNU when

		study following up pre-terms		up visit (when 2yrs old)			vaccines due/administered
Tooke & Louw (2019)	South Africa	Observational study	60	Infants' medical records	Descriptive	Delays associated with being on oxygen and concerns about sepsis	Authors state set in developing country New initiative to start routine 6wk vaccines on the unit
Wilson et al. (2012)	Canada	Data comparison	PT n= 656687 Term n=782917	Various databases	Descriptive	PT infants vaccinated later if hospitalised	Regional cohort
Woestenberg et al. (2014)	Netherlands		883747	National immunisation database	Cox regression analyses	Median vaccination age lower with higher GA and BW. Being vaccinated in hospital = timelier vaccination for extreme PT but not PT	National cohort studied

Appendix 2 Appraisals of studies

Elements influencing the credibility of the study	
Study details	Vaccination timeliness and completeness among preterm and low birthweight infants: a national cohort study
Author(s)	Bary-Weisberg & Stein-Zamir, both authors have a background in paediatrics and vaccine research
Source	Human Vaccines and Immunotherapeutics
Writing style	Good
Report title	Good summary of content
Abstract	Clear overview of study
Elements influencing the robustness of the research	
Purpose/research problem	Justified in the background/introduction section
Logical consistency	Yes – easy to read
Literature review	Yes, there is evidence of understanding of previous research which has led to this study
Theoretical framework	None cited, but the background/introduction sections indicate the idea of a delay
Aims/objectives/research question/hypotheses	Yes, this is clearly stated at the end of the introduction section
Sample	All infants born from 1st January 2016 to 31st December 2016 – had to have been born in Israel, have a unique identifier and survived 24 months. 181, 543 infants in total: ≥2500g = 167,647 2000-2499g = 9,661 1500-1999g = 2,629 1000-1499g = 1,025 <1000g = 580
Ethical considerations	There is no mention of any ethical or other approvals in the paper

Operational definitions	Any are defined clearly
Methodology • Design	Defined as a historical prospective study of a national annual cohort – creates some ambiguity over the use of 'prospective', but fits with definitions
Is secondary data used? If yes then consider: • Is there sufficient data? • What was the original purpose for which the data were collected?	Yes, the secondary data used is from National Newborn Registry and this seems to where immunization data were also obtained Under law in Israel, all births and associated data have to be entered onto this registry
• When and how were they collected?	Data were from 2016 – the actual date of extraction is not given, but study published in 2021
• Are the variables of interest included in the dataset?	Given that the researchers wanted to investigate vaccination timeliness and completeness against birthweight, this dataset had all the information the required
• What is the level of data aggregation?	Individual
• What data cleaning procedures have been applied?	None mentioned
• What sampling procedures were used?	None – all eligible in cohort were included
Data analysis/results • Results expressed in terms of prematurity, birth weight or both?	Both, although the focus on birthweight – the researchers explain how gestational age strongly correlated to birthweight.

• Degree of prematurity and/or birth weight classified?	Yes, GA - < 28 weeks, 28-31 weeks, 32-36 weeks and ≥ 37 weeks BW - NBW = ≥ 2500g, LBW = 2000-2499g, 1500-1999g 1000-1499g <1000g
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Both – infants <1000g faced the greatest delays, but this was not a significant finding when checked for completeness at 24 months
• Are predictors in rates or delay explored?	Some further characteristics studied included birth order, singleton or twin, ethnicity, socioeconomic status, month of birth and length of hospital stay
Discussion	Findings considered in light of policy and previous research – recommendations are made
References	Good comprehensive and appropriate sources are cited

Elements influencing the credibility of the study	
Study title	Evaluation of Vaccine Coverage for Low Birth Weight Infants During the First Year of Life in a Large Managed Care Population.
Author(s)	Batra et al. (2009) – all authors seem to have background appropriate to study.
Source	Pediatrics.
Writing style	Good.
Report title	Comprehensive and succinct.
Abstract	Clear inclusive overview.
Elements influencing the robustness of the research	
Purpose/research problem	Clearly outlined in the introduction.
Logical consistency	Yes.
Literature review	Clearly leads to research aims.
Theoretical framework	None identified.
Aims/objectives/research question/hypotheses	There is no clearly stated aim but the authors do report what they did and this has relevance to the purpose outlined in the introduction.
Sample	Target population identified and exclusion criteria defined. Sample identified through an established health provision scheme (SCKP) – all those infants registered were included (if eligible). The sample is categorised in terms of how many infants belonged to which weight range: ELBW n=506, VLBW n=788, LBW=6491 and NBW=120 048.
Ethical considerations	Given the observational nature of this study, it is low risk and consent is not a requirement. Institutional review board approvals have been declared.
Operational definitions	Not necessary, although further explanation of the SCKP would have been useful for non-familiar readers. There is a list of abbreviations which is useful.
Methodology • Design Is secondary data used? If yes then consider:	This is a retrospective cohort analysis which is an appropriate design given the purpose of the study; but if the authors had clearly stated an aim or an RQ, this could have been further validated. Yes.

• Is there sufficient data? • What was the original purpose for which the data were collected? • When and how were they collected? • Are the variables of interest included in the dataset? • What is the level of data aggregation? • What data cleaning procedures have been applied? • What sampling procedures were used?	There appears to be sufficient data. Data from an ongoing study (Vaccine Safety Datalink (VSD) project) were used which was established to monitor vaccine safety and usage. This is not specified, but the database was established in 1991 and the authors refer to publications where further details about it are available. Yes, as well as immunisation data, birth dates, gestational age, birth weight, health care usage, gender and race or ethnicity have been collected. The data provided by the dataset appear to have been available at a disaggregated level and the researchers state that the final data sets were anonymised. The researchers acknowledge that there may be errors regarding the misclassification of automated data, but that previous work on the VSD does not prove this to be a major concern. The researchers have included all eligible infants born between January 1997 and December 2002 (n=127,833).
Data analysis/results • Results expressed in terms of prematurity, birth weight or both?	The characteristics of the study population are described using descriptive statistics. Birth weight, and although prematurity is clearly implied, the authors do not define the association.

• Degree of prematurity and/or birth weight classified?	Yes birth weight (only) as ELBW, VLBW, LBW & NBW.
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Both: The results are presented in the following categories: <u>Age-appropriate immunisation (AAI) by vaccine</u> • For all vaccines, AAI rates were lower at the last recommended dose. • AAI rates for 1st, 2nd and 3rd doses of DTP (or DTaP) were lowest among ELBW infants when compared with NBW infants. • AAI rates for the same vaccine were lower but not as low for VLBW infants. • For polio, Hib and Hep B the lowest rates were again in the ELBW infants – the largest difference was in ELBW infants receiving 2nd dose of Hep B. • No significant differences were seen in AAI rates between LBW and NBW infants. <u>Up to date (UTD) immunisation status according to BW</u> • ELBW infants had lowest UTD immunisation levels. • This trend faded at 4,6,9,& 12 months • At 12 months ELBW infants UTD immunisation status was only 5% lower than NBW infants. • After 9 months of age, no major difference between UTD status between VLBW and NBW infants. • UTD immunisation status was not notably different between LBW and NBW infants at any age. <u>UTD immunisation status according to race/ethnicity</u> • Regardless of BW and for all races/ethnicities, UTD immunisation rates at 2 months ranged from 90-94%. • Lowest rates for each ethic group seen at 6 months. • At all ages, UTD rates were lower for black and Hispanic infants when compared to white infants. • UTD rates for Asian infants were significantly higher far for white infants at 4,6,9, & 12 months. <u>UTD immunisation status according to race/ethnicity and BW</u>. • UTD immunisation rates were lower for all ELBW infants in all ethnic groups compared to NBW infants at 2,4,& 6 months. • In the ELBW category, lower rates were seen in the black and Hispanic infants. • At 4 months for VLBW infants, UTD rates were lower in all other ethnic groups when compared to white infants.

• Are predictors in rates or delay explored?	• LBW and NBW black and Hispanic infants were significantly UTD at 2,4,6,& 9 months when compared to white infants. Yes, some: • Factors independently associated with delayed immunisation are ELBW, VLBW, Hispanic ethnicity, black race, and birth before 2001. Significant differences at $P<.05$ using Chi square testing are reported. Multivariate logistic regression analyses were also undertaken using variables including BW, ethnicity, gender and year of birth.
Discussion	The studies' findings are compared with previous studies' findings (mentioned in the literature review). Low UTD immunisation rates in black and Hispanic infants are suggested due to access to health care. Lower rates seen in infants with lower BWs may be due to concomitant illnesses and negative media coverage concerning vaccination. Education of health care providers and in particular, neonatologists play a key role in the promotion of vaccination during the transition of infants into the primary care setting. No claims of generalizability are made.
References	Appear accurate and comprehensive.

