Title page

Full title: Vaccination timeliness in preterm infants: an integrative review of the literature.

Concise title: Vaccination timeliness in preterm infants.

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Abstract

Aims and objectives. To take a systematic approach to reviewing the scientific literature examining the timeliness of vaccination in preterm infants and to identify any factors associated with timeliness.

Background. Preterm infants are vulnerable to infection and guidance advocates they are vaccinated in accordance with their full term peers. Vaccination is well tolerated and protective immune responses are observed, yet some early enquiries suggest that preterm infants experience unwarranted delays. The recent surge in pertussis cases and the increase in vaccinations administered make this a topic requiring further exploration.

Design. An integrative review of the empirical literature.

Methods. Studies were identified following a search of Medline, Academic Search Premier, Cochrane Database of Systematic Reviews and the Cumulative Index to Nursing and Allied Health Literature. The review methods used were influenced by a narrative synthesis approach. The retrieval of papers adhered to recognised reporting standards.

Results. Fourteen studies were identified, which indicated that infants with the lowest gestational ages and birth weights experience the greatest delays. Vaccination timeliness is influenced by hospitalisation, and increased post-discharge follow-up. There was a lack of consensus to indicate that parental socio-economic status and level of education were indicators for a delay. The studies propose that many delays are unjustified and not according to genuine contraindications.

Conclusion. This review indicates that preterm infants are not vaccinated in a timely manner. Those involved in vaccinating preterm infants must be informed of the genuine contraindications to avoid unnecessary delays putting preterm infants at an increased risk of infection.

Relevance to clinical practice. Care providers should acknowledge the risk of a delay in preterm infants and actively promote vaccination in this population. Regular training should help to negate the occurrence of inappropriate delays and careful discharge planning is needed to ensure that preterm infants are vaccinated on time.

What does this paper contribute to the wider global clinical community?

- Preterm infants experience delays in receiving their vaccinations but the delays are greater in those infants with the lowest gestational ages and the lowest birth weights. Vaccination timeliness is also associated with hospitalisation, and increased post-discharge follow-up. The influence of parental socioeconomic status on a delay requires further investigation.
- It is suggested that delays in vaccinating preterm infants are frequently unfounded rather than being in accordance with genuine contraindications. Strategies to address this issue may include increased follow up and better discharge planning and targeted education and information so that decisions about vaccinating preterm infants are made based on evidence and published guidance.

Keywords

Delay, immunisation, literature review, low birth weight, preterm, timeliness, vaccination.

INTRODUCTION

Vaccination is a fundamental public health activity, which globally is estimated to prevent between two and three million deaths each year (WHO, 2016a). Vaccination programmes are primarily aimed at infants and children because the burden of infectious disease in this population is vast with approximately 17,000 children from around the world under the age of five dying on a daily basis, often from infections which are avoidable through vaccination (UNICEF, 2016). Preterm infants are described as those born before 37 weeks gestation (WHO, 2015) and when compared to their full term counterparts, the risk of infection in this population increases nine fold (Sinha et al., 2012); furthermore and also in comparison to full term infants, preterm infants face an increased risk of diseases which are vaccine preventable (Bonhoeffer et al., 2006), emphasising the importance of vaccination. Data regarding preterm birth demonstrate a rate of about 8% in the UK (Royal College of Obstetricians and Gynaecologists, 2014), whilst in the US this is much greater at 11% (Centers for Disease Control and Prevention, 2014). However, the wider burden of preterm birth was less well known until the WHO and member states collaborated to publish an analysis of worldwide preterm birth estimates, and the findings of this analysis report a rate of 11.1% and indicate that there is a global increasing trend in preterm births (Blencowe et al., 2012). Nurses play a vital role in advising on and administering vaccinations, therefore given the increasing rate of preterm birth and the importance of vaccination in this vulnerable population, vaccination practices in preterm infants is a topic worthy of further critical examination. This paper presents a review of the literature investigating the timeliness of vaccination in preterm infants.

