**Factors that influence infant immunity and vaccine responses**

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**Abstract**

The neonatal period and early infancy are times of increased vulnerability to infection. The immune system of infants undergoes rapid changes and a number of factors can influence the maturation and function of the early infant immune system, amongst these factors are maternal infections and immunity. Infants who are HIV-exposed, but uninfected show important immune alterations, which are likely to be associated with the increased morbidity and mortality observed in these infants. Maternally derived antibodies are crucial in early life to protect infants from infection during the time when their own immune system is becoming more experienced and fully mature. However, maternal antibodies can also interfere with the infant’s own antibody responses to primary vaccination. Preterm infants are particularly vulnerable to infection, having not had the opportunity to benefit from the transplacental transfer of maternal antibodies in late pregnancy. In addition, differences have been observed in the innate and adaptive immune system between preterm and term infants. Here, we focus on maternal influences on the infant immune system, using HIV and maternal vaccination as examples and finish by considering how prematurity impacts on infant immune responses to vaccination.

**Introduction**

The neonatal period and infancy are times of particular vulnerability to infections, which are often associated with significant morbidity and mortality. The early immune system undergoes rapid changes, a process which is often called ‘maturation’. *In utero*, the immune system is largely protected from exposure to foreign antigens, while after delivery, it needs to quickly fight many potential pathogens. During the neonatal period, this mainly occurs through the innate immune system.1

Differences in both the innate and the adaptive immune system have been observed in neonates compared to the immune system later in life. The early immune system is biased towards an anti-inflammatory state. Compared to children and adults, production of anti-inflammatory cytokines (interleukin [IL]-6, IL-8, IL-10, IL-23)2-5 is higher, while production of pro-inflammatory cytokines (tumour necrosis factor [TNF-alpha], interferon [IFN]-alpha, IFN-gamma, IL-12, IL-1beta) is lower. There is also less activation of macrophages through IFN-gamma.6 Although, neonates have been reported to have higher numbers of natural killer (NK) cells, the cells have a lower cytotoxic capacity due to a reduced number of cytoplasmic granules and degranulation capacity.7 Similarly, although neonates have higher numbers of circulating neutrophils,8 the adhesion of neutrophils to endothelial cells,9 chemotaxis10, 11 and the neutrophil bactericidal activity12, 13 are diminished. Complement is not transferred across the placenta and term infants have between 10 to 80% of the adult complement concentrations.12, 14 Even though, neonates have higher numbers of circulating T cells, they have more naïve and regulatory T cells, and fewer memory and cytotoxic T cells.15-17 Furthermore, neonates show a diminished T helper type 1 (Th1) differentiation5, 18 and a polarisation towards Th2 cells.2 Cell-mediated immune responses are less strong and there is a suboptimal interaction between antigen-presenting cells and T cells.19 Similarly to T cells, neonates also have higher numbers of circulating B cells15 with more naïve and fewer memory B cells.16 Stimulation of B cells leads to fewer antibody-secreting plasma cells and therefore less antibody production.20, 21

These important differences in the neonatal immune system need to be considered when interpreting laboratory tests, but also when designing vaccine schedules. Although, infants should receive immunisations as early as possible to minimise the time that they are susceptible to infections, timing and composition of vaccines need to be adapted to the function of the early immune system.

There are a large number of factors which can impact the development and function of the immune system early in life. Amongst this multitude of factors, maternal immunity and infections can influence the functions of the infant immune system, including the infant’s response to vaccination.22 We use the examples of maternal HIV infection and vaccination in pregnancy as examples of how maternal factors impact on the immune system early in life. Finally, we consider how an important infant factor – prematurity – affects infant immunity and responses to vaccination.

