REVIEW

Immunisation of premature infants

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Premature infants are at increased risk of vaccine preventable infections, but audits have shown that their vaccinations are often delayed. Early protection is desirable. While the evidence base for immunisation of preterm infants is limited, the available data support early immunisation without correction for gestational age. For a number of antigens the antibody response to initial doses may be lower than that of term infants, but protective concentrations are often achieved and memory successfully induced. A 2-3-4 month schedule may be preferable for immunisation of preterm infants in order to achieve protection as early as possible, but an additional dose may be required to achieve persistence of protection. This update focuses on the use of routine childhood vaccines in premature infants.

Four million infants (2.2 million between 1 and 6 months of age) are estimated to die annually of infection. Many of these infections are vaccine preventable or may shortly become so (for example, rotavirus). Preterm and low birth weight infants are at increased risk of infections in general and suffer from an increased frequency and severity of vaccine preventable infections. The need for timely vaccination of preterm infants is therefore great. However, vaccination is more likely to be delayed in preterm than in term infants.[1 2]

Unfortunately, the evidence base for immunisation of preterm infants is limited. Most studies are small and differ in demographics, inclusion and exclusion criteria, vaccine combinations used, and schedules. Data on long term protection and vaccine efficacy are particularly scant. This review focuses on established vaccines and the evidence base for their use in preterm infants.

The problem

The risk of neonatal sepsis correlates inversely with gestational age. Twenty per cent of hospitalised very low birth weight infants suffer from one or more systemic infections.[3] With regard to vaccine preventable infections, over 50% of reported cases of pertussis occur in infants and low birth weight infants are at particular risk (RR 1.86; 95% CI 1.33 to 2.38) when compared to normal birth weight infants.[4] Invasive pneumococcal infections account for up to 11% of neonatal sepsis, and preterm and low birth weight infants are at increased risk of pneumococcal disease compared to term infants.[5] Preterm infants are also at increased risk of influenza virus infections.[6]

The immune response of infants

Antibody responses

Successful immunisation against bacterial infection relies on the induction of antibodies to prevent mucosal colonisation and invasive disease, or to neutralise toxins. For viral infections, cell mediated cytotoxic effects and cytokine release may be required in addition to antibody formation. Although IgG can be produced in utero, the response in infants is both qualitatively and quantitatively different to that of adults. The main reasons for this are the immaturity of the immune system and the presence of maternal antibody.

A gradual maturation of antibody responses is seen over the first 2 years of life.[7] Antibody responses are particularly limited against most polysaccharide antigens up to 2 years of age.[8–11] The increasing capacity to mount antibody responses is reflected in the response to vaccines. For example, one dose of Hib (*Haemophilus influenzae* type b) conjugate vaccine is significantly more immunogenic at 4–6 months of age than at 2–3 months of age and a single dose at 15–23 months generates significantly higher antibody concentrations than three doses given in the first 6 months of life.[12–14] Similarly, a single dose of measles vaccine induces significantly higher antibodies at 9–12 months than at 6 months of age.[15] The later the third dose of a vaccine series is given, the higher the final antibody response. For example, responses to hepatitis B vaccine (Hep B) when given at 0, 1, and 2 months of age are significantly lower at 7 months of age than when given at 0, 1, and 6 months of age (although protective concentrations are achieved earlier at the accelerated schedule).[16] The relative importance of older age at last vaccine dose versus increased interval between vaccine doses is not clear. These limitations of infant antibody responses may directly limit vaccine efficacy, as observed in South America where a protein vaccine against *Neisseria meningitidis* group B protected 74% adults and 47% children but no infants.[17–19]

Another limitation of the infants' antibody responses is their relatively short duration; most

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Abbreviations: AEFI, adverse events following immunisation; DTaP, diphtheria-tetanus-acellular pertussis vaccine; DTwP, diphteria-tetanus-whole cell pertussis vaccine; GMC, geometric mean concentration; GMT, geometric mean titre; Hep B, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio vaccine; MenC, meningococcal group C conjugate; MMR, measles-mumps-rubella; PCV, pneumococcal conjugate vaccine; PPD, purified protein derivative

infants will have low vaccine induced antibody concentrations again 6–9 months after vaccination.[20] This may translate into a limited duration of vaccine protection as suggested by the waning effectiveness against Hib and MenC (meningococcal group C conjugate) following the UK accelerated primary infant schedule without a booster dose.[21]