Background

Infants born prematurely are able to attain immunological responses to vaccination which are considered to be protective. Observed responses to the diphtheria, tetanus, pertussis, polio and

Hib components of the pentavalent vaccine and responses to the pneumococcal conjugate vaccine, both commonly administered in the first year of life, indicate that immunological protection is achieved; however for infants born prematurely, this level of protection does positively correlate with gestational age (Saari et al., 2003; Bonhoeffer et al., 2006; D'Angio, 2007). Similar findings are also reported for the meningococcal type C vaccine (D'Angio, 2007) and oral rotavirus vaccine (Omeneca et al., 2012), also both given in infancy. Preterm infants are capable of tolerating the administration of vaccines and Bonhoeffer et al. (2006) cite similar rates of vaccination associated side effects in preterm infants to those seen in their full term counterparts. However, some studies report an increase in respiratory and cardiac symptoms in preterm infants post vaccination, although this increase is associated with previous history of the symptoms (Klein et al., 2008; Hacking et al., 2010). The symptoms observed post vaccination in preterm infants are predominantly self-limiting and a period of observation may be appropriate (Schulzke et al., 2005; Faldella et al., 2007). However, when the increased infection risk associated with prematurity is considered, such side effects are no justification for withholding vaccination (Esposito et al., 2009).

Globally, policy advocates that preterm infants are vaccinated in accordance with their full term peers (The American Academy of Pediatrics, 2015; Australian Government, 2016; Salisbury and Ramsay, 2014). Nonetheless, despite well-established vaccination programmes resulting in respectable uptake rates, some early enquiries have suggested that preterm infants are not being vaccinated in a timely manner (Vohr and Oh, 1986; Wariyar et al., 1989). Given that preterm infants are particularly vulnerable to infection, the changes made to the vaccination schedule globally in response to the development of new vaccines and epidemiological data, and the recent surge in pertussis cases in infants which saw a 15% increase in the US between the years of 2013 and 2014 (CDC, 2015), this is an issue worthy of further contemporary investigation. Several studies have been undertaken to explore this issue,

and this review presents a synthesis of their findings which is guided by the work of Popay et al. (2006).

The review

AIMS

The aim of this integrative review was to undertake a search of the scientific literature guided by a narrative synthesis approach (Popay et al., 2006) investigating the timeliness of vaccination in preterm infants. More specifically, the review aims to answer the questions: (1) is there a delay in the vaccination of preterm infants?, and (2) what are the factors associated with vaccination timeliness in preterm infants? Owing to a substantial level of heterogeneity across the selected studies regarding methods and outcomes, a more traditional meta-analysis approach associated with systematic reviews was not possible. This review presents a narrative synthesis of the literature referring to the guidance by Popay et al. (2006) which consists of four elements; developing the theory, preliminary synthesis, exploring relationships and assessing the robustness of the synthesis. It is emphasised that these four elements are not undertaken sequentially and reviewers should move between them in an iterative manner (Popay et al., 2006).

METHODS

To identify relevant studies, the electronic databases Medline, Academic Search Premier, Cochrane Database of Systematic Reviews and the Cumulative Index to Nursing and Allied Health Literature were systematically searched using pertinent terms including ‘vaccination’, ‘preterm’, ‘delay’ and associated synonyms. The titles and abstracts of the identified sources were reviewed and excluded if they were not primary studies with a quantitative design, did not feature preterm infants, were not peer reviewed or did not recognise published guidance on the recommendations for the vaccination of preterm infants. Additional inclusion criteria were that the studies needed to be in English and focus on routine scheduled vaccines. To facilitate

a comprehensive review, there were no limitations on year or place of publication, this would also identify any trends over time. The sources which met these criteria were subjected to further review by accessing the full text versions.

Search outcome

For the retrieval of the relevant studies, the Preferred Reporting System for Systematic Reviews and Meta-analyses (PRISMA) (Moher et al. 2009) was adhered to (Figure. 1). Following the removal of duplicates (n=128), the initial search identified 761 sources. After screening the titles and abstracts, a further 713 sources were excluded for not meeting the inclusion criteria leaving 48 to be assessed by full text. At this stage, an additional 34 sources were excluded for reasons including not being a primary source, not available in English and not being focused on preterm infants. This left 14 studies for inclusion in the review. No additional relevant studies were identified via reviewing the reference lists of identified studies or citation searching. The entire search and identification of relevant studies was undertaken by one author (HS). In accordance with the inclusion criteria, the identified studies adopted quantitative designs and were undertaken in the United Kingdom (UK), United States (US), Australia, Italy, France, Canada, Switzerland and The Netherlands between the years of 1988 and 2014. A summary of the studies included in the review is presented in Table 1.