Elements influencing the credibility of the study	
Study title	Immunisation practice in infants born prematurely: Neonatologists' survey and clinical audit.
Author(s)	Crawford et al. (2009)
Source	Journal of Paediatrics and Child Health
Writing style	Clear aiding understanding of the study.
Report title	Indicative of the paper's content.
Abstract	Good - structured well and logical.
Elements influencing the robustness of the research	
Purpose/research problem	Not explicitly stated, but clearly arrived at from introductory discussion.
Logical consistency	Yes.
Literature review	Previous reviews addressing the issue of timely vaccination in preterm infants are referred to collectively as 'previous reviews' – greater detail may have added to the rationale of this study. The researchers do identify a 'gap' in that no previous data have studied the need for additional boosters for infants with a GA of <28 weeks or BW of <1500g.
Theoretical framework	None cited.
Aims/objectives/research question/hypotheses	Again, not explicit but aim in abstract as: *To determine Australian neonatologists' recommendation for the immunization of ex-preterm infants and compare their actual immunization status with recommended Australian guidelines.* Further on in the abstract, the methods identified for reaching this aim are: (i) the self-administration of a nine-part questionnaire on current immunization practices for all neonatologists in Australia. (ii) a retrospective immunization audit.
Sample	(i) 130 neonatologists identified (from national directory of NICUs). 19 excluded for reasons; retired, not involved in neonatal management any more or insufficient contact details. 76 responses received from neonatologists practicing at 22 different centres.

	(ii) Audit conducted between October 2006 and May 2007. 97 children ID from Australian Childhood Immunisation Register (ACIR) – 17 parents declined, 31 could not be contacted. 47 interviews completed with parents where consent was gained to access GP immunization records and 43 GP questionnaires were completed returned.
Ethical considerations	Consent and ethical approval are discussed.
Operational definitions	None.
Methodology • Design • Data collection • Instrument design • Validity and reliability Is secondary data used? If yes then consider: • Is there sufficient data? • What was the original purpose for which the data were collected? • When and how were they collected? • Are the variables of interest included in the dataset? • What is the level of data aggregation?	Survey (neonatologists) & retrospective audit. **<u>Survey</u>** Survey sent three times to neonatologists at monthly intervals and yielded a 68% response rate (9 part questionnaire). The survey was developed by 4 of the study's authors (2 neonatologists, 1 GP and 1 vaccinologist) which demonstrates some insight, but other than this, there is no mention of what was used to guide the development or if any of the previous work on the topic had influenced this. There is no mention of how the validity and reliability of the questionnaire used in the survey was tested – no pilot study. **Audit** See last point in this section (sampling procedures). ACIR is a national database which collates immunization data on vaccination (stated as 99% complete). Not stated how the ACIR is completed. Yes, it records routine vaccinations alongside BW and GA at an individual level. Individual.

• What data cleaning procedures have been applied?	The researchers state that the SCIR data correlated closely with the GP records regarding immunization status. A national study is quoted to have found that the ACIR under reported vaccination coverage by only 2.7-5%.
• What sampling procedures were used?	Sample size of 100 was randomly selected through a computer generated list. This allowed estimation of proportions within ±10% or better with 95% confidence.
Data analysis/results	The results of the **survey** are reported using descriptive statistics: 89% (66/74) said they were aware of the guidance as stated in the Australian Immunisation Handbook. Adherence to the guidance varied from 43-79%
• Results expressed in terms of prematurity, birth weight or both? • Degree of prematurity and/or birth weight classified?	Both: Categorized as: BW <1500g or ≥1500g and Gestational age: <28 weeks or 28-32 weeks.
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Both: UTD: BW not associated with UTD status. Infants <28 weeks GA or hospitalized for more than 30 days were more likely to be UTD at 2 months. AAI: 46% of preterm infants had a recorded dose of Hep B with only 17% being administered within 7 days (as per recommendations).

• Are predictors in rates or delay explored?	77% received recommended 3 doses of PCV. 93% received recommended varicella vaccine (given at 18m). Timeliness worsened with increasing age. *Additional vaccines* Additional doses of Hep B, Hib, PCV are recommended for preterm infants – only 19% 23% and 35% of infants received the additional doses (respectively). Only 20% of infants received recommended annual influenza vaccine. Chi-square testing was used to determine independence between data sets with P-value <0.05 being statistically significant. The **audit** results - logistic regression used to determine UTD immunization status at 2,4,6,12 & 18 months and the relationship between BW, GA and days of hospitalization. Other variables studied were which hospital the infants were in and incidence of chronic lung disease.
Discussion	Variability in findings regarding lower rates could be due to ever changing schedule. Educating neonatologists about the changes is essential for guidelines to be implemented. Opportunities to vaccinate decrease and barriers increase post discharge. Maybe due to confusion over schedule changes & perceived fragility of infants.
References	Comprehensive list of relevant sources.

Elements influencing the credibility of the study	
Study title	Immunization Levels Among Premature and Low-Birth-Weight Infants and Risk Factors for Delayed Up-to-Date Immunization status.
Author(s)	Davis et al. (1999)
Source	Journal of the American Medical Association.
Writing style	Logically presented and structured.
Report title	Clear and indicative of content.
Abstract	Logically presented and inclusive yet succinct.
Elements influencing the robustness of the research	
Purpose/research problem	Clearly derived from the introductory discussion.
Logical consistency	Yes.
Literature review	Relevant literature incorporated to add to the justification of the study.
Theoretical framework	None stated.
Aims/objectives/research question/hypotheses	*To describe current immunization practices for premature and low birth weight infants and ascertain risk factors for poor immunization status, using large population-based data sources.*
Sample	Children enrolled onto Vaccine Safety Datalink (VSD) database from birth to 2 years old who were from 3 identified sites (health maintenance organizations or HMOs).
Ethical considerations	It could be assumed that the publication status of the study infers ethical approval, however, there is no mention of this in the study, nor is it stated that data were anonymised.
Operational definitions	Many acronyms are used and although these are explained as they appear, owing to the amount of them, a section detailing each one and a full explanation would have been beneficial.
Methodology • Design Is secondary data used? If yes then consider: • Is there sufficient data?	Stated as cohort and case-control analyses. Yes. 11,580 LBW and preterm infants enrolled from birth to 2 months, and of these, 6,832 were continuously enrolled from birth to 24 months.

	At 2 months there were 173,373 term NBW controls enrolled and 103,324 of these controls at 24 months.
• What was the original purpose for which the data were collected?	Immunisation data from an ongoing VSD project (created in 1991) were used which was established to monitor vaccine safety and usage. It links medical event history to vaccination status. Some demographic information was obtained from automated databases of Group Health Cooperative (GHC).
• When and how were they collected?	Not detailed but more information about the VSD project and the HMOs are referenced. The relationship between the VSD, HMOs and GHC is not clearly presented.
• Are the variables of interest included in the dataset?	Yes.
• What is the level of data aggregation?	The data provided by the dataset appear to have been available at a disaggregated level.
• What data cleaning procedures have been applied?	The researchers do not make a comment on the quality of the data they use. The VSD is an established database but its reliability and validity are not considered by the researchers here.
• What sampling procedures were used?	The abstract states that all eligible infants enrolled on the VSD database between March 1991 and March 1997 were included. The GHC data – 694 enrolled from birth to 2 months. 50% had BWs between 1500-2500g and 12% had BW less than 1500g. 35% of those followed up to their 2nd birthday had been diagnosed as having bronchopulmonary dysplasia and/or hyaline membrane disease.
Data analysis/results	
• Results expressed in terms of prematurity, birth weight or both?	Birth weight and prematurity but this is not very clear.
• Degree of prematurity	