**Maternal HIV infection**

In the past three decades, a dramatic decrease in the rate of HIV mother-to-child transmission, from around 30% to less than 3%, was achieved in both high- and low-income countries.23, 24 This remarkable progress has led to a large increase in the numbers of infants who have been HIV-exposed, but who are not themselves HIV infected (HEU). In Sub-Saharan Africa, it is estimated that up to 30% of all infants have been exposed to HIV *in utero*, but remain uninfected.25 In the era before widespread roll out of antiretroviral therapy, HIV-exposed, uninfected infants were observed to have increased morbidity and mortality and even in the era of widespread availability of anti-retrovirals in pregnancy this disadvantage is still evident, with an increase in infections26-33 (e.g. gastroenteritis, respiratory tract infections and invasive streptococcal diseases) and an increased mortality.29, 34-38 The reasons for this are likely multi-factorial and include differences in socioeconomic and nutritional status.39 However, HEU infants have been reported to have important immunological differences compared to HIV-unexposed infants which may have a contributory role (Table 1).23 Potential reasons for these observed differences include exposure to HIV viral particles *in utero,* maternal anti-retroviral medication during pregnancy, shorter duration or lack of breastfeeding, differences in the maternal microbiota and consequently infant colonisation, as well as a greater exposure to opportunistic pathogens.37, 40-42 HEU infants have been reported to have notable immunological alterations in both the innate and adaptive immune systems. These alterations include lower numbers of neutrophils43-45 and monocytes,43 and higher numbers of myeloid dendritic cells46 with higher pro-inflammatory responses of monocytes47 and myeloid dendritic cells.47 For NK cells, lower numbers of activated and perforin-producing cells have been observed in HEU infants.48 Cytokine concentrations are balanced towards a pro-inflammatory state: HEU infants have been reported to have higher concentrations of IL-4,49 IL-7,49, 50 IL-23,51, 52 IFN-gamma51 and TNF-alpha,51 but lower concentrations of IL-2,53 IL-4,52 IL-10,49, 52 IL-1254 and IFN-gamma.49, 55 Infants born to women with detectable viremia, have been observed to have a higher IL-23, IFN-gamma and TNF-alpha concentrations and higher *in vitro* lymphoproliferation after stimulation with polyclonal activators, but lower IL-4 and IL-10 concentrations compared to infants of mothers without detectable viremia.51, 52

HIV-exposed infants have also been reported to have a reduced thymic size with a reduced T cell output.56, 57 Overall, HEU infants have lower numbers of naïve T cells,50 but higher numbers of activated and memory T cells, suggesting a more ‘experienced’ immune system at birth.50, 53, 58 However, they have lower numbers of CD4 cells,50, 57, 59, 60 and higher numbers of CD8 cells50, 58 with skewed T cell subset distributions.58, 59, 61 Higher numbers of B cells49 in particular immature B cells, 49 and increased T and B cell apoptosis have been observed in HEU compared to HIV-unexposed infants.60, 62

Multiple studies have shown lower transplacental antibody transfer to infants from mothers who are HIV-infected and this is likely to be associated with higher rates of certain infections.63-74 For example, in HIV-infected mothers, impaired transplacental transfer of respiratory syncytial virus (RSV)-neutralising antibodies has been observed.70 In line with these findings, lower respiratory tract infections, in particular those caused by RSV and human metapneumovirus are observed more frequently in HIV-exposed, uninfected infants compared to unexposed infants.33 HEU infants have also been reported to have a 12-fold increased risk of death from RSV during the first 6 months of life while RSV-specific antibody is particularly important in the protection against severe disease.33 Similarly, for Group B *Streptococcus* (GBS)-specific immunoglobulin (Ig) G, it has been reported that there is reduced transfer from HIV-infected mothers to their infants73, 74 and HEU infants have been reported to have a 13-fold higher risk of invasive GBS infection, while when affected, these infants have more severe disease.32

Many studies have reported that HEU have lower concentrations of specific IgG prior to vaccination,68, 75-77 which is likely due to decreased mother to infant IgG transfer.63-74 However, most studies report similar56, 59, 68, 75, 77-80 or higher68, 69, 76, 77, 81 humoral vaccine responses following primary vaccination or booster doses. The lower antibody concentration found in HEU infants, likely diminishes blunting (a phenomenon discussed in the next section), which might explain the higher antibody responses observed after vaccination in these infants.68 In contrast, only three studies have reported lower antibody responses to vaccines in HEU infants. Two studies after vaccination against hepatitis B (HepB), which may be due to higher rates of HIV-hepatitis B co-infection in this population of pregnant women and consequently higher concentrations of Hep B surface antigen antibodies in infants at birth,76, 82 and one study, after oral polio (OPV) vaccination.83 Several studies reported that T cell responses after vaccination did not differ between HEU infants and HIV un-exposed infants (BCG,84, 85 pertussis86). However, some studies did report reduced polyfunctionality of T cells after vaccination with BCG86 or against tetanus.87

**Maternal vaccination during pregnancy**

The aim of antenatal vaccination is to protect women in pregnancy and infants in the vulnerable period before they can complete their primary vaccinations or until the period of increased susceptibility has passed. Maternal vaccination during pregnancy has been proven to be safe and effective, and is currently recommended against tetanus,88 pertussis89, 90 and influenza in many areas of the world.91-95 For pertussis in infants less than 3 months of age, it has been shown that maternal vaccination is 91-94% effective in protecting infants against hospitalisation and 69-90% in protecting against infection or mild disease.96-98 Antenatal vaccination is the cornerstone of maternal and neonatal tetanus programmes which have resulted in a reduction of 96% in neonatal tetanus since the 1980s.88 Additional vaccines for use in pregnancy or prior to pregnancy against cytomegalovirus, GBS and RSV are currently being developed.