In addition to the limitations of the magnitude and duration of vaccine antibody responses, there are qualitative differences between infant responses and those elicited later in life. However, there is little evidence to suggest that these differences limit the response capacity or affinity maturation process.[22] For example, the induction of antigen specific memory B cells can be achieved in early life, even during the neonatal period.[23] The implication of this is that although antibody levels may decline to even non-protective levels after infant vaccination, they may be boosted to reach protective levels rapidly after exposure or re-vaccination.[24]

Another important determinant of infant antibody responses is inhibition by maternal antibody. This has been documented for a number of antigens and both live and non-live vaccines (for example, measles, varicella, influenza, pertussis, Hib). The mechanism proposed is binding of maternal antibody to epitopes of the antigen, thereby preventing access of infant B cells to these epitopes (epitope masking).[25] As with any competitive process, the ratio of maternal antibody to antigen concentrations is critical in defining the degree of antibody suppression.[26]

T cell responses

Adult-like antigen specific T cell responses can be achieved earlier than B cell responses. For example, BCG immunisation at birth elicits comparatively stronger INF-γ (that is, T cell) than IL-5 (that is, B cell) responses that are similar to adult responses.[27] However, early life T cell responses are also subject to immune maturation.[28] For example, stronger purified protein derivative (PPD) responses are seen when BCG vaccination is delayed from birth to 2–6 months of age.[29] Immaturity of antigen presenting cells is considered a critical determinant of early infant T cell responses: the response of neonatal dendritic cells to in vitro activation by Toll-like receptor ligands is incomplete and results in limited IL-12 responses as compared to adult responses.[30 31]

T cell responses and immune memory are largely unaffected by the presence of maternal antibody.[32] It is hypothesised that the immune complexes formed of maternal antibody and antigen are taken up and processed by infant antigen presenting cells with subsequent engagement of CD4/8 cells in the usual way. For example, measles specific INF-γ responses in measles vaccinated infants are independent of the presence of maternal antibody and a reduction in measles mortality and morbidity is evident despite a failure to seroconvert in the presence of maternal antibody.[33 34]

The immune response of preterm infants

Many aspects of the infants' immune system immaturity will be more pronounced in preterm infants. At 8 weeks of age (that is, the age at first immunisation), preterm infants have lower absolute counts of lymphocytes, T cells, B cells, and T helper cells and a lower CD4/CD8 ratio than term infants. By the age of 7 months (that is, after the completion of primary immunisation), B cell numbers in the preterm group have reached term equivalent, but the reduced absolute lymphocyte count, total T cell count, and T helper count persist.[35] The range of antigens recognised by preterm B cells may also be limited when compared to term infants, because intense development of the B cell receptor repertoire actually occurs during the third trimester of pregnancy. However, there are no data supporting limited responsiveness and there is intriguing evidence that premature exposure to antigens can accelerate this development. The significance of this is that infants born at 28 weeks' gestation may actually have a more diverse antibody repertoire by the time they reach ''term'' than infants who are born at term.[36] This provides one theoretical argument against delayed immunisation of preterm infants.

Table 1 presents data from a vaccine study demonstrating the competing influences of gestational age, maternal antibody, and age at third vaccination on the vaccine response of preterm infants.[37] In particular, it demonstrates the independent and critical effect of gestational age on antibody responses to vaccine antigens.

One physiological reason why premature infants may respond better to vaccination than anticipated is the kinetics of transplacental transfer of maternal antibody. Maternofetal transport of IgG commences around the 17th gestational week, is at equilibrium around the 33rd week, and reaches up to twofold higher values in the neonate at term.[38] Thus, preterm infants, depending on their gestation, will have low or absent concentrations of maternal antibody. While this in part explains susceptibility to infections, it may provide an advantage in response to vaccines.