Quality appraisal

The quality appraisal of the studies was guided by the stage termed by Popay et al. (2006) as assessing the robustness of the synthesis. An element of this included best evidence synthesis, described as an assessment of the studies' methodological quality. Popay et al. (2006) recognise the variety of methods used by studies in a review and therefore rather than recommend a single approach to appraisal, a systematic approach in assessing study quality is advocated. Consequently, undertaking the quality assessment in this review, necessitated the use of two

approaches; initially the appraisal framework developed by Coughlan et al. (2007) for quantitative studies was used, but to supplement this the work of Mongan (2013) was incorporated (Table 2). Mongan (2013) specifically questions the quality of secondary data sources, which was deemed entirely appropriate given that nine out of the fourteen studies included in the review used secondary data. Whilst the quality appraisal highlighted differences in both the methods used and the outcomes observed across the studies, they were all considered to be of adequate methodological quality to be included in the review, therefore none were excluded at this stage.

Data abstraction and synthesis

The quality appraisal stage as previously described required the identification of key methodological data, and this meant that the processes of quality appraisal and data extraction naturally overlapped. Relevant data from all included studies were captured using a template (Table 2) which was specifically developed for the review, and included features defined by Coughlan et al. (2007) and Mongan (2013). In addition to the information captured in Table 1, the template facilitated the extraction of data concerning the methods used within the studies. Popay et al. (2006) describe the element of preliminary synthesis as an initial description of the included studies where patterns across them begin to emerge; an element which was facilitated by this data abstraction. As the studies were analysed using a narrative synthesis approach, this stage of the review was significantly guided by the elements described by Popay et al. (2006) as preliminary synthesis and exploring relationships. More specifically, the processes of tabulation, developing groupings and clusters, vote counting and data translation facilitated the analysis.

RESULTS

Description of included studies

The process of tabulation and the development of groupings and clusters were activities in the synthesis which identified similarities and differences between the concepts defined in each of the studies. Given that the studies were all addressing the timeliness of vaccination in preterm infants, the concepts explored at this stage were vaccination, preterm infants and timeliness. The vaccinations studied depended on the schedule in the countries where the studies were undertaken, but they all included the combined diphtheria, tetanus and pertussis vaccine. All but four studies included the *Haemophilus influenza* type b vaccine (Langkamp et al., 2001; Roper & Day, 1988; Ruiz et al., 1991; Woestenberg et al., 2014) and except for three studies (Roper & Day, 1988; Ruiz et a., 1991; Slack & Thwaites, 2000), the remainder included polio vaccination in their analyses. Other vaccines investigated across the studies included hepatitis B (*n*=3) (Batra et al., 2009; Crawford et al., 2009; Tozzi et al., 2014), pneumococcal conjugate vaccine (*n*=4) (Crawford et al., 2009; Denziot et al., 2011; Tozzi et al., 2014; Wilson et al., 2012), meningococcus type C vaccine (*n*=3) (Crawford et al., 2009; Slack & Thwaites, 2000; Toxxi et al., 2014), measles, mumps and rubella combined vaccine (*n*=6) (Crawford et al., 2009; Davis et al., 1999; Langkamp et al., 2001; Magoon et al., 1995; Tillmann et al., 2001; Tozzi et al., 2014) and varicella vaccine (*n*=2) (Crawford et al., 2009; Tozzi et al., 2014). The definition of prematurity also varied between the included studies, but most of them defined full term as ≥37 weeks gestational age. Some studies used a combination of gestational age and birth weight to identify infants (Davis et al., 1999; Roper & Day, 1988; Tillmann et al., 2001; Woestenberg et al., 2014), whereas others used either gestational age only (Crawford et al., 2009; Denziot et al., 2011; McKechnie & Finlay, 1999, Slack & Thwaites, 2000; Tozzi et al., 2014 Wilson et al., 2012) or birth weight (Batra et al., 2009; Langkamp et al., 2001; Magoon et al., 1995). One study classified infants by risk, where one of the criteria for being high risk was a birth weight of less than or equal to 1500g Ruiz et al., 1991). Of those using birthweight alone, in the majority of studies, normal birth weight was defined as ≥2500g. Eight of the studies used data

from one or more neonatal units (Crawford et al., 2009; Denziot et al., 2011; Magoon et al., 1995; McKechnie & Finlay, 1999; Roper & Day, 1988; Ruiz et al., 1991; Slack & Thwaites, 2000; Tillmann et al., 2001) three used regional data (Batra et al., 2009; Davis et al., 1999; Wilson et al., 2012), and three used national data (Langkamp et al., 2001; Tozzi et al., 2014; Woestenberg et al., 2014). The way in which timeliness of vaccination was interpreted between the studies also varied. Some explored age specific vaccination status, expressing the findings in terms of the infants being up to date at a defined age, whereas others compared uptake rates between full term and preterm infants. Some also measured the extent of any delays, reporting the differences between full term and preterm infants in mean days. All of the studies acknowledged the clinical importance and recommendations of vaccinating preterm infants without delay and in accordance with guidance. This review presents a narrative synthesis of data concerning 149,754 preterm or low birth weight infants and 1,910,388 full term or normal birthweight infants from across the included studies.