One of the crucial determinants of IgG transfer from mother to infant is the serum concentration of IgG to a specific antigen in the mother. Women who are vaccinated during pregnancy have significantly higher IgG concentrations compared to unvaccinated women.95, 99-104 Higher infant antibody concentrations at birth lead to increased protection of longer duration.105 However, despite the clear benefits of antenatal vaccination, it is important also to understand how high concentrations of maternally-derived IgG might impact on the infant response to vaccination. An increasing number of studies have shown that these high concentrations of maternal IgG are associated with a reduced infant response to primary vaccination – a blunting effect. Infants born to women vaccinated with diphtheria-tetanus-acellular pertussis (dTpa) vaccine during pregnancy have lower specific-IgG concentrations against antigens in the maternal vaccine including diphtheria100, 101, 103, 106-108 and pertussis,100, 101, 103, 106, 108, 109 but have higher antibody concentrations against tetanus100, 101, 103, 107, 109 and *Haemophilus influenzae* type b (conjugated to tetanus)103, 107, 109 one month after completing their primary vaccination compared to infants whose mothers did not receive the vaccine. Interestingly, infants born to women vaccinated with a pertussis-containing vaccine in pregnancy also have lower concentrations of specific antibodies following pneumococcal and meningococcal vaccination.107, 108, 110 This is likely due to carrier proteins: the carrier protein CRM197 in the 13-valent conjugated pneumococcal vaccine is a modified diphtheria toxin. Similarly, in the conjugated meningococcal C vaccine the meningococcal polysaccharide is either conjugated to CRM197 or a modified tetanus toxin (TT). Concurrently, in infants whose mother received dTpa during pregnancy lower antibody responses have been found after vaccination with meningococcus C (MenC)-CRM and higher antibody responses after vaccination with MenC-TT.107 In contrast to dTPa, maternal influenza vaccination during pregnancy has not been reported to have a consistent effect on infant vaccine responses (Table 2).108

Despite the half-life of antibodies of approximately 4 to 6 weeks,111 interaction with infant vaccine responses has been reported to persist following booster vaccination in some studies. Lower vaccine responses after a booster dose have been reported for diphtheria,106, 108 pertussis,103, 106, 108, 109 IPV103, 108 and pneumococcus108 in infants whose mothers received dTpa during pregnancy compared to infants whose mothers did not receive the vaccine. In contrast, higher responses to tetanus103, 106 and Hib103 were observed in these infants.

One proposed mechanism for the inhibition of infant antibody production after vaccination is that maternal antibodies bind to vaccine epitopes and mask them from infant B cells. This leads to attenuation of immune responses to these antigens. Additionally, B cells responses can be inhibited through cross-linking of the B-cell receptor with FcγRIIB.112-114 The clinical relevance of this blunting is currently unclear. However, data from the UK suggests that the reduction in pertussis-specific IgG is not associated with an excess of pertussis disease following primary immunisation in infants born to vaccinated compared to unvaccinated women.115 Most vaccines induce high antibody responses and small differences in antibody concentrations may not be of clinical significance. For pertussis, the period with the highest morbidity and mortality is the first few months of life and maternal vaccination is crucial to reduce the burden of early pertussis. However, for pneumococcus, infants in the second year of life are especially vulnerable for invasive disease and blunting of infant antibodies through maternal antibodies might cause an increase in disease. Strategies, such as additional booster doses in the second year of life, particularly for pertussis and pneumococcus, should be considered to address this. Alternatively, a monovalent pertussis vaccine used during pregnancy would avoid interaction with other antigens.