Another consideration in the immune response of preterm infants is the possible impact of iatrogenic factors. Preterm infants are exposed to corticosteroids, both antenatally and postnatally, and may receive blood and immunoglobulin transfusions during their neonatal stay. It is conceivable that any of these might impair the immune responses of preterm infants. While some studies report satisfactory responses to immunisation with DTaP (diphtheria-tetanus-acellular pertussis) and Hib in infants treated with steroids for chronic lung disease, other studies suggest that postnatal steroid administration may suppress antibody responses to DTwP (diphteria-tetanus-whole cell pertussis), Hep B, and Hib.[37 39–43] In one study, post immunisation Hib antibody levels appeared to be significantly lower in infants receiving steroids for chronic lung disease (geometric mean concentration (GMC) 0.51; 95% CI 0.25 to 1.4) compared to those who did not (GMC 4.63, 95% CI 2.10 to 10.22).[40] However, if there is an effect of neonatal steroid therapy it may not be long lasting. In a recent opportunistic study investigating former premature infants who were immunised with a single meningococcal serogroup C conjugate vaccine at 13 months of age, infants who had received steroids in the neonatal period did not appear to have attenuated immune responses compared with those who had not.[44] Administration of antenatal steroids does not seem to reduce the responses to MenC vaccine.[45] Based on the available evidence, there is no good justification to delay immunising steroid treated infants, as the demonstrated benefit of early protection of many infants outweighs the added benefit of potentially improved antibody responses of some infants.

Table 1 Percentage change in IgG titre per unit change

	Gestational age (weeks)	Pre-immunisation IgG levels (IU/ml)	Age at third vaccination (weeks)
Diphtheria	+2.2†	−4.5	+1.1
Tetanus	+7.1*	−18.3**	+5.3**
Pertussis			
FHA	+5.9*	−17.0*	+2.2
PRN	+7.4*	−36.4**	+5.6**
PT	+10.6**	−11.3	+0.9

Competing influences of gestational age, maternal antibody, and age at third vaccination on the vaccine response of PT infants.[37] FHA, filamentous haemagglutinin; PRN, pertactin; PT, pertussis toxin.
†Example: 2.2% increase in diphtheria IgG for each week of gestational age at birth.
*$p<0.05$; **$p<0.01$.

There are limited data on the impact of blood transfusions or immunoglobulin infusions on the antibody responses of premature infants. Stepwise logistic regression identified significantly reduced antibody responses to a first dose of Hib immunisation given to low birth weight infants who had received intravenous immunoglobulin in one study.[43] In the same study, administration of blood transfusions and fresh frozen plasma did not reduce antibody responses to Hib when analysis was controlled for gestational age.

Safety

Vaccine safety assessment in preterm infants is particularly challenging due to the frequency of adverse events intrinsically associated with prematurity. It appears that the risk of adverse events following immunisation (AEFI) in preterm infants cannot be predicted by gestational age or birth weight alone (or in combination) or by age at immunisation. However, the clinical condition (that is, underlying disease affecting cardiorespiratory stability) at the time of immunisation is associated with an increased relative risk of AEFI.[46] For example, in an observational study evaluating the safety of hexavalent vaccines (DTaP-IPV-Hib) involving 78 preterm infants, immunisation triggered transient cardiorespiratory events in 47% of infants (15% apnoea, 21% bradycardia, 42% desaturations). Infants with pre-existing cardiorespiratory symptoms appeared to have a fivefold to eightfold higher relative risk of cardiorespiratory events post immunisation.[46] In a retrospective study involving 53 infants, transient apnoea or bradycardia was observed in 13% of infants following immunisation with pentavalent or hexavalent vaccines. A higher rate of fever (>38℃) following immunisation was observed in affected infants (3/7 *v* 2/46, p = 0.01).[47] While severe episodes of apnoea have been reported in temporal relation to DTwP immunisation of infants of <31 weeks' gestation,[48] this seems less frequent and less severe following DTaP.[46 49–52] Studies of the heptavalent pneumococcal vaccine have shown that preterm infants (32–36 weeks' gestation) had more fever, vomiting, irritability, tenderness, and swelling than term infants.[5] Data on serious AEFI of preterm infants are summarised in table 2.