and/or birth weight classified?	Only BW as: <1500g, 1500-2500g and >2500g
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Findings presented as % UTD At each age assessed, infants with BW <1500g had lower up to date immunization status than infants with a BW of 1500 – 2500g or preterm infants with BW >2500g. By 6 months 52%-65% infants with BW <1500g were up to date. At the same age for infants with a BW of 1500-2500g , 69%-73% were up to date. Infants with BW of >2500g were 66%-80% up to date. Normal BW infants – 65%-76% were up to date at 6 months which was significantly higher than the infants with BW <1500g but no different from infants in other BW categories. Similar differences in rates were seen between the groups at 24 months. Descriptive and inferential statistics are used. Logistic regression modelling is used to assess the relationship between different BW categories and immunization status at 2,4,6,15,18, & 24 months. Males were more likely to be under immunized than females but this was not statistically significant. Immunisation status at 6 and 24 months was not affected by the amount of hospitalisations prior to these age points. Infants hospitalized 8-14 days in first month of life were more likely to be up to date with immunisations – significant at 6 months but not at 24 months.
• Are predictors in rates or delay explored?	Bronchopulmonary dysplasia (BPD) or hyaline membrane disease (HMD) did not affect immunization status at 6 or 24 months. Children with BPD and HMD who were on medication had up to date rates which were comparable to children with pulmonary disease and not on medication. Children receiving frequent 'well-child' visits were more likely to be up to date at 24 months than children with less than 3 well-child visits.
Discussion	Authors relate own findings back to those mentioned in the introduction and additional previous research. Children with pulmonary disease are perhaps more likely to have up to date or even better immunization rates than the others because of the amount of contacts with health services they receive. Only one

	limitation to the study is stated as a 'potential' limitation, and the researchers say that it would not have impacted on the findings. The researchers say that because their study is population based (where previous studies had been based on a single unit) it provides a better picture of what is happening in the LBW population.
References	Comprehensive reference list.

Results only expressed in terms of BW and little detail about GA is included. Only <38 weeks (and <1500g, 1500-2500g) or term (and >2500g).

Elements influencing the credibility of the study	
Study details	Hospital initiation of a vaccinal schedule improves the long-term vaccinal coverage of ex-pre-term children.
Author(s)	Denziot et al. (2011)
Source	Vaccine
Writing style	Clear and well structured.
Report title	Reflects one of the main findings of the study but is not too long.
Abstract	Very brief but gives a fair summary of the study.
Elements influencing the robustness of the research	
Purpose/research problem	Purpose of the study is justified by a short background which incorporates the relevant literature.
Logical consistency	Yes.
Literature review	Some evidence of this but not very detailed. Much of the literature referred to in this section was familiar (to me) suggesting there was an appropriately focused review of sorts.
Theoretical framework	None cited.
Aims/objectives/research question/hypotheses	Aim is clearly stated at the end of the introductory section.
Sample	602 infants <36 weeks GA (74.6% survey response rate).
Ethical considerations	Ethical approval and parental consent are both evidenced.
Operational definitions	All terms and abbreviations are explained sufficiently.
Methodology • Design • Data collection • Instrument design • Validity and • reliability	Postal or telephone survey (completed by parents) including socio-demographic data and vaccination history. Secondary data extracted from NICU database for information including GA and BW. The parental questionnaire was constructed in collaboration with INSERM Unit INED 822 but there is no explanation of what or who this is provided anywhere in the paper. It is therefore difficult to know the value of this. Additionally, the validity and reliability of the questionnaire as a data collection tool is not mentioned in the paper.

Is secondary data used? If yes then consider: • Is there sufficient data? • What was the original purpose for which the data were collected? • When and how were they collected? • Are the variables of interest included in the dataset? • What is the level of data aggregation? • What data cleaning procedures have been applied? • What sampling procedures were used?	A NICU database was accessed, but the purpose of the database is unclear. There appears to be sufficient data which is relevant to the RQ. Study data were obtained from the database for children with a GA <36 weeks who were born between January 2003 and July 2005. It is not stated when or how the data were originally entered. Yes – BW and GA. Individual. Not known. All infants born within a certain timeframe were identified and included if consent was obtained.
Data analysis/results • Results expressed in terms of prematurity, birth weight or both? • Degree of prematurity and/or birth eight classified? • Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	GA only, but of the responding participants, 14.5% were small for gestational age (SGA). GA as: <28, 28-30, 31-32, 33-34 weeks. Mainly UTD but also, median age at first vaccination was 3 months and 5 days (recommended 2 months for first vaccination). At 5 months, 38.9% were up to date for DTCoqPolio Hib and 22.2% for PCV.

	At 24 months, coverage was still low at 67% for DTCoqPolio Hib and 36% for PCV. 22% had received 3 doses of Hep B by 24 months. Univariate analyses using Chi-square and Mann-Whitney testing. Odds ratio and CI of the risk of a delay in immunizations were calculated using logistic regression. Better coverage of PCV was significantly linked to lower GA, a low family income and follow up network vaccinator. Any primary vaccination before discharge from the unit was linked with better coverage.
• Are predictors in rates or delay explored?	
Discussion	Reference to previous research is made highlighting similarities in the findings. Families with social difficulties receive more input from welfare services which may explain better coverage in low income groups. Lower rates of PCV coverage may be due to its recent introduction into the schedule. Initiating vaccination programmes for infants in the NICU at 2 months may be a strategy to increase future coverage in this population.
References	Comprehensive enough.

Elements influencing the credibility of the study	
Study details	Five year follow up of extremely low gestational age infants after timely or delayed administration of routine vaccinations
Author(s)	Fortmann et al. (2021) – all with a background of paediatrics, neonatology and research
Source	Vaccines
Writing style	Good, but some clumsy statements – researchers are German so may not have English as first language
Report title	Good - informative
Abstract	Good – unstructured but an aim, design, methods and results are clear
Elements influencing the robustness of the research	
Purpose/research problem	Not very clearly stated in main article but it is in the abstract
Logical consistency	Yes – follows the conventions of most research reports
Literature review	Some evidence but main focus of this is on immunological aspects – probably because of the study's aim of identifying risk factors for delay and long-term consequences
Theoretical framework	None stated
Aims/objectives/research question/hypotheses	Only what is cited in the abstract
Sample	8401 infants between 2010-2019. These are all extremely low gestational age infants (ELGANs)
Ethical considerations	Yes, this is described
Operational definitions	Yes, clearly described
Methodology • Design Is secondary data used? If yes then consider:	Observational study

• Is there sufficient data?	Seems to be enough data – 8401 ELGANs identified over a nine-year period
• What was the original purpose for which the data were collected?	Data from larger German neonatal cohort and annual questionnaires to parents
• When and how were they collected?	Data extracted from dataset and parents completed questionnaires over nine-year period – study published 2021
• Are the variables of interest included in the dataset?	Seems so – given the aim of studying associated neonatal risk factors, there are several relevant characteristics included e.g. duration of ventilation and any surgeries
• What is the level of data aggregation?	Individual
• What data cleaning procedures have been applied?	Data quality checked by trained physician
• What sampling procedures were used?	Included if fitted definition of extremely low gestational age
Data analysis/results • Results expressed in terms of prematurity, birth weight or both?	Both, but focus on gestational age.
• Degree of prematurity and/or birth eight classified?	No
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Both
• Are predictors in rates or delay explored?	Yes, risk factors studied included infants born small for their gestational age, impaired growth and complex medical histories
Discussion	Reasons for reported delays explored and previous studies considered.
References	Good, appears to be a comprehensive list of relevant sources

Elements influencing the credibility of the study	
Study details	Early Childhood Vaccination Status of Preterm Infants
Author(s)	Hofstetter et al. (2019) authors have a background in paediatrics and research. There is also a connection to the 'immunisation office' which could be assumed to be related to the administration aspect of the immunisation data used in the study
Source	Pediatrics
Writing style	Nice and clear – no ambiguity
Report title	Yes, this summarises the content of the paper
Abstract	Good well-structured abstract using the headings: background, methods, results and conclusion
Elements influencing the robustness of the research	
Purpose/research problem	This is outlined by the introduction – the notion of vaccines being delayed in preterm infants
Logical consistency	Yes – follows the conventions of most research reporting
Literature review	Evidence of this in the introduction
Theoretical framework	None explicitly stated, but the evidence discussed implies the notion of a delay
Aims/objectives/research question/hypotheses	Not really explicitly stated – more cited in the past tense: "we compared early childhood vaccination among preterm and term/postterm infants…."
Sample	Infants born in the defined period of January 2008 and December 2013 in the state of Washington, US – 10,367 in total Gestational ages: 37-43 weeks = 8,302

