Vaccinating preterm infants: why the delay?

Premature infants are at an increased risk of infection and vaccination is recommended for these children in accordance with the routine schedule. Despite this guidance, evidence suggests that vaccination in this population is often delayed. This article explores the benefits, risks and rates of vaccination in preterm infants.

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Key points

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1. In the UK, vaccination is recommended for all infants who are eight weeks' old, regardless of prematurity.
2. Preterm infants are able to mount a protective immune response to vaccination.
3. Preterm infants are vulnerable to infectious diseases and vaccination is a vital intervention in the prevention of infection in this population.
4. Evidence suggests that vaccination rates in preterm infants are lower than those seen in term infants.

The benefits of vaccination

Since the introduction of routine vaccination in the UK and globally, its benefits have been widely reported. Cases of diseases once considered commonplace are now rarely seen[1] and in some cases eradication has been achieved[2]. Vaccination programmes primarily target children under five years of age, as this is where the burden of disease lies[1]. In the UK during the second reporting quarter of 2013, the proportion of children being fully immunised for all scheduled vaccinations at the age of 12 months was above 95%[3], indicating that the childhood immunisation programme is acceptable to the vast majority of parents and carers. Routinely, vaccination is advocated for all children from the age of eight weeks (**TABLE 1**) and current guidance stipulates very few exceptions to this recommendation[4].

In the UK, the United States, Canada and Australia, it is recommended that preterm infants should receive their vaccinations according to their chronological age and not their gestational age[4-7]. Premature infants are a population at an increased risk of morbidity and mortality from vaccine-preventable diseases[8-10] and although empirical evidence indicates that antibody responses may be suboptimal in preterm infants, a response which is generally recognised to be protective is achieved in the majority[8,11]. However, there are data which suggest that vaccination rates are lower in preterm infants when compared to term infants[10,12-14]; this may be due to reports associated with an increase in adverse reactions, such as respiratory deterioration[11,15]. Given the significance of vaccination for preterm infants, it is worthwhile revisiting this vital intervention in such a vulnerable population.

Prematurity and birth weight

The World Health Organization (WHO) defines a preterm infant as a live birth prior to week 37 of pregnancy. This is further categorised into:

- moderate to late preterm (32 to <37 weeks' gestation)
- very preterm (28 to <32 weeks' gestation)
- extremely preterm (<28 weeks' gestation)[16].

Similarly, low birth weight is also categorised into:

- low birthweight (LBW), for infants weighing less than 2500g at birth

Child's age	Diseases protected against	Administration route
8 weeks	Diphtheria, tetanus, pertussis (whooping cough), polio, Hib (DTaP/IPV/Hib)	Intramuscular (IM) injection
	Pneumococcal disease (PCV)	IM injection
	Rotavirus	Oral
12 weeks	Diphtheria, tetanus, pertussis, polio, Hib (DTaP/IPV/Hib)	IM injection
	Meningococcal group C disease (MenC)	IM injection
	Rotavirus	Oral
16 weeks	Diphtheria, tetanus, pertussis, polio, Hib (DTaP/IPV/Hib)	IM injection
	Pneumococcal disease (PCV)	IM injection

TABLE 1 UK immunisation schedule 2013/2014 (up to four months of age).

- very low birthweight (VLBW), referring to infants weighing less than 1500g at birth
- extremely low birthweight (ELBW), where infants are born weighing less than 1000g[17].

While a low birth weight is not indicative of prematurity, there is a strong correlation and the majority of infants born prematurely have a birth weight which decreases in accordance with gestational age.

Infection and preterm infants

Maternal IgG antibody transfer begins as early as 13 weeks *in utero*, but the vast majority of transfer occurs in the final trimester with a significant increase after 36 weeks' gestation. This passive antibody transfer is remarkably efficient and the cord blood of term infants shows levels of IgG that correlate with maternal levels[18]. This transfer is more successful for protection against some infections than others; for example it is more effective for measles and tetanus and less so for polio and pertussis[4]. Yet this means that infants born prematurely and prior to this transfer do not benefit from this passive protection and even those that do, see these levels drop dramatically in the first weeks of life[4].

Due to the immaturity of the newborn's immune system, the risk of infection is higher than the rest of the population[18,19]; a risk which is further increased in premature infants[17]. In terms of vaccine-preventable infections, data from a study of pertussis risk in LBW children demonstrated that this population was significantly more likely to have reported a pertussis infection when compared to children of a normal birth weight[20]. Furthermore, the risk of infection in VLBW infants was even greater. However, this study refers to LBW and VLBW infants and the association between birth weight and the extent of prematurity in this sample can only be assumed. Explanations for the differences in rates of reporting pertussis focus on the transmission of infection and it is also suggested that reporting rates in LBW children may be higher due to increased parental and medical surveillance in this population[20]. In 2009, the National Institute for Health and Care Excellence (NICE) produced guidance aimed at reducing differences in the uptake of immunisations[21]. In this, preterm infants are not specifically referred to, however children who are hospitalised or have a chronic illness are considered to be at risk of not completing the immunisation schedule.