Main findings

The preliminary synthesis element of the guidance by Popay et al. (2006) suggests the processes of vote counting and data translation in the identification of findings. Vote counting is described as a method of calculating the frequency of different results across the studies (Popay et al., 2006) and although this review does not attempt to synthesise the results of the studies using statistical methods, an element of this was adopted by grouping similar findings. This activity naturally drew on the stage described by Popay et al. (2006) as translating data (a process akin to thematic analysis), and the additional element of exploring relationships (Popay et al., 2006). As a result, the findings expressed are grouped into the themes of gestational age and birth weight, hospitalisation, and infants and family characteristics.

Gestational age and birth weight

Two studies observed an overall delay in vaccination uptake in preterm infants, and relative to full term infants, preterm infants had lower up-to-date statuses (Denziot et al., 2011; Tillmann et al., 2001). A similar association between gestational age and lower rates of vaccination was reported by Wilson et al. (2012) but only in conjunction with the infant being hospitalised. This is in contrast to the finding that hospitalisation meant that infants with a gestational age of <28 weeks were significantly more likely to be up-to-date at 2 months (Crawford et al., 2009). Magoon et al. (1995) reported a significant delay for the first vaccinations which increased as gestational age decreased and this trend was also observed for the second and third vaccinations by McKechnie and Finlay (1999). Slack and Thwaites (2000) found that median age at first and third scheduled vaccinations negatively correlated to gestational age, and a higher median age at first vaccination in extremely preterm infants (<32 weeks) relative to full term infants was observed by Woestenberg et al., (2014). Of significance is the finding that as gestational age decreased, delays in vaccination increased and up-to-date vaccination rates were lower (Magoon et al., 1995; McKechnie & Finlay, 1999; Slack & Thwaites, 2000). Two of the studies did not find an association between gestational age and delays or up-to-date rates (Davis et al., 1999; Tozzi et al., 2014).

Infants with an extremely low birth weight (ELBW) consistently experienced substantial delays in vaccination relative to normal birth weight (NBW) infants, and these infants were also considerably less up-to-date compared to NBW infants (Batra et al., 2009). However, the same study did not find a significant difference in delays or up-to-date rates between low birth weight (LBW) and NBW infants. These findings are comparable with others where it is reported that very low birth weight (VLBW) and moderately low birth weight (MLBW) infants received their first and second scheduled vaccinations later than NBW infants (Langkamp et al., 2001). Similarly, the rate of vaccination at one year for high risk infants (which included those with a birth weight ≤1500g) was substantially lower than infants in the normal and low risk categories

(Ruiz et al., 1991). A further study found that extremely low birth weight infants had a higher median age at first vaccination relative to NBW infants (Woestenberg et al., 2014) and compared to their NBW peers, LBW infants also experienced delays in the administration of the first scheduled vaccines (Roper & Day, 1988; Magoon et al., 1995).These findings support the observation of an important negative correlation between median age at first and third vaccination and birth weight (Slack & Thwaites, 2000). These studies featuring birth weight report findings which are consistent; low birth weight is associated with delays in vaccination and lower up-to-date vaccination status. Some of the studies reported that the lowest birth weight infants experienced the greatest delays and were less likely to be up-to-date (Magoon et al., 1995; Slack & Thwaites, 2000; Batra et al. 2009).

The associations between gestational age, and birth weight and vaccination timeliness are important observations. Despite variability in the methods used and the quality of the studies involved, the frequency and consistency of their occurrence strengthens these findings. Of equal importance is the date range of the relevant studies with the earliest being published in 1988 (Roper & Day) and the most recent in 2014 (Woestenberg et al.), suggesting that the association between prematurity, birth weight and vaccination timeliness is a long standing issue.