	<37 weeks = 1,991 which was further classified as: 34-36 weeks = 1,053 23-33 weeks = 938 Birthweights: ≥ 2500g = 8,557 1500-2499g = 1,146 < 1500g = 568
Ethical considerations	Approvals are cited
Operational definitions	Nothing which is unclear
Methodology • Design Is secondary data used? If yes then consider: • Is there sufficient data? • What was the original purpose for which the data were collected? • When and how were they collected? • Are the variables of interest included in the dataset?	Retrospective cohort study Data were used from electronic health record (EHR) (demographics and some immunization data) and Washington State Immunisation Information System. There appears to be sufficient data The EHR appears to be a generic health database for infants Data collected from a eight-year period – study published in 2019 but not clear when data were extracted The dataset has what the researchers need to study, but it is stated in the discussion that a limitation was that they were unable to study parental or other factors which may have contributed to under-vaccination

• What is the level of data aggregation?	Individual
• What data cleaning procedures have been applied?	None described
• What sampling procedures were used?	Infants included if they met eligibility criteria
Data analysis/results • Results expressed in terms of prematurity, birth weight or both?	Predominantly prematurity – birthweight characteristics were described, but owing to its strong correlation with gestational age, was not a key feature of the findings
• Degree of prematurity and/or birth weight classified?	Yes – as described in the 'sample' section
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Expressed as being up to date at 19 months and 36 months
• Are predictors in rates or delay explored?	Yes, including race/ethnicity, insurance status, maternal language, hospitalisation
Discussion	Findings are discussed in the context of practice and prior research. Some suggestions to explain the findings are made
References	Clear comprehensive list

Elements influencing the credibility of the study	
Study details	Are pre-terms born timely and right immunized? Results of an Italian cohort study
Author(s)	Laforgia et al. (2018) authors from biomedical science backgrounds – uncertain of knowledge and experience around preterms and vaccination
Source	Human Vaccines and Immunotherapeutics
Writing style	This is OK but there are some clumsy statements. The researchers are Italian, so it could be that English is not the first language
Report title	Again, this is a little clumsy – although the message gets across
Abstract	This is clear and presented in a chronological fashion
Elements influencing the robustness of the research	
Purpose/research problem	The basis for the research is presented in the introduction
Logical consistency	This has an odd structure: Introduction, results, discussion – followed by methods at the end
Literature review	Evidence of this in the introduction adding to the rationale for the current study
Theoretical framework	None cited but implied in previous discussion
Aims/objectives/research question/hypotheses	Clearly cited at end of introduction
Sample	159 infants born prematurely in 2013 in specified hospital
Ethical considerations	There is no mention of any approvals
Operational definitions	Some abbreviations described
Methodology • Design Is secondary data used? If yes then consider: • Is there sufficient data?	 Cross-sectional study Yes, data were taken from the hospital database and immunisation register – data

• What was the original purpose for which the data were collected?	were collected on a standardized form. It is unclear if this was developed for the study or normal collection methods
• When and how were they collected?	Data from 2013 – date of extraction not stated
• Are the variables of interest included in the dataset?	Key variables are available
• What is the level of data aggregation?	Individual
• What data cleaning procedures have been applied?	None discussed
• What sampling procedures were used?	All eligible infants in defined cohort included
Data analysis/results	
• Results expressed in terms of prematurity, birth weight or both?	Findings expressed in terms of prematurity, although birthweight was studied
• Degree of prematurity and/or birth eight classified?	No classifications are cited
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Both – preterm infants experience delays (not vaccinated on time) but all completed by 24 months
• Are predictors in rates or delay explored?	This is not clear – data from the dataset used included weight and age at discharge from the NNU, but these are not mentioned n any further analyses. However, at the end of the results section, there is a statement that no statistically significant associations were found between outcomes and determinants.
Discussion	Findings are considered in light of previous research and reasons for the findings are suggested.
References	Fairly comprehensive list

Elements influencing the credibility of the study	
Study details	Delays in Receipt of Immunizations in Low-Birth-Weight Children.
Author(s)	Langkamp et al. (2001)
Source	Archives of Pediatric and Adolescent Medicine.
Writing style	Clear and concise.
Report title	Outlines scope of study in a concise way.
Abstract	Informative and sectioned logically.
Elements influencing the robustness of the research	
Purpose/research problem	Study purpose clearly stated and justified by previous discussion.
Logical consistency	Yes.
Literature review	Yes, and justifies current study.
Theoretical framework	None noted.
Aims/objectives/research question/hypotheses	Clearly defined in the abstract.
Sample	8285 children who mothers completed a survey.
Ethical considerations	It is not stated that ethical approval was received for the study.
Operational definitions	Terminology and abbreviations explained.
Methodology • Design Is secondary data used? If yes then consider: • Is there sufficient data? • What was the original purpose for which the data were collected? • When and how were they collected?	Logistic regression analysis. Yes. The study analyses data from two data sets – the 1988 National Maternal and Infant Health Survey (NMIHS) and the 1991 Longitudinal Follow-up Survey. The original purpose for which these data were collected is not stated. In 1988 and 1991 by surveying mothers identified.

• Are the variables of interest included in the dataset? • What is the level of data aggregation? • What data cleaning procedures have been applied? • What sampling procedures were used?	Yes – birth weight and timing of specified vaccinations. Individual although children categorized as VLBW, MLBW (moderately low BW) and NBW. Data cleaning measure are not identified although the researchers do acknowledge in their limitations that this could be a problem. All children born in 1988 for whom complete immunization records were obtained.
Data analysis/results • Results expressed in terms of prematurity, birth weight or both? • Degree of prematurity and/or birth weight classified? • Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	BW only although prematurity implied. BW as: VLBW, MLBW and NBW As timeliness and UTD: Mean age at receipt of each dose of DTP, polio, and MMR vaccines were compared between the three BW categories using an adjusted Wald statistic. MLBW and VLBW infants received their first and second vaccines significantly later than NBW infants. VLBW infants also received their 3rd dose later than NBW infants but not the same for MLBW infants.

• Are predictors in rates or delay explored?	No significant difference noted between all groups at 4th DTP, 3rd polio or MMR. The relationship between BW and up to date vaccination status was assessed using logistic regression at 12, 24 and 36 months. VLBW and MLBW infants less likely to be UTD for all immunisations at 12, 24 and 36 months of age when compared with NBW infants. VLBW children without health insurance were significantly less likely to be UTD at 12 months compared to NBW children. No differences were noted between these two groups when the VLBW child was insured. VLBW children with mothers who had less than high school education were significantly less likely to be UTD at 12 months compared to NBW children. No differences were noted between these two groups when the VLBW child's mother had completed high school. LBW children whose mothers did not have insured prenatal care were less likely to be UTD at 24 months compared with NBW children. These odds were no different if the mother's prenatal care was insured.
Discussion	The study's findings are compared to previous research and emphasises the importance of access to care for maintain timely vaccinations. Limitations are recognised as the aged nature of the data used – since then more vaccines have been introduced meaning that the challenges of vaccinating smaller infants may be even greater than this study suggests. Another limitation is the use of secondary data - incomplete data mean that rates may be even lower than the study reports,

	although on balance this this may not affect the relationship between the three groups studied.
References	Comprehensive and relevant.

Focus on BW and not explicitly linked to GA

Elements influencing the credibility of the study	
Study details	Delays in Immunizations of High-Risk Infants During the First Two Years of Life: Special Care for the High-Risk Infant Should Not Mean Special Immunization Schedules.
Author(s)	Magoon et al. (1995)
Source	Journal of Perinatology.
Writing style	Clear and concise.
Report title	Indicative of paper's content.
Abstract	Good outline of paper.
Elements influencing the robustness of the research	
Purpose/research problem	Arrived at following discussion of practice experience and previous research.
Logical consistency	Yes.
Literature review	Some alluded to appropriately in introduction.
Theoretical framework	None mentioned.
Aims/objectives/research question/hypotheses	Not explicitly stated as aims of study but clear at the end of the introduction.
Sample	153 families and 58 care providers responded to questionnaire.
Ethical considerations	Ethical approval is not cited. The parental questionnaire sought permission to access children's' medical records.
Operational definitions	Adequately explained.
Methodology • Design • Data collection • Instrument design	 No design is specified but the study takes a quantitative approach using parental and care provider questionnaires. Completed by parents of children who met inclusion criteria and were attendees at a specified clinic. The care provider's questionnaire was distributed to those in the region to examine their practice – this mainly was via meetings, or in person. There is no information on how or by who the questionnaires were developed.