Well controlled studies are needed to confirm these results and to further delineate the indication, modalities, and duration of monitoring required for preterm infants following immunisation. While the observed AEFI do not seem to have a negative impact on the infants' clinical course, monitoring all preterm infants still hospitalised in neonatal units at the time of immunisation seems prudent. An observation period of 48 h post-immunisation has been proposed based on the distribution of AEFI in this population.[46] Observation does not appear to be required when preterm infants are considered clinically stable and discharged from the neonatal unit prior to 60 days of life. Infants scheduled for discharge between 50 and 60 days of age may benefit from NICU immunisation if this reduces the likelihood of a possibly marked delay before the first vaccine dose is eventually administered in a non-NICU setting. Preterm infants with severe cardiorespiratory events following the first vaccine dose do not seem to remain at higher risk of such events at the time of second immunisation (C-A Siegrist, unpublished observation). However, until more evidence on the incidence of clinically significant cardiorespiratory events after the second vaccine dose is available, cardiorespiratory monitoring may be considered for infants sent home after significant reactions to the first vaccine dose.

Studies evaluating the immunisation of preterm infants have comparatively small numbers and optimisation of data comparability between studies would add to the value of the collected data. To standardise immunisation safety assessment of maternal and neonatal immunisation, the Brighton Collaboration (http://brightoncollaboration.org), an international organisation aiming to standardise vaccine safety research, is currently developing guidelines for neonatal vaccine safety studies to improve the accuracy and completeness of collection, analysis, and presentation of vaccine safety data.[53] These guidelines will also be applicable for preterm infants. As multiple factors exert combined and complex influences on vaccine responses of preterm infants, future studies should include multivariate analyses controlling for potentially relevant factors. This includes factors affecting both prenatal (gestational age, weight, titres of maternal antibodies at time of immunisation, administration of steroids, etc) and postnatal (age/weight at first and at last immunisation, administration of IgG or steroids, etc) maturation.

Specific vaccines

Diphtheria-tetanus-acellular pertussis (DTaP)

Safety and immunogenicity of DTaP has been shown with schedules commencing at 2 months of age.[50] While protective antibody responses to D and T are achieved even in preterm infants of 25–35 weeks' gestation, antibodies against aP (pertussis toxin, filamentous haemagglutinin) may be significantly lower in preterm compared to term infants. The significance of this is uncertain, as pertussis antibody levels do not correlate well with clinical efficacy. In recent studies of pentavalent and hexavalent DTaP containing combination vaccines, preterm geometric mean titres (GMTs) approximated term levels for all relevant pertussis antigens.[54 55]

Table 2 Transient serious adverse events following immunisation of PT infants

Vaccine	n	Mean gestational age	Cardiorespiratory events	F/U	Comment
DTwP[49]	97	28.1 weeks (range 24–34)	20%	24 h	A/W younger GA, longer IPPV, CLD
DTwP±Hib[79]	98	<32 weeks	17%	24 h	Not A/W GA, birth weight
Hib, Hep B, DTaP, IPV[80]	48	26.4 weeks (SD 1.7)	No change in apnoea, no serious AEFI	48 h	
DTwP+Hib[48]	97	<37 weeks	12% had recurrence of apnoea 11% had >50% increase in apnoea, bradycardia	72 h	A/W lower birth weight, more severe apnoea previously, CLD
DTwP, Hib, Hep B[81]	79	28 weeks (SD 2) (range 24–33)	30% abnormal cardiorespiratory signs	72 h	Unrelated to CRP and IL-6 elevations, 48 h sufficient F/U time
DTaP, IPV, Hib[46]	78	28 weeks (SD 2)	47% transient apnoea, bradycardia, and/or desaturation	48 h	
DTaP, IPV, Hib, Hep B[47]	53	28 weeks (range 25–30)	13% transient apnoea, bradycardia	72 h	Associated with febrile illness

AEFI, adverse events following immunisation; A/W, associated with; CLD, chronic lung disease; CRP, C-reactive protein; F/U, follow up; GA, gestational age; IL-6, interleukin 6; IPPV, inspiratory positive pressure ventilation; n, sample size.