Hospitalisation

Several of the included studies included hospitalisation in the analyses and demonstrated how this may influence vaccination patterns in preterm and low birth weight infants; however, a lack of consensus was apparent. Although the details of the findings between studies differed, some of them suggested that in certain circumstances, hospitalisation promotes timely vaccination (Crawford et al., 2009; Davis et al., 1999; Woestenberg et al., 2014). Alternatively, other findings associated hospitalisation with delays and lower up-to-date vaccination rates

(Wilson et al., 2012; Tozzi et al., 2014; Slack and Thwaites, 2000). The methodological quality of these studies was not in question, suggesting that further investigation of the impact of hospitalisation on vaccination timeliness is needed.

Infant and family characteristics

One study explored ethnicity and race in relation to vaccination statuses of low birth weight infants. When compared with white infants, ELBW and VLBW infants from all other ethnicities and races demonstrated significantly lower up-to-date vaccination levels (Batra et al., 2009). Magoon et al. (1995) did not find an association between delays in vaccination and level of parental income, but this finding is refuted by a later study where it was reported that VLBW infants of mothers who had completed high school were significantly more up to date than infants of mothers who did not (Langkamp et al., 2001). Two population based studies reported that a lower socio-economic status was associated with lower vaccination rates (Langkamp et al., 2001; Tozzi et al., 2014) although this finding is at odds with the observation that a lower family income was associated with greater up-to-date vaccination levels (Denziot et al., 2011). In spite of this latter finding, the strength of the two large population based studies by Langkamp et al. (2001) and Tozzi et al. (2014) signifies that this is an important finding.

Additional findings

Vaccination rates and timeliness in preterm infants was also considered to be influenced by the follow up care the infant received post discharge, where improved rates were seen in those children who received more than the standard number of well-child visits (Davis et al., 1999; Denziot et al., 2011). Some studies asked respondents directly about their practice or how they decided whether or not to vaccinate. Ninety-five per cent of neonatologists surveyed confirmed that there was a local policy in place to support timely vaccination of preterm infants, but the survey also revealed a lack of adherence to the policy (Crawford et al., 2009). Earlier enquiries

dating from the 1990s reported that family practitioners were more likely to deviate from the recommended schedule and that parental reasons to withhold vaccination included low gestational age, low birth weight and minor infections (Magoon et al., 1995). Some primary healthcare providers cited concerns over their own liability, based on the perceived risk of neurological injury as a reason to withhold vaccination in preterm infants (Ruiz et al., 1991).

DISCUSSION

The findings of this review reveal a strong association between a delay in vaccination and gestational age or birth weight. Some of the studies focussed on birthweight as the independent variable, where others concentrated on gestational age. With the exception of three of the studies (Ruiz et al., 1991; Batra et al., 2009; Langkamp et al., 2001) the remainder indicated an association between birth weight and gestational age. Low birth weight is not always suggestive of prematurity; infants may be born at term small for gestational age (Lissauer & Clayden, 2012). However, prematurity is a leading cause of low birth weight (WHO, 2016b), therefore, in their entirety, the findings of all of the studies contribute to this review.

It is suggested that delays may not be due to true contraindications rather, that inappropriate worries relating to gestational age or birth weight may be the cause (Roper & Day, 1988). Illnesses associated with prematurity may warrant a delay although this is unlikely to extend beyond the date of the first vaccination (McKechnie & Finlay, 1999) and the increased respiratory symptoms experienced by some preterm infants may prompt further unwarranted delays (Slack and Thwaites, 2000). This suggests that targeted education and information aimed at parents and practitioners, which focusses on the importance and effectiveness of vaccination, is justified. Although only a feature of one study, the biggest delays are reported among non-white ELBW infants (Batra et al., 2009). Greater delays are also reported among those infants from a lower socio-economic background (Langkamp et al., 2001; Woestenberg

et al., 2014). The delay seen in non-white preterm infants reflects previous investigations suggestive of a link between lower socio-economic status and poor access to healthcare services; being from a non-white ethnic background is associated with under-vaccination in infants irrespective of prematurity (Rainey et al., 2011).

Hospitalisation was seen as both a facilitator and a barrier to vaccination in preterm infants. The increase in age appropriate vaccination reported in hospitalised infants which was found by Crawford et al. (2009), Davis et al. (1999) and Woestenberg et al. (2014) may be attributed to the monitoring these infants receive whilst inpatients, increasing their chances of being vaccinated on time. Conversely, hospitalisation was reported as increasing the chances of preterm infants experiencing a delay by Wilson et al. (2012), Tozzi et al. (2014) and Slack and Thwaites (2000), and this may be related to the reason for hospitalisation; an unstable health status or concurrent problem which presents a true contraindication to vaccination may be present. However, prematurity itself is not a contraindication to vaccination (Salisbury & Ramsey, 2013), so it is vital that legitimate contraindications are understood by health care providers. Again, the necessity of education is highlighted here, and it is recommended that practitioners regularly acquire contemporaneous information regarding vaccination in preterm infants, so that decisions made in practice are evidence based.