• Validity and reliability	This validity and reliability of the questionnaire cannot be confirmed because of the lack of detail about how it was developed. However, it is stated that some parental reports were randomly checked against medical records for accuracy, but the results of this checking is not reported in the study.
Is secondary data used? If yes then consider: • Is there sufficient data? • What was the original purpose for which the data were collected? • When and how were they collected? • Are the variables of interest included in the dataset? • What is the level of data aggregation? • What data cleaning procedures have been applied? • What sampling procedures were used?	Secondary data is used to an extent to check the accuracy of responses provided by the parents. Details of these records is not mentioned so it is not possible (or appropriate) to respond to the rest of the questions.
Data analysis/results	
• Results expressed in terms of prematurity, birth weight or both?	Both. The delay of first DTP and OPV vaccinations increased with prematurity and LBW. The delays in subsequent vaccinations ranged from 6-40 weeks and occurred in 30-77% of the infants depending on the vaccination. These delays did not correlate with GA.
• Degree of prematurity and/or birth weight classified?	Yes: BW: <1000g, 1000-1499g, 1500-1749g, 1750-2499g, >2500g.

	GA: <29, 30-31, 32-33, 34-37, ≥38 weeks.
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Expressed as delays against expected time and any vaccination given more than two weeks after the recommended time was considered as a delay. Logistic regression was used to determine significant factors which related to a delay in vaccination. Separate analysis for term and preterm infants was conducted. Possible predictors of delay tested were: weight, some morbidities associated with preterm birth, age at discharge and parental educational level. Two time periods were also compared – period A (1983-1986) and period B (1987-1991) using the Wilcoxon rank sum test. For DTP vaccine, interventricular hemorrhage predicted a delay. For OPV, predictors were GA, BW, BPD and age at discharge. For term infants, predictors for a delay in starting DTP and OPV were the number of diagnoses on discharge. Delays did not correlate with parental level of education for either term or preterm infants.
• Are predictors in rates or delay explored?	Parental reasons for delays included GA and some illnesses. Parental perception of delays was underestimated with parents not reporting delays to the true extent with which they occurred.

	Public health clinics and neonatologists were most adherent to AAP vaccination recommendations. Influences on the decision to vaccinate for care providers were BW (pediatricians) and GA (family practitioners). Reasons not to vaccinate cited by care providers were not in keeping (so not seen a true contraindications to vaccinate) with AAP guidance. When practice in periods A and B were considered, there was less delay in period B when compared to period B.
Discussion	The level of non-responders to the questionnaire may mean that the level of delay is greater than the study reports. Exclusion criteria may mean that infants with even greater pathologic conditions may have even greater delays. Parental education prior to discharge may improve uptake and prevent delays. The difference in delays seen in periods A and B suggests that guidance has been supportive in the practice of vaccinating preterm infants. The lack of prior research on this topic means that there is nothing to compare these findings with.
References	Comprehensive.

Elements influencing the credibility of the study	
Study details	Uptake and timing of immunisations in preterm and term infants.
Author(s)	McKechnie and Finlay (1999).
Source	Professional Care of Mother and Child.
Writing style	Clear and succinct.
Report title	Encapsulates what the study is about.
Abstract	Good summary.
Elements influencing the robustness of the research	
Purpose/research problem	Justified by reference to previous studies.
Logical consistency	Yes.
Literature review	Relevant literature referred to in the introduction although not stated that a full review was undertaken.
Theoretical framework	None stated.
Aims/objectives/research question/hypotheses	Not explicitly stated although clearly determined.
Sample	110 preterm infants and 220 controls (term infants).
Ethical considerations	Ethical approval is not cited.
Operational definitions	Not a lot of jargon used but explanations are present where needed.
Methodology • Design	Cited in abstract as a retrospective study
Is secondary data used? If yes then consider: • Is there sufficient data?	Yes. The data appears sufficient and although the authors claim statistical significance, there is no mention of how a sample size was calculated to determine power.
• What was the original purpose for which the data were collected?	For infant identification, the data were taken from the Admissions Register which is completed on the unit for each admission. This appears to be a register completed for administrative purposes

	onlyImmunisation details were obtained from Child Health Department computer for the area.
• When and how were they collected?	The register is completed on admission but no further details are given. It is unclear how the Child Health Dept. data were collected.
• Are the variables of interest included in the dataset?	Yes, the Child Health Dept. data provided details for the identified infants regarding that dates of their DTP, OPV and HiB immunisations.
• What is the level of data aggregation?	Individual.
• What data cleaning procedures have been applied?	The reliability and validity of the data obtained is not determined.
• What sampling procedures were used?	All infants meeting defined criteria who were admitted to the unit for the year 1996 were included in the analyses.
Data analysis/results	
• Results expressed in terms of prematurity, birth weight or both?	GA only
• Degree of prematurity and/or birth eight classified?	<28, 28/29, 30/31, 32/33, 34/35 weeks
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Expressed as % AAI

	Descriptive statistics (median ages) are used to describe the age of infants for the 1st, 2nd and 3rd vaccinations. The difference in vaccination ages between term and preterm infants were tested using the chi squared test. Term infants were more likely to receive their vaccinations on time compared with preterm infants (statistically significant) for all three vaccinations. The greater the GA, the more likely infants were vaccinated on time.
• Are predictors in rates or delay explored?	No
Discussion	Overall, the uptake rates for all infants in the unit was better than for that of the general population – maybe due to exposure to health professionals. Delayed vaccination in the most preterm infants may be due to associated illnesses necessitating a delay – this may account for a delay in the first vaccination but does not account for subsequent delayed doses.
References	Complete and relevant.

Elements influencing the credibility of the study	
Study details	Immunization completion in infants born at low birth weight
Author(s)	Nestander et al. (2018) from a paediatric background
Source	Journal of Pediatric Infectious Disease Society
Writing style	Clear
Report title	Succinct
Abstract	Good and structured as background, methods, results and conclusion
Elements influencing the robustness of the research	
Purpose/research problem	Defined in the introduction – focus on ascertaining vaccination coverage in LBW infants after adjusting for other factors
Logical consistency	Yes
Literature review	Yes, there is evidence of previous studies
Theoretical framework	None cited
Aims/objectives/research question/hypotheses	Not especially clear, although a hypothesis is cited at the end of the introduction
Sample	135, 964 infants in total. Infants born between 1st October 2007 and 30th September 2011 who had a birth record on the military health system (MHS) database and an immunization record on the same MHS database Birthweight: NBW = ≥2500g (*n* = 129,296) LBW = 1500-2499g (*n* = 5,406) Very LBW = 1000-1499g (*n* = 826) Extremely LBW = <1000g (*n* = 436)

	Gestational age: ≥37 weeks (*n* = 126,224) 33-36 weeks (*n* = 7,811) ≤32 weeks (*n* = 1,929)
Ethical considerations	There is a statement that the study was approved by the relevant boards
Operational definitions	Yes, there is nothing unexplained
Methodology • Design	Retrospective cohort study
Is secondary data used? If yes then consider:	Yes, the MHS for both infant and immunisation data
• Is there sufficient data?	Yes, this is a large cohort
• What was the original purpose for which the data were collected?	The MHS is a health database for members of the military and their families – health data are collected so that members and their dependents can be treated anywhere in the world providing care at a military treatment facility
• When and how were they collected?	Data were collected for the period 1st Oct 2007-30th Sept 2011, but date and details of extraction is given
• Are the variables of interest included in the dataset?	Seem to be although some assumptions were made, for example, members military rank was used for socioeconomic status
• What is the level of data aggregation?	Individual, although results reported aggregated

• What data cleaning procedures have been applied? • What sampling procedures were used?	A process for cross checking is mentioned but no further details are provided All eligible in cohort defined were included
Data analysis/results • Results expressed in terms of prematurity, birth weight or both? • Degree of prematurity and/or birth weight classified? • Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)? • Are predictors in rates or delay explored?	Defined mostly in terms of birthweight – this corresponds with the aims of the study Yes (see section 'sample') Results are expressed as odds of completion at 24 months Yes, although these were adjusted for – certain diagnoses
Discussion	Findings are discussed alongside previous research and current practice – recommendations are made
References	Comprehensive and relevant sources

