Immunisation of Preterm Infants

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Importance of immunising preterm infants

In 1993, there were 16,207 preterm births (37 weeks gestation) in Australia, representing 6.3% of all confinements. The majority of preterm births were delivered at 32 - 36 weeks (5.1% of all confinements), but 0.7% and 0.6% of all confinements occurred at 28-31 weeks and 20 -27 weeks respectively.[1] Improvements in neonatal care have resulted in the survival of more infants of lower gestational age.[2] All preterm infants are prone to infection, and infants of lower gestational age with underlying lung disease from long term ventilation are especially susceptible to respiratory pathogens. These infants can benefit greatly from immunisation, and health care providers have a responsibility to ensure that they receive appropriate and timely immunisations.

This brief report provides a summary of current knowledge about the safety, efficacy and duration of immunity of the Australian standard schedule vaccines in preterm infants.

Diphtheria-tetanus-pertussis

Pertussis is a major problem in Australia.[3,4] Hospitalisation and deaths relating to pertussis are more likely to occur in preterm infants.[5,6] Initial studies in preterm infants born at 26 - 36 weeks (mean 31 - 33 weeks) using a combined diphtheria, tetanus and whole cell pertussis (DTPw) vaccine showed that immunogenicity and reactogenicity were similar in preterm and term infants.[7,8,9,10] Recent studies have shown that infants of lower gestational age (range 24 - 34 weeks, mean 27 -28 weeks) do not tolerate DTP immunisation as well as the infants in the earlier studies.[11,12,13] New or increased episodes of apnoea and bradycardia were reported in the 24 - 72 hour period following immunisation for some infants born at 31 weeks gestation. The majority of the apnoeic episodes were minor and self limiting. The authors recommend that all hospitalised preterm infants be commenced on cardiorespiratory monitoring prior to immunisation and that monitoring be continued for at least 48 hours.[12,13] However, preterm infants well enough to be discharged home can safely start their immunisations at 2 months of age (i.e. 2 months after birth), in line with current National Health and Medical Research Council (NHMRC) recommendations that preterm infants be immunised at the same chronological age as term infants.[14]

The studies of reactogenicity in very low birth weight infants did not examine immunogenicity, but a satisfactory antibody response to tetanus toxoid after three immunisations has been reported in a study of 16 preterm infants (<29 weeks and <1000g at birth).[15] The immune responses to diphtheria and pertussis were not measured at this time but the children were followed up 3 - 4 years later (see under Duration of immunity, p 219).[16]

Acellular pertussis vaccines, now available in Australia and licensed for all age groups, may be better tolerated than whole cell vaccines, but few data are available on their use in preterm infants. A 1995 report of a three component acellular vaccine trial in Italy showed the vaccine to be safe and immunogenic in 87 preterm infants (gestation 26 - 37 weeks) but did not state whether these infants were monitored following vaccination.[17]

Haemophilus influenzae type b (Hib)

Hib conjugate vaccines have been available in Australia since 1992 and are routinely commenced at 2 months of age. PRP-OMP, which produces an early antibody response, is preferred for groups at high risk of early Hib disease and is the recommended vaccine for Aboriginal and Torres Strait Islander infants on a 2, 4,12 month schedule. However, several studies have shown that after 2 doses, preterm infants (mean gestational age 28 weeks) do not respond as well to PRP-OMP as term infants. Antibody levels indicative of long term protection were obtained in only 53 - 55% of infants[18,19] PRP-T given on a 2,4,12 month schedule also produced a reduced response in preterm infants after 2 doses, although no difference was seen after the third dose.[20] A study of HbOC vaccine, which has a 4-dose schedule at 2,4, 6 and 18 months, showed that, after 3 doses of HbOC, preterm infants (mean gestational age 26 weeks) had a comparable response to that of term infants.[15] Therefore, the NHMRC recommends that preterm infants receiving PRP-OMP be given an additional dose at 6 months, but that there be no change to the schedule for preterm infants receiving HbOC.[14]

Polio

Protection against polio is achieved by giving 3 doses of oral polio vaccine (OPV) commencing at 2 months of age. After administration of OPV the virus is excreted in the stool for about 6 weeks. Because of the theoretical risk of transmission to other infants, the vaccine should not be given to preterm infants until they are discharged from hospital. Inactivated polio vaccine (IPV) may be used for long term hospitalised infants. It is also the vaccine of choice for infants who have a disease, or are receiving treatment, which lowers immunity. Limited data are available on the use of polio vaccines in preterm infants. Two studies showed that OPV and IPV produce a satisfactory response to all serotypes after 2 doses,[21,22] while a third study showed a poor response to serotype 3.[14] Sick preterm infants given 2 doses of IPV showed a poor response to all 3 serotypes.[23]