**Prematurity**

Preterm infants are at increased risk of infections, including vaccine-preventable infections, as reported for Hib,116 influenza,117 pertussis,118 pneumococcus119, 120 and rotavirus.121 Immune alterations as a consequence of prematurity have been identified in the innate and adaptive immune system (Table 3). Preterm infants, have been reported to have impaired Toll-like receptor signalling122 (diminished pathogen recognition by macrophages and dendritic cells)123 and lower concentrations of mannose-binding lectin.124 Furthermore, preterm infants also have lower complement concentrations with a complement system that has lower chemotactic opsonising and lytic capacity.14 Compared to term infants, preterm infants have been reported to have lower numbers of neutrophils,11, 125 decreased neutrophil chemotaxis10, 11, 126 (partly because of decreased expression of P-selections by endothelial cells),127 as well as diminished phagocytic128 and bactericidal activity of neutrophils (diminished respiratory burst).129 Furthermore, NK cells of preterm infants have been observed to have a lower perforin production.130 Cytokine production also differs in preterm infants. Compared to term infants, preterm infants have been reported to have lower IL-6, TNF-alpha and IFN-gamma production,128, 130, 131 but higher IL-8 and IL-10 production.128, 131

Preterm infants have also been reported to have lower numbers of circulating T and B cells16, 132 with diminished T cell activity (especially Th1 activity) and diminished B cell interaction with T cells.123

Transplacental antibody transfer increases during pregnancy: by 30 weeks of gestation the antibody concentration of infants is about 50% that of mothers and towards the end of pregnancy about 120%.133, 134 Consequently, preterm infants have lower concentrations of transplacentally acquired antibodies when they are born.135

Preterm infants have significantly lower antibody concentrations after primary immunisation against diphtheria,136 HepB,136-138 Hib,137, 139-143 PCV7,119, 144 IPV type 3137 and pertussis.136, 145-148 Seroprotection rates were diminished against HepB,137 Hib,137, 139-143 pertussis147 and IPV type 3.149 Additionally, preterm infants have also been reported to have quicker waning of antibodies against meningococcus C.150 Preterm infants do not only have lower vaccine responses after primary immunisation, but also after booster doses. At two years of age, they have been reported to have lower antibody concentrations to HepB,138, 151 Hib151 and IPV type 3151 and at five years of age to HepB151 and pertussis.152 To optimise protection, it could, therefore be considered to add additional booster doses to the vaccine schedule of prematurely born infants.

**Conclusion**

Infant immunity is influenced by multiple factors. Both impairment of maternal immunity, as illustrated by maternal HIV infection, and enhancement of maternal immunity by vaccination in pregnancy can have an impact on infant immunity and responses to vaccination. Moreover, infant factors such as prematurity can have a profound impact on vulnerability to infection as well as ability to respond to infant vaccination.

**Competing interests**

The authors declare that they have no competing interests.

**Conflict of interest**

The authors declare no conflict of interest.

**Authors’ contributions**

PZ drafted the initial manuscript. CJ critically revised the manuscript and both authors approved the final manuscript as submitted.

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**Table 1** Immune alterations in HIV-exposed, uninfected infants compared to HIV unexposed infants

|  |  |
| --- | --- |
| **Feature** | **Observed differences** |
| **Neutrophils** | Lower numbers of neutrophils43-45 |
| **Monocytes** | Lower numbers of monocytes43Higher pro-inflammatory responses of monocytes47 |
| **Dendritic cells** | Higher numbers of myeloid dendritic cells with up-regulated CD80, CD86 and B7-H1 receptors after stimulation46Higher pro-inflammatory responses of myeloid dendritic cells47 |
| **Natural killer cells** | Skewed natural killer cells subset distributions with lower numbers of activated and perforin producing cells48 |
| **Cytokines** | Higher concentrations of IL-4,49 IL-7,49, 50 IL-23,51, 52 IFN-gamma51 and TNF-alpha51Lower concentrations of IL-2,53 IL-4,52 IL-10,49, 52 IL-1254 and IFN-gamma49, 55No difference in concentrations of IFN-alpha46 |
| **Thymus** | Reduced thymic size56Lower thymic output57 |
| **T cells** | Lower numbers of naïve T cells50Higher numbers of activated T cells50, 53, 58Higher numbers of memory T cells50, 53Lower numbers of CD4 cells50, 57, 59, 60Higher numbers of CD8 cells50, 58Skewed T cell subset distributions58, 59, 61Higher T cell apoptosis62 |
| **B cells** | Higher numbers of B cells49Higher numbers of immature B cells49Higher B cell apoptosis60, 62 |
| **Immunoglobulins** | Lower transplacental antibody transfer63-74 |
| **Humoral vaccine responses after primary vaccination** | Higher responses to measles,81 pertussis68, 76, 77 and pneumococcus68 vaccinationHigher responses to Hib69 vaccinationLower responses to HepB76, 82 vaccinationLower responses to OPV83 vaccinationNo difference in responses to BCG,59 HepB,77, 78 Hib,56, 68, 77 measles,77, 79 pneumococcal,75, 80 IPV59 and tetanus68, 77 vaccination |
| **Cellular vaccine responses after primary vaccination** | Lower polyfunctionality of T cells after tetanus87 vaccinationLower T cell responses after BCG55, 59, 86 vaccinationNo difference in T cell responses to BCG84, 85 vaccinationNo difference in T cell proliferation after pertussis86 vaccination, but reduced polyfunctionality of CD4 and CD8 responses |