Discharge planning is a crucial influence on vaccination uptake. There is a suggestion that parents want their children to ‘have a rest’ after discharge by delaying vaccination, and that vaccination is not prioritised in discharge care plans (Tillmann et al., 2001). In addition, the transfer of care for the infant from the hospital to the community setting may give rise to confusion over who is responsible for administering the vaccination (Woestenberg et al., 2014), indicating the importance of coordinated discharge planning. One of the studies noted improved future coverage if the vaccination schedule had been initiated on the neonatal unit (Denziot et al., 2011), and 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.

An increase in vaccination uptake was noted in those infants who received more than the standard number of visits post-discharge (Davis et al., 1999; Denziot et al., 2011). This finding was also associated with low-income; in one study, infants of families with social difficulties including low income, were routinely offered mother-infant welfare visits, during which vaccination status was addressed (Denziot et al., 2011). In the UK, policy has standardised contacts with all children under the age of five regardless of prematurity, and these contacts are an opportunity for primary health care providers to address vaccination status (Department of Health, 2009). However, the identification of any overdue vaccines still relies on the parents having the means and motivation to take their children to be vaccinated. Domiciliary vaccination is recommended for those families experiencing difficulties accessing services but this is not a service which is offered consistently in the UK (National Institute for Health and Care Excellence, 2009).

None of the studies in this review were located in low-income countries and with the exception of five studies (Batra et al., 2009; Davis et al., 1999; Langkamp et al., 2001; Magoon et al., 1995; Ruiz et al., 1991) which were undertaken in the United States, the remainder were located in countries offering some form of universal health coverage (Rodin & de Ferranti, 2012). This may impact on accessing health services and vaccination uptake in general across all sections of the population and could therefore, have influenced the findings of these studies.

This review has some limitations. The heterogeneity of the studies included meant that a more traditional meta-analysis was not possible, and whilst narrative synthesis is considered a legitimate method of analysis there were some elements of the synthesis which were considered

inappropriate, and other elements were adapted prior to use. It is possible that in this interpretation and adaptation of the elements suggested by Popay et al. (2006), some objectivity has been lost. Furthermore, the searching and identification of the studies included in the review was undertaken by one author and no inter-rater agreement was achieved. This may have compromised the inclusiveness and relevance of the studies included.

The methodological quality assessment of the included studies highlighted some of the limitations associated with the use of secondary data, namely 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. A final limitation concerns vaccine hesitancy generally. This review has focused on vaccination timeliness and associated factors in preterm infants, yet there is an increasing need to better understand the reasons for vaccine hesitancy across the population (WHO, 2017), and the scope of this review means that this has not be addressed.

CONCLUSION

This integrative review aimed to answer the questions: (1) is there a delay in the vaccination of preterm infants?, and (2) what are the factors associated with vaccination timeliness in preterm infants? The process of narrative synthesis guided the analysis of the studies included and the following conclusions can be drawn: firstly, the studies used a variety of methods to investigate the topic but overall, they support the notion that vaccinations are delayed in preterm infants. Low birth weight is a strong indicator of a delay and given that prematurity is a leading cause of low birth weight, gestational age as an indicator must also be acknowledged. Certain family characteristics were associated with a delay, more specifically, the level of parental education and income. In accordance with previous population based enquiries, some

studies found that a lower level of education and income meant that a delay was more probable in preterm infants. Others found the opposite, and postulated that this was more than likely due to the increased amount of follow up support visits these families receive. The findings of the review suggest that increased follow up, targeted education and information, and better discharge planning may be strategies employed to increase vaccination uptake and rates in preterm infants.

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 nurses enact policies aimed at populations of unspecified individuals (Verweij & Dawson, 2007); equally, the decision to vaccinate a preterm infant in the acute care setting is likely to be based on clinical judgement centred on individual infants. Therefore it is vital that vaccination rates in this population along with an understanding of the barriers and facilitators are fully understood so that nurses and parents alike are supported in making informed decisions which are in the interests of those in their care.

RELEVANCE TO CLINICAL PRACTICE

Care providers need to be aware that preterm infants face an increased risk of a delay in being vaccinated. Therefore, health promotion strategies concerning vaccination should ensure inclusion of this population. Inappropriate delays in vaccinating preterm infants should be avoided by attendance at regular vaccination training and education events. Finally, thorough discharge planning for preterm infants must ensure a seamless transfer between services to avoid the risk of any vaccination delays.