Elements influencing the credibility of the study	
Study details	Vaccine schedule compliance among very low birth weight infants in Lima, Peru
Author(s)	Ochoa et al. (2015) from a public health and 'hospital' background. No further information given
Source	Vaccine
Writing style	Good, nice and clear
Report title	This is a good indication of the content
Abstract	Structured abstract – Objective, patients and methods, results and conclusions
Elements influencing the robustness of the research	
Purpose/research problem	Outlined in initial introductory section
Logical consistency	Yes, this is logical
Literature review	Evidence of this in the introduction
Theoretical framework	None cited
Aims/objectives/research question/hypotheses	Stated in abstract and at the end of the introduction as 'to describe compliance with vaccine schedule in very low birth weight infants'
Sample	Over a year, March 2009 – March 2010. Infants were enrolled if admitted to one of the four identified hospitals in the region. 222 enrolled in total, but not all included in analyses Birthweight: <1000g = 48 1000-1500g = 157
Ethical considerations	Approval details are provided
Operational definitions	Nothing to be clarified

Methodology • Design Is secondary data used? If yes then consider: • Is there sufficient data?	Prospective cohort study – part of a larger cohort study
• What was the original purpose for which the data were collected?	Hospital records are used
• When and how were they collected?	One assumes for hospital care – no details are provided. Data also collected via follow up contact over a year, every two weeks
• Are the variables of interest included in the dataset?	Yes, some data in the hospital records, but it is unclear what data the follow up contacts were to obtain, although this was part of a larger study to determine the incidence of RSV in preterm infants in the first year of life
• What is the level of data aggregation?	Individual but results reported as aggregated
• What data cleaning procedures have been applied?	None mentioned
• What sampling procedures were used?	All eligible infants included
Data analysis/results • Results expressed in terms of prematurity, birth weight or both? • Degree of prematurity and/or birth eight classified?	Birthweight, although prematurity is described Birthweight as <1000g or 1000-1500g
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Both – lowest birthweight had greatest delays
• Are predictors in rates or delay explored?	No
Discussion	Results are considered alongside previous research and practice – recommendations are made
References	Relevant and complete

Elements influencing the credibility of the study	
Study details	Vaccination rate of premature infants at 6 and 24 months of age: a pilot study
Author(s)	Pinquier et al. (2009) from a neonatology and paediatric background
Source	Archives de Pediatrie
Writing style	Only the abstract was in English so this was difficult to interpret in places
Report title	Yes, this is informative
Abstract	Gives an overview of the study
Elements influencing the robustness of the research	
Purpose/research problem	Ascertained from the abstract, although the introduction alludes to research which is cited by other researchers in the papers reviewed so far
Logical consistency	Appears to be logical
Literature review	Yes – prior research is referred to in the abstract
Theoretical framework	None noted
Aims/objectives/research question/hypotheses	There is an aim clearly cited in English in the abstract to: examine the vaccine coverage in this population (infants born before 33 weeks) according to the French schedule at 6 and 24 months
Sample	From a region in France – infants born before 33 weeks. 87 infants in total
Ethical considerations	Ethical approval is cited
Operational definitions	Nothing was left unexplained
Methodology • Design Is secondary data used? If yes then consider: • Is there sufficient data?	Regional prospective study Appears to be for the purpose of the study

• What was the original purpose for which the data were collected?	The data appeared to have come from a larger regional cohort study – 'cohort 2000' but it is unclear what this study was aimed to do
• When and how were they collected?	Not sure
• Are the variables of interest included in the dataset?	Some basic gestational age and vaccination data as well as some other descriptive data
• What is the level of data aggregation?	Individual
• What data cleaning procedures have been applied?	Cannot tell
• What sampling procedures were used?	All infants in defined cohort were eligible but some exclusion criteria are mentioned
Data analysis/results	
• Results expressed in terms of prematurity, birth weight or both?	Prematurity – birthweight is described but not analysed
• Degree of prematurity and/or birth eight classified?	Not really – just <33 weeks
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Being up to date – findings were that 70% of these infants were not up to date at 24 months
• Are predictors in rates or delay explored?	Hopsitalisation was studied along with oxygen therapy
Discussion	Gleaned only from the abstract, recommendations are to initialize vaccinations in hospital where due.
References	Relevant sources are cited

Elements influencing the credibility of the study	
Study details	Timeliness of immunisations in preterm infants in the Netherlands
Author(s)	Rouers et al. (2019) researchers are from paediatric, primary care and infectious disease backgrounds
Source	Vaccine
Writing style	Good
Report title	Good – covers what is to come
Abstract	Informative and structured as: background, methods, results and conclusion
Elements influencing the robustness of the research	
Purpose/research problem	Described in the introduction
Logical consistency	Yes, the format follows usual research report conventions
Literature review	Yes, there is evidence of this in the introduction
Theoretical framework	None cited
Aims/objectives/research question/hypotheses	Clearly cited at the end of the introduction as 'to describe the timeliness of routine Dutch national immunization schedule in preterm infants in their first year of life and to evaluate possible determinants of delay'
Sample	All preterm infants GA ≤36 weeks between October 2015 and Novemebr 2017. 276 in total: < 28 weeks = 79 28-32 weeks = 114 32-36 weeks = 83
Ethical considerations	Ethical approvals received and study registered on research database
Operational definitions	These are described

Methodology • Design	No specific design stated but data analysed was part of larger cohort study
Is secondary data used? If yes then consider: • Is there sufficient data?	Yes
• What was the original purpose for which the data were collected?	For ongoing evaluation of immunological protection in preterm infants
• When and how were they collected?	Parental questionnaires and medical records
• Are the variables of interest included in the dataset?	Immunisation data, pregnancy and delivery details, SES, length of hospital stay. Any medical diagnoses and teatments.
• What is the level of data aggregation?	Individual
• What data cleaning procedures have been applied?	None stated
• What sampling procedures were used?	All infants in defined settings eligible
Data analysis/results • Results expressed in terms of prematurity, birth weight or both?	Both although focus on gestational age
• Degree of prematurity and/or birth eight classified?	Yes – as defined in 'sample'
• Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)?	Vaccinated on time
• Are predictors in rates or delay explored?	Yes – some sociodemographic and lifestyle data studied
Discussion	Findings discussed in light of previous research and explanations for then are explored
References	Good detailed list

Elements influencing the credibility of the study	
Study details	A successful preterm vaccination program in a neonatal unit in a developing country
Author(s)	Tooke & Louw (2019)
Source	Heliyon
Writing style	OK – quite brief, paper only two pages long
Report title	Concise
Abstract	Succinct and clear
Elements influencing the robustness of the research	
Purpose/research problem	Problem outlined in the introduction
Logical consistency	Yes
Literature review	Some evidence that prior research has been considered
Theoretical framework	None stated
Aims/objectives/research question/hypotheses	Yes – clear and stated as objectives: to determine whether vaccines were given at the correct chronological age, to describe a administrative/ logistical problems and to record and side effects of vaccination
Sample	Timeframe for inclusion stated 60 in total – infants who were still inpatients by time of six- week vaccine
Ethical considerations	Approval received
Operational definitions	Defined as discussed
Methodology • Design Is secondary data used? If yes then consider: • Is there sufficient data? • What was the original purpose for which the data were collected? • When and how were they collected? • Are the variables of interest included in the dataset?	 Observational study Seems so for purpose of study Medical notes Entered onto Exel spreadsheet and required data extracted from the notes

• What is the level of data aggregation? • What data cleaning procedures have been applied? • What sampling procedures were used?	Individual None None – just those eligible included
Data analysis/results • Results expressed in terms of prematurity, birth weight or both? • Degree of prematurity and/or birth eight classified? • Results expressed as infants being up to date (rates) or vaccinated on time (age appropriate vaccination)? • Are predictors in rates or delay explored?	Both No Vaccinated on time Yes, reasons for late administration cited in results as oxygen dependency, unknown, concerns of sepsis and post-surgical procedure
Discussion	Quite brief, focusing on the achievements of the NNU in vaccinating preterm infants
References	Brief