Inactivated polio vaccine (IPV)
Safety and immunogenicity of IPV in preterm infants was shown at schedules commencing at birth and at 2 months of age.[56 57] The response of preterm and term infants was comparable.[57] As a component of a hexavalent vaccine, 100% seroconversion rates for polio serotypes I, II, and III were observed in preterm and term infants. However, GMTs for all serotypes were significantly lower in preterm infants (term/preterm GMT ratio: serotype I: 1.8 (95% CI 1.28–2.61), II: 1.36 (95% CI 0.93–2.00), III: 2.58 (95% CI 1.75–3.80)).[54] As part of a pentavalent product, lower responses were seen in preterm infants for serotypes II and III although protective titres were achieved.[55]

Haemophilus influenzae type b (Hib)
Safety and immunogenicity of Hib in preterm infants has been shown at a number of different schedules commencing at 2 months of age.[58] Hib antibody levels may be lower in preterm infants compared to term infants after the first two doses.[58] This remains true after the third dose for accelerated schedules of Hib immunisation at 2-3-4 months.[45 59] However, for extended schedules at 2-4-6 and 2-4-12 months, concentrations after the third dose approach those of term infants.[58 60]

Protective antibody levels are generally accepted as being above 0.15 μg/ml for short term protection and 1 μg/ml for long term protection.[61 62] The appropriateness of these levels for conjugate vaccines in premature infants remains to be determined.

Long term follow up studies have demonstrated the persistence of antibody concentrations above 0.15 μg/ml after 3 and 7 years following a four dose regimen for both preterm and term infants. At 7 year follow up, overall GMCs are significantly lower in preterm infants and a lower percentage of preterm infants have concentrations above 1 μg/ml (62 *v* 75%).[63] Analysis of Hib antibody avidity in preterm infants demonstrates that avidity maturation occurs after vaccination and suggests that memory is induced. This is particularly so for individuals who mount a response >0.15 μg/ml after primary vaccination.[64]

The only available data relating to efficacy are based on invasive Hib disease occurring in vaccinated preterm and term infants.[20] This study included 165 vaccine failures of which 18 were in former preterm infants. The risk ratio was 1.5 (95% CI 0.9 to 2.6) suggesting a modest increase in vaccine failure, which was probably explained by the lower antibody concentrations seen in preterm infants vaccinated at this accelerated three dose schedule.

Hepatitis B (Hep B)
Routine Hep B immunisation at birth is recommended by a number of countries, with the schedule dependent on maternal Hep B status. One study showed that seroconversion rates in preterm infants <2000 g were lower if the first dose was given at birth but comparable to term infants if the first dose was deferred until the infant reached 2000 g or 60 days of age.[65] Several subsequent studies have shown that protective levels of anti-HBs antibody are achieved in almost all preterm infants following the third dose when the first dose is given after 30 days of age, regardless of gestational age and birth weight.[66] Antibody levels of preterm and term infants are then maintained in a similar fashion at 3 and 7 years of age.[63 67] It is important to stress that infants of HBsAg positive mothers should be immunised at birth regardless of their gestational age. In recognition of the lower seroconversion rates that may be seen in very low birth weight infants, a pragmatic approach recently recommended in the UK is to additionally provide hepatitis B specific immunoglobulin to all babies <1500 g born of carrier mothers (regardless of their e antigen status).[68] For babies born to carrier mothers serological evaluations should be considered after the primary hepatitis B schedule to identify those who have inadvertently become infected as well as those who may require additional vaccine doses.

Meningococcal group C conjugate (MenC)
The only data available on MenC vaccines in preterm infants is based on a 2-3-4 month schedule. Two studies have shown this vaccine to be safe and immunogenic. While GMTs following primary vaccination were lower in preterm compared to term infants, differences were not significant and antibody persistence to 12 months was similar for preterm and term infants.[45 69] Memory responses were seen in both groups, albeit with a trend towards a lower response in preterm infants.