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Figure 1: Study selection flowchart (PRISMA)

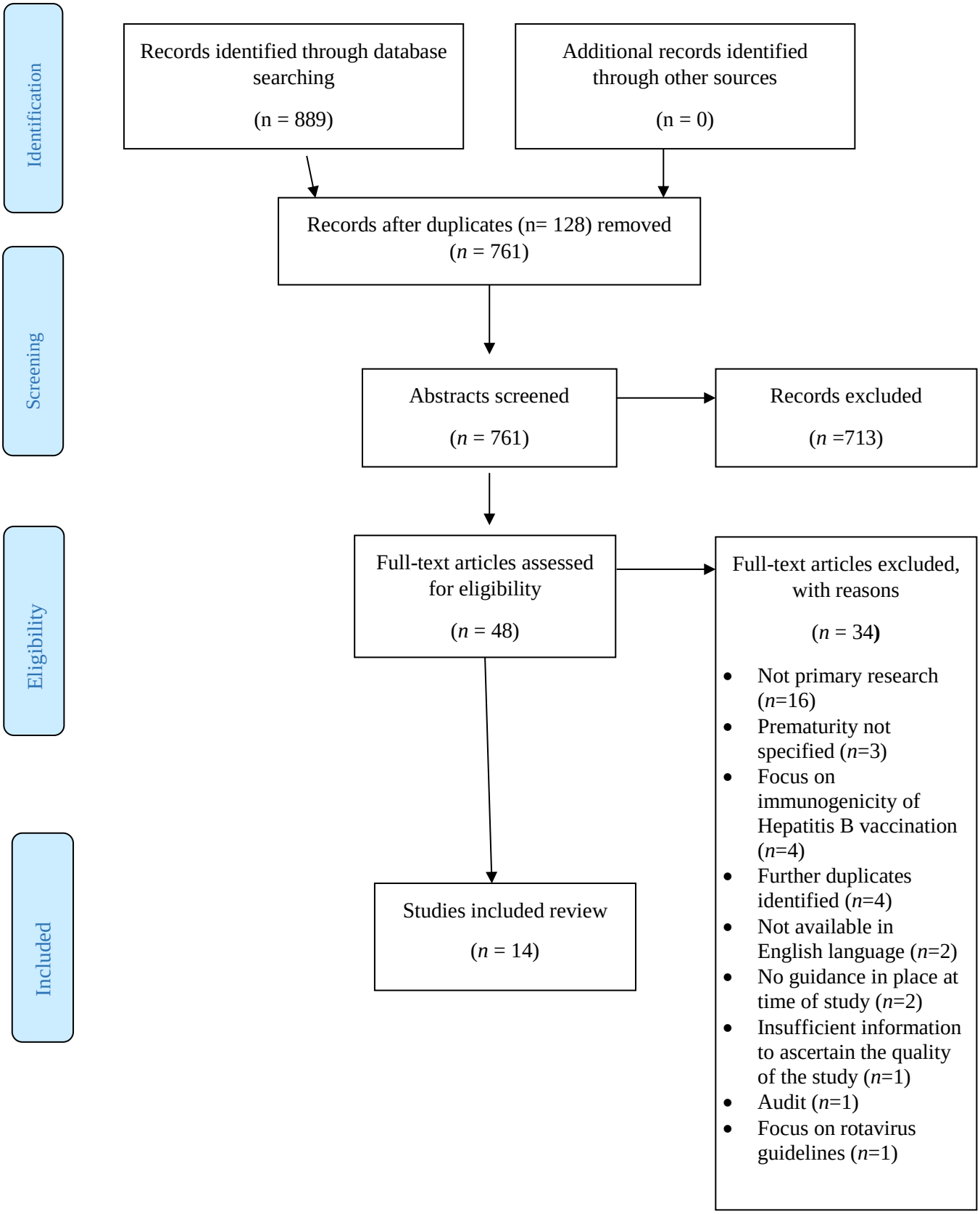

Table 1. Summary of studies included in the review.