Appendix 3 Review findings matrix

Birthweight	Gestational age
LBW = delayed start compared to NBW Delays greatest in <1000g but caught up by 24 months (Bary-Weisberg & Stein Zamir, 2021)	<28 more UTD (Crawford et al., 2009)
Timeliness lower in ELBW compared to NBW ELBW lower completion rates VLBW lower UTD rates compared to NBW (Batra et al., 2009)	No link between GA and delay (Davis et al., 1999, Tozzi et al., 2014)
No association between BW and UTD (Crawford et al., 2009)	Delay seen at 5 and 24 months, <28 weeks lower UTD (Denziot et al., 2011)
LBW = lower UTD at 24 months (Davis et al., 1999)	EGLANS late receipt of 1st HEXA and PCV (Fortmann et al., 2021)
LBW = greater age at vaccination but UTD at 24 months (Laforgia et al., 2018)	GA 23-33 & 34-36, lower UTD at 19 and 36 months (Hofstetter et al., 2019)
VLBW & MLBW had 1st 1nd 2nd doses later than NBW – only VLBW received 3rd dose later (Langkamp et al., 2001)	Lower GA = greater age at vaccination, but UTD at 24 months (Laforgia et al.)
Delay for lower BWs – 1st vaccines only (Magoon et al., 1995)	Delay for 1st vaccines only in low GA (Magoon et al., 1995)
Odds of completion at 24 months less for LBW, VLBW & ELBW (Nestander et al., 2019)	PTs less likely to get on time (all vaccines) (McKechnie & Finlay, 1999)
<1000g less likely UTD at 7 months compared to 1000-1500g – all vaccines apart from 2nd rota (Ochoa et al., 2015)	Lower odds of UTD when ≤32 weeks (Nestander et al., 2018)
Delays in LBW but not sig. by 3rd dose (Roper & Day, 1988)	<32 vaccines later than >32 and lower UTD at 7 months in same groups (Ochoa et al., 2015)
Findings = GA findings, timeliness worse in lowest (Rouers at al., 2019)	<33 7/10 incomplete at 24 months (Pinquier et al., 2009)
≤1500g – lower rates at 12 months (Ruiz et al., 1991)	PT = delays but UTD by 3rd dose (Roper & Day, 1988)
Median age increases as BW decrease for 1st and 3rd (Slack & Thwaites, 2000)	<28 less timely (1st vaccines only) (Rouers et al., 2019)
LBW = delay in HEXA (Tozzi et al., 2014)	Median age for 1st & 3rd higher as GA lower (Slack & Thwaites (2000)
ELBW higher median age at 1st vaccines (Woestenberg et al., 2014)	DTP rates lower for PT but higher for Hib & MMR (Tillmann et al., 2001)
	GA associated with lower rates when hospitalised (Wilson et al., 2012)

	EPT greater median age at 1st vaccines (Woestenberg et al., 2014)
Hospitalisation 2/3 not vaccinated on time (Bary-Weisberg & Stein-Zamir, 2021) >30 days + better UTD at 2 months (Crawford et al., 2009) Better UTS status (at 6 months) if stay = 8-14 days (Davis et al., 1999) Hosp = timelier vaccines (Fortmann et al., 2021) Longer stay = later vaccines (Laforgia et al., 2018) Prolonged stay = poorer timeliness (Rouers et al., 2019) Longer stay = higher median age of vaccination (Slack & Thwaites, 2000) LBW and hospitalisation = delay for MMR & HEXA (Tozzi et al., 2014) Lower rates for hospitalised infants (EPT at 2 & 4 months and VPT at 2 months) (Wilson et al., 2012) Vaccines in hospital on time EPT compared to PT (Woestenberg et al., 2014) Vaccines started in hospital = better coverage (Denziot et al., 2011)	Other diagnoses/treatments BPD & HMD no affect on UTD (Davis et al., 1999) SGA, inotropes, NEC surgery and O2 therapy on discharge = less timely vaccines (Fortmann et al., 2021) IVH predictor for delay (Magoon et al., 1995) Chronic ling disease = decreased odds of completion (Nestander et al., 2018) O2 therapy, sepsis concern and post-op procedures associated with late vaccines (Tooke & Louw, 2019) CP = delay for MMR (Tozzi et al., 2014) Other factors Male gender, unmarried mother, Jewish, non 1st born, and lower SES associated with delay (Bary-Weisberg and Stein=-Zamir, 2021) ELBW, VLBW, Hispanic ethnicity, black race, birth before 2001 associated with delay (SS) Batra et al., 2009) More well child visits = more UTD (Davis et al., 1999) As number of healthcare visits increased, so did UTD (Nestander et al., 2018) FU vaccine visit = more UTD (Denziote et al., 2011) Mothers not completed high school and no health insurance= lower UTD for VLBW (Langkamp et al., 2001) Parental education = no effect on delay (Magoon et al., 1995) Maternal unemployment = delay MMR, Paternal unemployment and number of sibs = delay HEXA (Tozzi et al., 2014)

	Lower SES = poorer timeliness (Rouers et al., 2019) Lower SES for EPT = higher rate of delay, and both parents born in Netherlands = less rate of delay (Woestenberg et al., 2014)

Appendix 4 Data management plan

University of Hull

Faculty of Health Sciences

Data Management Plan

(NB: This form should be completed <u>at the start</u> of all projects where data are <u>not being stored in alternative sources</u>, e.g. Clinical Trial Data held in the NHS). Shaded areas are considered essential.

Date	12th March 2019
Researcher(s)	Helen Sisson (PhD Candidate – referred to as Chief Investigator (CI) in this document) Dr Eric Gardiner (Supervisor 1) Professor Roger Watson (Supervisor 2)
Project title	An investigation to determine if vaccinations are delayed in preterm infants, and the factors associated with vaccination timeliness in preterm infants.
Brief description	This research is a contemporary investigation of the timeliness of vaccination in preterm infants along with any factors which might be associated with vaccination timeliness. It uses data from existing datasets, pertaining to approximately 5,000 individuals, comprised of full term and preterm infants.

Contents

Section 1: Project Information

Project title: An investigation to determine if vaccinations are delayed in preterm infants, and factors associated with vaccination timeliness.
1.1 Project duration Approximately 1st June 2019 – 1st October 2021
1.2 Partners (if applicable) N/A
1.3 Brief description This research is a contemporary investigation of the timeliness of vaccination in preterm infants along with any factors which might be associated with vaccination timeliness. It uses data from existing datasets, pertaining to approximately 6,000 individuals, comprised of full term and preterm infants.
1.4 Faculty or University requirements for data management Completion of data management plan prior to commencement of the research (with support from Research Services).
1.5 Funding body(ies) N/A although there are some costs – see 1.7
1.7 Budget (estimate if necessary) There are some costs associated with data extraction and data management. These are estimated at approximately £5,826.00 and are being met by the University.
1.8 Funding body requirements for data management Please see 1.7.

Section 2: Data, Materials, Resource Collection Information

2.1 Brief description of data sources

Data will be collected from three existing datasets:

1. Maternity Services Dataset (MSDS)

Infant details

NHS number
Date of birth
Gender
Birth weight
Gestational age

Parental details

Mothers' date of birth
Number of previous pregnancies/births
Ethnicity

2. National Neonatal Research Database (NNRD)

Infant details

NHS number
Date of birth
Birth weight
Gestational age
Reason for admission
Unit admitted to
Diagnosis at admission
Diagnosis at discharge
Discharged on oxygen
Date of discharge
Date of death

Parental details

Mothers' occupation
Fathers' date of birth
Fathers' ethnicity

3. Child Health Information Services (CHIS)

Infant details

NHS number
Date of birth

Immunisation data

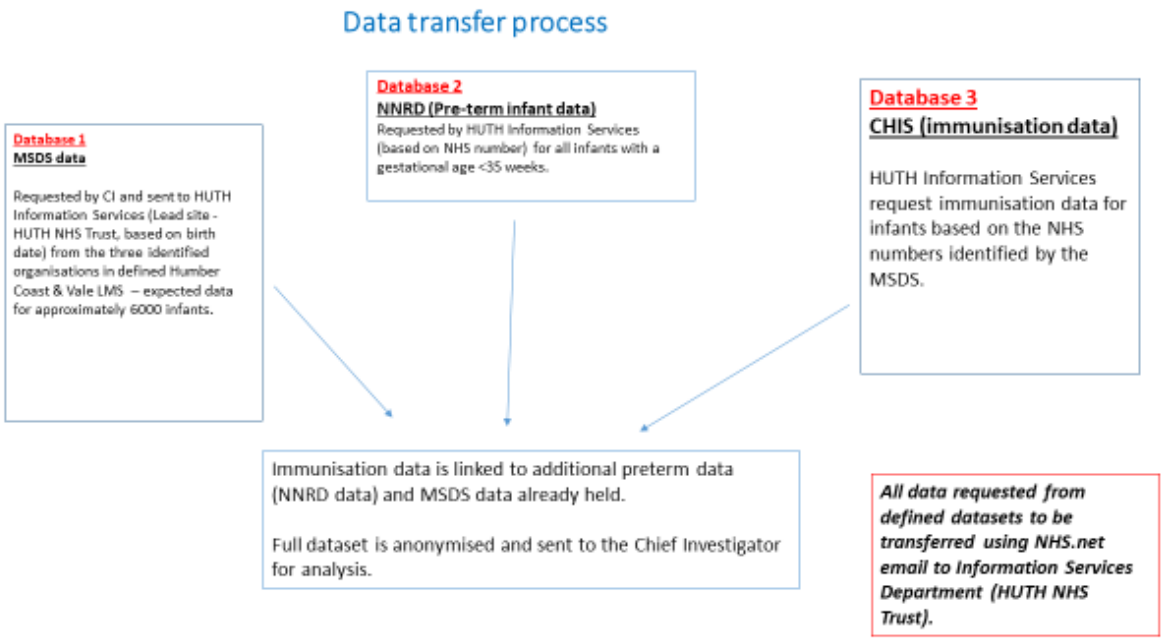
- Date of 8 week scheduled vaccines: DTaP/IPV/Hib & Hep B, PCV, MenB, Rotavirus
- Date of 12 week scheduled vaccines: DTaP/IPV/Hib & Hep B, Rotavirus