Pneumococcal conjugate vaccine (PCV)
Several studies have demonstrated the safety and immunogenicity of a 7 valent conjugate pneumococcal vaccine when used at different schedules: 2, 4, 6, and 12 months; 3, 5, and 11 months; and 2, 3, and 4 months of age. A recent Italian study found no significant difference in antibody levels to PCV7 vaccine serotypes between term and preterm infants after a three dose vaccination schedule given at 3, 5 and 11 months.[70] Of note, only healthy preterm infants of >32 weeks' gestation who had not received any blood products or treatment likely to affect the immune response were included in this study. Similarly, the large efficacy study of the 7 valent conjugate pneumococcal vaccine in the United States enrolled only healthy preterm infants (gestational age not defined) who had been discharged home by 2 months of age. The immunogenicity of all vaccine serotypes were found to be *higher* in preterm than term infants and the efficacy against invasive pneumococcal disease was equivalent to that of term infants.[5] In contrast, a UK study included all preterm infants and vaccine was administered at 2, 3, and 4 months of age. Virtually all preterm infants had post primary antibody concentrations well above the threshold expected to provide protection against invasive pneumococcal disease. However, absolute concentrations were lower in preterm infants than in term infants. These reduced antibody concentrations persisted until 1 year of age as well as after the booster dose, although a memory response was evident in preterm infants.[71]

Measles-mumps-rubella (MMR)
MMR vaccine given to term infants before 9 months of age results in reduced seroconversion rates.[72] This is also seen in infants in whom maternal antibody has waned, suggesting that the major influence is immune immaturity. As the transfer of maternal antibody is dependent on the gestational age of the infant, passive protection is lost early in preterm infants. A recent study indicated that antibodies to measles were already absent at birth in 62% of preterm versus 29% of term infants.[73] In another study, most preterm infants of less than 28 weeks' gestation had lost maternal antibodies by 3 months of age.[74] Consequently, MMR immunisation may be recommended earlier (that is, at 6–9 months) to preterm infants at risk of exposure to measles. The second dose of MMR can be given as early as 1 month after the first. However, to allow for a more mature immune response, a second dose 3 months after the first appears to be preferable. As yet, there are no published studies assessing responses of preterm infants to early MMR immunisation.

Influenza
There is a paucity of data on the safety, immunogenicity, and efficacy of influenza vaccination in both preterm and term infants. Preterm infants were shown to develop significantly lower antibody and cell mediated immune responses

compared to term infants at 6 months to 4 years of age. However, responses to haemagglutinin antigen were dose dependent and when responses were measured by haemagglutination inhibition antibody assays, almost all infants developed GMTs of ⩾1:32 (a level thought to correlate with protection), independent of gestational age.[75 76]

Due to the lack of data on the safety and immunogenicity of influenza vaccines administered to infants less than 6 months of age, vaccination of this age group is currently not recommended. Vaccine induced protection of preterm infants <6 months of age may be achieved by a cocooning strategy in which all family members receive influenza immunisation. From 6 months onwards, a two dose schedule is required for the primary immunisation against influenza, whereas a single dose is sufficient for annual vaccination thereafter.

What is the best vaccine schedule for preterm infants?

A number of different immunisation schedules have been used in preterm infants. Due to the gradual maturation of the immune system in early life, the later a single dose is given, the later the last dose in a primary immunisation series is given, and the wider the intervals between doses, the higher are the respective post immunisation antibody titres.[7 16 64 77] It is conceivable that an accelerated 2-3-4 month schedule may achieve protective concentrations earlier (for example, at 5 months of age) than the more extended 2-4-6 and 3-5-11 month schedules that are commonly used in other countries. However, particularly for less immunogenic antigens, antibody levels are likely to be lower following the third immunisation of an accelerated schedule, with less persistence of antibody at 12 months of age when compared with the extended schedules.[63 77] This suggests that a booster dose is likely to be critical for preterm infants vaccinated at a 2-3-4 month schedule. There is a paucity of studies that allow direct comparisons between different vaccine schedules for preterm infants to be made. Data comparability across trials is challenging due to different study populations, vaccines, blood sampling ages and intervals following immunisation, and antibody assays used. Comparative studies using standardised methods for the assessment of safety, immunogenicity, and efficacy of vaccines administered to preterm infants at different schedules are needed to inform best practice.