Hepatitis B

Although the NHMRC recommends that all infants receive hepatitis B vaccine, universal vaccination will not be incorporated into the standard vaccination schedule until a combination vaccine has been licensed.[14] Currently, hepatitis B vaccine is only routinely given to infants of women who are hepatitis B surface antigen (HBsAg)

positive or who come from communities with carrier rates over 2%. Vaccination of these infants is recommended at birth, 1 month and 6 months. A number of studies have examined the response of preterm infants to hepatitis B vaccine with conflicting results. Several studies have shown a lower seroconversion rate and reduced antibody response in preterm infants immunised at birth.[24,25,26] An improved response was seen if immunisation was delayed until the infants reached a weight of 2kg, or if it was given at about 1 month of age.[25,26,27] Other studies have demonstrated a satisfactory antibody response in preterm infants.[28,29,30] However, the studies showing a reduced response had more infants of lower gestational age and birth weight.

The NHMRC currently suggests two options for hepatitis B immunisation in preterm infants:[14]

1. Give 1st dose at birth, then at 1, 6 and 12 months (4 dose schedule)
2. If birthweight is <2kg, delay immunisation until 2 months of age and give at 2, 3 and 8 months (3 dose schedule)

Option 1 is recommended if the mother is HBsAg positive, when immunoglobulin must also be given, ideally within 12 hours of birth. For both options it is advisable to measure antibody levels 1 month post immunisation.

Duration of immunity

An early British study of 69 preterm infants (gestation 26 – 35 weeks, mean 32 weeks) given DTPw and OPV showed that all had antibody concentrations consistent with protection for diphtheria, tetanus and polio to the age of 19 months (minimal protective levels for pertussis have not been established).[10] There is only one published study of immunisation in extremely preterm infants.[16] This followed 16 neonates born at <29 weeks and <1000g at birth. At 3 - 4 years of age their geometric mean antibody titres (GMT) were similar to a control group of term infants for diphtheria, tetanus and pertussis, and were consistent with protection for diphtheria and tetanus. However, these preterm infants had a lower GMT for Hib and polio serotype 3 than the control group. Twelve of these infants had also received hepatitis B vaccine, and protection was comparable to that of term infants. A study of hepatitis B vaccine in Native Alaskan infants showed that only 8.1% of the preterm infants had protective levels at 3 years of age but a similar decline was also seen in the term infants, in whom only 15% had protective levels.[31]

A longitudinal study of Hib immunity is currently in progress in preterm infants in Adelaide and the results will soon be available. Longitudinal studies of antibody responses in preterm infants receiving vaccines according to the Australian immunisation schedule will be important in determining the immunogenicity and duration of immunity of new vaccines in this group of infants.

Conclusion

Well preterm infants can be safely immunised at the same time as term infants. Full doses of all vaccines should be given. The response of sick and very low birth weight infants appears to be reduced for Hib and hepatitis B vaccines and schedule modifications may be needed. The response of sick infants to diphtheria, pertussis (whole and acellular) and polio vaccines is uncertain and further studies in this population may be warranted.

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The NCIRS was established by the National Centre for Disease Control, Commonwealth Department of Health and Family Services. The Centre analyses, interprets, and evaluates national surveillance data on immunisation coverage and vaccine preventable diseases. NCIRS also identifies research priorities, and initiates and coordinates research on immunisation issues and the epidemiology of vaccine preventable diseases in Australia.

Measles Control Campaign Update

During the three month period of the Campaign, the uptake of measles-mumps-rubella (MMR) vaccine given at primary school clinics and the number of adverse events following MMR vaccination are being monitored. Data are forwarded to the National Centre for Disease Control for collation and publication in *CDI*.

Measles Control Campaign activity data, cumulative to 25 September 1998

Sum total students	661,194
Total forms returned	612,989
Consents to vaccinate	519,068
Total students immunised	487,174
Percentages are:	
Of total students	93% returned their forms
Of total forms returned	85% consented to vaccination
Of total consents to vaccination	94% have been vaccinated
Of total students	74% have been vaccinated.

Adverse events

Faints/syncopy	14
Syncopal fits	10
Hyperventilation	3
Anaphylaxis	3
Rash	2
Local allergic reaction	1
Local reaction	1
Arthropathy	1
Fever	1
Myalgia	1
Lymphadenapathy/ headache/stiff neck/rash	1

Enquiries can be directed to Sue Campbell-Lloyd, National Manager of the Measles Control Campaign, Sydney Office, Commonwealth Department of Health and Family Services.