- Date of 16 week scheduled vaccines:

DTaP/IPV/Hib & Hep B, PCV, MenB

2.2 Data collection process

Each organisation involved in the study hosts a database which records all births, referred to as the Maternity Services Data Set (MSDS). Data from the MSDS will be requested from each of the hosting organisations, and held by Information Services at the lead site (Hull University Teaching Hospitals NHS Trust – HUTH NHS Trust). The data to be requested from the MSDS is detailed in section 2.1.
Using the NHS number (from data already obtained from MSDS), data for infants born <35 weeks will be requested from the National Neonatal Research Database (NNRD), so that additional information regarding the infants' health status and some demographics can be obtained. See section 2.1 for data to be collected.
Finally, and again using the NHS number, immunisation data will be requested from the Child Health Information Systems (CHIS); again details are in section 2.1. The data requested from CHIS will be for the defined six-month period for preterm and full term infants (for control purposes).



Data requested will be sent to the Lead site, HUTH NHS Trust for matching and anonymisation before being sent to the Chief Investigator at the University of Hull for analysis. For the purposes of this data management plan, the un-anonymised dataset held by HUTH NHS Trust is referred to as the primary dataset and the anonymised dataset sent to the CI for analysis, is referred to as the raw dataset. Based on ONS data (ONS, 2017) the sample size should be around 5,000 infants in total, a proportion of which will be classed as preterm (born before 37 weeks) and based on a preterm birth rate of 7.3% (NICE, 2015) this number is expected to be in the region of 420.

2.3 Will data be available in electronic format (if so then state format(s))?

The personal data used in this study are the participants' NHS numbers. These are required to match data from across the datasets and will not be seen at any stage by the CI, but will be stored by the lead site, HUTH NHS Trust. Anonymised study data will be sent to the CI electronically in an Excel format – this raw dataset will be transferred into SPSS for analysis. All electronic data will be held on a password protected University drive.
2.4 Will the data be available in hard copy (if so then state format(s))? No personal information will be stored either electronically or in hard copy by the CI. Nonetheless, any paperwork generated by the study will be kept in the CI's office in a locked cabinet.
2.5 Will the data stand alone and be comprehensible to a third party or be accompanied by explanatory documentation? The dataset held at the university will have accompanying information to define and explain its purpose. This additional information will be kept in a separate file.
2.6 Describe quality assurance process for data management The progress of the project will be monitored during bi-monthly supervision sessions.

Section 3: Ethics, Intellectual Property

3.1 How have the ethical aspects of data storage and subsequent access been addressed? • The primary dataset containing identifiable information (NHS numbers) will be kept securely by the lead site and subject to their data protection and information governance procedures – this is being addressed in the IRAS submission. • The raw dataset and any associated outputs will be held by the CI at the University under the conditions discussed in sections 2.3 and 2.4.
3.2 Will the data comply with relevant legislation such as Data Protection Act, Copyright and Intellectual Property? Yes. • Only data relevant for the project will be collected and stored appropriately (sections 2.1, 2.4. and 2.4). • The raw dataset and associated outputs will be kept for 5 years after completion of the project and will be stored appropriately for this duration. • Electronic data will be stored on a password protected University drive. Data will not be transferred to countries outside of the EEA.
3.3 If several partners are involved how will compliance with 3.2 be assured? The lead site is an NHS organisation bound by regulations/policies associated with data protection and information governance, and this is addressed in the accompanying IRAS submission.

Section 4: Access and Use of Information

4.1 Are you required, and with whom, to share the data subsequent to completion of the project? The analysed data will be written in a report and submitted for publication in scientific journals. The CI may also present the study's findings at conferences, and provide direction to the published report on selected social media.
4.2 If 'yes' to 4.1, in what format will data be shared? The final written report would be submitted for publication. No identifiable information would be used in the sharing of any study data (the CI will not have access to this in any case).
4.3 Will the data have to be stored for a specific period (if so, how long)? The raw dataset and associated outputs will be saved for 5 years. The primary dataset will be stored according to the lead site's policies and this addressed in the IRAS submission.
4.4 Who may need to have access to the data? The CI and supervisors will have access to the data for the analysis and write up of the project.
4.5 How do you anticipate the data being used subsequent to the project? At this stage, it is not anticipated that the raw data will be used after it has been analysed for this study. However, it is possible that it may be revisited for further analyses in the future.

Section 5: Storage and Backup of Data

5.1 Where and how will the data be stored **during the lifespan of the project?** Hardcopy Hardcopy of data will be stored in the CI's office at the University of Hull in a locked cabinet. This may include any printed copies of raw data and associated outputs. Electronic Electronic files (Excel and SPSS formats plus any other study information) will be password protected and saved on the CI's personal computer on the University network. *None of the raw data stored by the CI is identifiable.*
5.2 Where and how will the data be stored **on completion of the project?** It is anticipated that on completion of the project the raw data will be stored as in section 5.1. However, should the CI leave the University, then access to the data will be via a suitable repository determined by the University.
5.3 What provision is being made for backup of the data? Data will be backed up by secure University drives for the duration of the project.
5.4 Will different version of the data be stored? If different versions of data need to be stored, this will be done clearly, in a logical and chronological order.

Section 6: Archiving and Future Proofing of Information

6.1 What is the long-term strategy for storage and availability of the data? See section 5.2.
6.2 Will the information be kept after the life of the project, for how long and in what format? Information will be kept for 5 years after completion of the project under the conditions stated in section 5.2.
6.3 If the data include confidential or sensitive information, how will these data be managed? No confidential or sensitive information will be stored at the University.
6.4 If meta data or explanatory information is to be stored, how will this be linked to the data? Explanatory information regarding the dataset will be stored with it in case it is revisited for further analyses.
6.5 How will the data be cited? The explanatory information (section 6.4) will have details for citation purposes.

Section 7: Resourcing of Data Management

7.1 List the specific staff who will have access to the data and denote who will have the responsibility for data management. The CI will have responsibility for data management under scrutiny of the supervisors.
7.2 How will data management be funded? By the University of Hull.
7.3 How will data storage be funded? No additional costs of storage are anticipated and data will be held on University secure drives for the stated storage period.

Section 8: Review of Data Management process

8.1 How will the data management plan be adhered to? The plan outlined in this document has been written by the CI who will also implement the data management of this project. Furthermore, the CI will have bi-monthly supervision meetings where adherence to the plan can be monitored.
8.2 Who will review the data management plan? The CI and research supervisors will review this for the duration of the project. Additionally, for approval purposes, the plan will initially also be reviewed by the Faculty Ethics Committee.

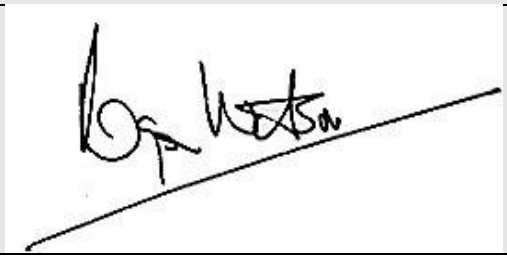
Section 9: Statements and Personnel Details

9.1 Statement of agreement

~~I~~/we agree to the specific elements of the plan as outlined:

Principal investigator or PhD supervisors

Title	Dr
Designation	Principal Supervisor
Name	Eric Gardiner
Date	4th April 2019
Signature	

Title	Professor
Designation	
Name	Roger Watson
Date	16 April 2019
Signature	

Researcher

Title	Miss
Designation	PhD Candidate & Chief Investigator
Name	Helen Sisson
Date	19/03/2019
Signature