Preterm infants are at an increased risk of infection. Their prematurity could mean that they have not benefitted from maternal antibody transfer and the immune system may not be sufficiently mature, increasing susceptibility to infection[17]. However in terms of vaccine-preventable diseases, the empirical data available focus only on pertussis[20]. UK guidance reports the possibility of some children not receiving the full complement of vaccinations, yet it may only be assumed that this includes preterm infants. These factors emphasise the vulnerability of preterm infants and underline the importance of interventions such as vaccination to prevent infection in this population.

The preterm infant's response to vaccination

Studies reporting on the immune response to certain vaccines provide a good indication of the preterm infant's ability to respond to vaccination:

DTaP/IPV/Hib

Immune responses to all of the components of this vaccine are satisfactory in preterm infants, however protective levels decrease as prematurity increases[8,22,23]. The Hib component has variable results which appear to depend on the schedule used, particularly if it is an accelerated schedule (two, three and four months, as in the UK), but since the publication of these studies, an additional dose of Hib has been introduced at 12 months. An earlier study observed good levels of protection against diphtheria, tetanus, pertussis and polio[11], although the date of this study (1989) indicates that whole cell pertussis and live attenuated polio vaccination were given, and that at this time the vaccine schedule also commenced at three months rather than two. It is worth noting, there is uncertainty regarding what is considered to be a protective correlate against pertussis[24].

MenC

Lower but acceptable responses have been observed with this vaccination[8] even in VLBW infants[22]. However, similar to Hib, these findings may also depend upon the scheduling of vaccination[25] and, since the publication of these findings, the UK has amended the schedule so that rather than two, three and four months, MenC is now given at three and 12 months.

PCV

Although preterm infants demonstrate an immunogenic response considered to be protective to the pneumococcal conjugate vaccine (PCV7)[8,22,23], this is lower than in term infants. However, changes to the scheduling of this vaccination and the replacement of the 7-valent pneumococcal vaccine with a 13-valent version mean that these data are now debatable[25].

Rotavirus

The most recent addition to the childhood vaccination schedule in the UK is the rotavirus vaccine and data on its immunogenicity in preterm infants are limited. However, one study reports that the preterm infant's response to this vaccine is comparable to that of a term infant[26].

All of the above studies focus on the vaccine's ability to provoke an immune response (immunogenicity) in premature infants, but this is not the same as the efficacy of the vaccine – its ability to reduce the incidence of disease[27]. Although in vaccine development immunogenicity is generally relied on as a predictor for vaccine efficacy[28]. Furthermore, the continual updating of the childhood vaccination schedule means that any data on the immunogenicity of these vaccines in preterm infants is quickly outdated. Overall the data suggest that these vaccines are able to provide an effective level of protection for preterm infants, confirming the value of timely vaccination in these children.

Adverse reactions

The available data suggest that preterm infants are at an increased risk of adverse events following vaccination. An increase in respiratory symptoms, frequently reported as apnoeic episodes, is commented on[15,29-33] as are bradycardia and desaturation[15,33]. Nevertheless the studies also report that the adverse events are of limited clinical significance and should not be an influencing factor in the decision to immunise. It is recommended that preterm infants undergo a period of cardio-respiratory monitoring post-vaccination[15,29,30,32,33].

Rates of vaccination in preterm infants

Several studies have reported a positive correlation between delayed vaccinations and preterm and LBW infants[10,12-14,34-41]. Additionally, the greater the prematurity and lower the birth weight, the more likely

it is that vaccination will be given later than recommended[37-39]. Although vaccination may have been administered on time while the infant was an inpatient, there is an indication that subsequent doses following the infant's discharge can be delayed[13,36,39]. Conversely, Wilson et al found that vaccination rates among preterm infants in the community were similar to those of term babies[34] but that rates were lower if the child was hospitalised at the time the vaccination was due. Of these reports on vaccination rates in preterm infants, only three have been produced using data from the UK[13,38,41] and the most recent of these is 14 years old[13]. Additionally the studies tend to focus on the primary immunisations, which do not include those scheduled for 12-13 months and beyond.

Vaccination may be justly delayed in some cases when a preterm infant's unstable condition contraindicates[4]. While there is little empirical evidence to draw on to explore other reasons for delay, some suggestions are made in the literature. For instance, concerns over prematurity and LBW from parents and health professionals[13,37,41] and the presence of persistent symptoms exhibited in the preterm infant[13,37,38] are both given as reasons for delay. Alternatively, delay may be the result of parents and health professionals being misinformed about when to commence vaccination[13,35] and the perceived fragility of premature infants[35].

Conclusion

Recommendations to vaccinate preterm infants in accordance with the routine schedule are not always adhered to. Although premature babies are at an increased risk of infection, studies indicate that vaccination is often delayed in this population. While it is reported that the risk of cardio-respiratory symptoms following vaccination is greater in preterm infants, these symptoms tend to be self-limiting and monitoring is considered to be an appropriate response to this risk. However, there are no recent UK data on vaccination rates in this population and little empirical evidence which explores the reasons why vaccination may be delayed. Therefore, there is a need for further investigation to identify any necessary strategies aimed at increasing vaccination in this vulnerable population.

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