The UK Department of Health has recently announced a change to the vaccine schedule for term infants.[78] Two doses of MenC at 3 and 4 months of age will replace the current three doses at 2, 3, and 4 months of age with a third dose at 12 months of age (as a Hib/MenC combination vaccine). The current Hib schedule at 2, 3, and 4 months of age is unchanged, but a fourth dose at 12 months of age is added. The 7 valent PCV is to be incorporated into the schedule with three doses to be given at 2, 4, and 13 months of age. There are no changes to the schedule for D, T, aP, IPV (three doses at 2, 3, and 4 months of age). There is no official guidance yet with regard to preterm infants and no published data on their responses at this new schedule. The available data suggest that antibody responses to D, T, aP, IPV will be satisfactory and the additional doses of Hib and MenC vaccines should improve the duration of protection offered by these vaccines. Additional studies are required to address the immunogenicity of pneumococcal and meningococcal C conjugates when given at a two dose schedule (2-4 and 3-4) in the first 6 months of life and especially the persistence of antibody through to their respective third (booster doses). A direct comparison with a 2-3-4 month schedule would be of interest as the latter may be preferable for those born preterm. Pending the availability of further evidence, a suggested schedule for the immunisation of preterm infants is included in table 3.

Table 3 Suggested schedule for preterm infants

Schedule	Vaccine				
2 months	DTaP-IPV	Hib	PCV7	(MCC)	
3 months	DTaP-IPV	Hib	(PCV7)	MCC	
4 months	DTaP-IPV	Hib	PCV7	MCC	
⩾6 months	Influenza*				
From 9 months If needed					MMR
12 months		Hib		MCC	
13 months			PCV7		MMR

DTaP-IPV, diphtheria, tetanus, acellular pertussis, inactivated polio vaccine; Hib: *Haemophilus influenzae* b conjugate; MCC, meningococcus group C conjugate; MMR, measles-mumps-rubella vaccine; PCV7, 7-valent pneumococcal conjugate vaccine.
*Two doses 1 month apart, before the influenza season.

CONCLUSIONS

While absolute primary antibody responses may be lower in preterm infants vaccinated according to chronological age than in term infants, the majority achieve concentrations generally accepted to correlate with protection. For vaccines where there are no clear serological correlates of protection, such as pertussis, such conclusions must be made with caution. For both preterm and term infants, antibody concentrations decline rapidly after primary immunisation, but this may be more clinically relevant in preterm infants as they start from a lower baseline. This reinforces the need for a booster dose in such infants, particularly as memory induction on the whole does not appear to be compromised by prematurity.

It seems likely that an accelerated 2-3-4 month schedule will achieve protective concentrations earlier in such infants than a more extended schedule, which is important given their susceptibility to infection. However, such schedules may be less immunogenic overall and require an early additional or booster dose to ensure persistence of protection. The timing of such booster doses requires further study.

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Classification of childhood vasculitides

Some vasculitides affect both adults and children: some occur almost exclusively in children (Kawasaki disease), some in adults (temporal arteritis) and some have different features in adults and children (polyarteritis and Wegener's granulomatosis). There is a need, therefore, for a classification of childhood vasculitides. Consensus criteria for such a classification have been reached using the Delphi technique with many paediatric rheumatologists, followed by a consensus conference of 10 experts using a nominal group technique (Seza Ozen and colleagues. *Ann Rheum Dis* 2006;**65**:936–41).

The proposed classification groups the childhood vasculitides predominantly according to the size of the vessels affected as large, medium or small, and a miscellaneous group of ''other'' vasculitides. The classification is (1) predominantly large vessel vasculitis (Takayasu's arteritis); (2) predominantly medium-sized vessel vasculitis (childhood polyarteritis nodosa, cutaneous polyarteritis and Kawasaki disease); (3) predominantly small vessel vasculitis: (a) granulomatous (Wegener's granulomatosis and Churg–Strauss syndrome), (b) non-granulomatous (microscopic polyangiitis, Henoch–Schönlein purpura, isolated cutaneous leucocytoclastic vasculitis and hypocomplementic urticarial vasculitis); (4) other vasculitides (Behçet's disease, vasculitis secondary to infection, malignancies, and drugs, vasculitis associated with connective tissue diseases, isolated vasculitis of the central nervous system, Cogan's syndrome and unclassified vasculitis).

Detailed classification, or diagnostic, criteria are presented for Henoch–Schönlein purpura, Kawasaki disease, childhood polyarteritis nodosa, cutaneous polyarteritis, microscopic polyangiitis, Wegener's granulomatosis and Takayasu's arteritis. These criteria are endorsed by the European League Against Rheumatism and the Paediatric Rheumatology European Society, and are under review by the American College of Rheumatology.