Author, year, country	Title of Study	Study design	Main outcomes	Sample size	Limitations
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.	Retrospective cohort analysis.	Age specific up to date and age appropriate immunisation rates by birth weight in first year of life.	ELBW n=506, VLBW n=788, LBW n=6491, NBW n=120,048	Potential misclassification of data from existing database used in study.
Crawford et al. (2009) Australia	Immunisation practice in infants born prematurely: Neonatologists' survey and clinical audit.	Retrospective audit.	Up to date immunisation status at 2, 4, 6, 12 and 18 months.	100 preterm infants	No evidence of questionnaire testing for validity or reliability.
Davis et al. (1999) US	Immunization Levels Among Premature and Low-Birth-Weight Infants and Risk Factors for Delayed Up-to-Date Immunization status.	Cohort & case/control analyses.	Age specific immunisation status by prematurity and birth weight, and characteristics associated with timeliness.	LBW n=11,580 NBW n=173,373	Unclear how 'up-to-date' vaccination status is defined.
Denziot et al. (2011) France	Hospital initiation of a vaccinal schedule	Secondary data analysis and survey.	Up to date immunisation status at 5 and 24 months.	602 preterm infants	Unable to determine quality of data from database used and lack

	improves the long-term vaccinal coverage of ex-pre-term children.				of clarity regarding how the survey was developed.
Langkamp et al. (2001) US	Delays in Receipt of Immunizations in Low-Birth-Weight Children.	Logistic regression analysis	Age at receipt of first 4 doses of DTP vaccines, first 3 polio vaccines and first MMR vaccine for MLBW, VLBW and NBW infants. Up to date status also examined at 12, 24 and 36 months for infants in all weight categories.	VLBW n= 447 MLBW n= 648 NBW n= 7,190	Lack of more contemporary data.
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.	Survey	Immunisation delays of more than 2 weeks in high risk infants, significant predictors of delays and practices among primary care providers.	153 preterm infants	Questionnaire used not tested for validity and reliability.
McKechnie and Finlay (1999) UK	Uptake and timing of immunisations in preterm and term infants.	Retrospective secondary data analysis	Mean vaccination age for preterm and full term infants at primary schedule (2, 3, and 4 months).	110 preterm infants 220 full term infants	The 220 controls used were term infants also admitted to the unit, but the 'normal' health status of these infants cannot be confirmed so their value as a control could be compromised.

Roper and Day (1988) UK	Uptake of immunisations in low birthweight infants.	Retrospective secondary data analysis	Percentage uptake of first and third doses of primary immunisations by gestational age and birth weight.	LBW n= 395 NBW n= 3426	Authors acknowledge there were some missing data.
Ruiz et al. (1991) US	Pertussis Immunization Patterns in Special Care Nursery Graduates.	Survey	Complete versus incomplete immunisation status in high risk and low risk infants at 1 year of age.	38 'high risk' infants (includes infants with BW ≤1500g) 89 'low/normal risk' infants	Small sample and poor survey response rate, especially in the high risk group.
Slack and Thwaites (2000) UK	Timing of immunisation of premature infants on the neonatal unit and after discharge to the community.	Retrospective case/control study	Median age at first and third doses of primary schedule by gestational age and birth weight.	212 preterm infants 153 controls	Completeness and accuracy of secondary data sources cannot be determined.
Tillmann et al. (2001) Switzerland	Vaccination rate and age of premature infants weighing <1500 g: a pilot study in north-western Switzerland.	Retrospective case/control study	Age in days of first 4 scheduled doses of DTP, Polio, Hib and first MMR in preterm and full term infants.	60 preterm infants 60 full term infants	No information regarding the development of the questionnaire.
Tozzi et al. (2014) Italy	Timeliness of routine immunization in a population-based Italian cohort of very preterm infants: Results of	Prospective cohort study	Proportion of children who had received at least 1 dose of HEXA, Pnc, MenC, MMR and Var at 24 months of age.	1102 preterm infants	Much of the follow up data relied on parental recall and compliance.

	the ACTION follow-up project.				
Wilson et al. (2012) Canada	On-time Vaccination Coverage in Premature Infants in Ontario, 2002-2009.	Secondary data analysis	Proportion of children (by gestational age) who had received at least 1 vaccination during the 2, 4 , and 6 month visits within recommended time frame.	65,687 preterm infants 782,917 full term infants	Original purpose of the database from which the study data were extracted is unclear.
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.	Secondary data analysis	Individual age at first scheduled vaccination visit and median age at 5^{th} and 95^{th} percentiles by gestational age and birth weight.	60,835 preterm infants 822,912 full term infants	Researchers were restricted by the amount of variables to study.

Table 2. Appraisal framework.

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, 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?	
Discussion	
References	