BCG – Bacille Calmette-Guérin

HepB – hepatitis B

Hib – *Haemophilus influenzae* type b

IL – interleukin

IFN – interferon

IPV – inactivated polio

OPV – oral polio vaccine

TNF – tumour necrosis factor

**Table 2** Changes in antibody concentrations in infants whose mothers were vaccinated during pregnancy

|  |  |
| --- | --- |
| **Feature** | **Observed differences** |
| **Diphtheria-tetanus-acellular pertussis vaccine**  |
| **Humoral vaccine responses after primary vaccination** | Lower responses to diphtheria100, 101, 103, 106-108 and pertussis100, 101, 103, 106, 108, 109 Lower responses to HepB,103 IPV103 and pneumococcus107, 108, 110 Lower responses to MenC-CRM107 and higher antibody responses to MenC-TT107 vaccination Higher responses to tetanus100, 101, 103, 107, 109 and Hib103, 107, 109  |
| **Humoral vaccine responses after booster vaccination** | Lower responses to diphtheria,106, 108 pertussis,103, 106, 108, 109 IPV103, 108 and pneumococcus108 vaccinationHigher responses to tetanus103, 106 and Hib103 |
| **Influenza vaccine**  |
| **Humoral vaccine responses after primary vaccination** | Lower responses to pertussis108 (pertussis toxin) vaccinationHigher responses to pneumococcal serotype 1 and 19F108No differences in responses to diphtheria, tetanus, Hib, IPV, pertactin, filamentous haemagglutinin and other pneumococcal serotypes108 |
| **Humoral vaccine responses after booster vaccination** | No differences in responses to diphtheria, tetanus, pertussis toxin, pertactin, filamentous haemagglutinin, Hib, IPV, pneumococcus, measles mumps, rubella, MenC108 |

CRM – cross-reaction material

HepB – hepatitis B

Hib – *Haemophilus influenzae* type b

IPV – inactivated polio

OPV – oral polio vaccine

MenC – meningococcus C

TT – tetanus toxin

**Table 3** Immune alterations in preterm infants compared to term infants

|  |  |
| --- | --- |
| **Feature** | **Observed differences** |
| **Different components of the innate immune system** | Impaired Toll-like receptor signalling122Lower concentrations of mannose-binding lectin124Lower complement concentrations with a complement system that has lower chemotactic opsonising and lytic capacity14 |
| **Neutrophils** | Lower numbers of neutrophils,11, 125 Decreased neutrophil chemotaxis10, 11, 126 (lower expression of P-selections by endothelial cells)127 Lower phagocytic128 and bactericidal activity of neutrophils (diminished respiratory burst)129 |
| **Monocytes** | Decreased pathogen recognition by macrophages123 |
| **Dendritic cells** | Decreased pathogen recognition by dendritic cells123 |
| **Natural killer cells** | Lower perforin production130 |
| **Cytokines** | Lower concentrations of IL-6, TNF-alpha and IFN-gamma128, 130, 131 Higher concentrations of IL-8 and IL-10128, 131 |
| **T cells** | Lower numbers of T cells16, 132Decreased T cell activity (especially Th1 activity)123 |
| **B cells** | Lower numbers of B cells16, 132Decreased B cell interaction with T cells123 |
| **Immunoglobulins** | Lower transplacental antibody transfer133-135 |
| **Humoral vaccine responses after primary vaccination** | Higher responses to pneumococcal serotype 19F, 9V and 4119 vaccinationLower responses to diphtheria,136 HepB,136-138 Hib,137, 139-143 pneumococcus,144 IPV137, 149 and pertussis136, 145-148 vaccinationNo difference in responses to diphtheria,136, 137, 145, 146, 148 Hib,149 MenC,141 150 OPV,153 IPV,137, 149 pertussis136, 137, 145, 146, 148 and tetanus137, 145, 146, 148, 149 vaccinationQuicker waning of antibodies after MenC150 vaccination |
| **Humoral vaccine responses after booster vaccination** | Lower responses to HepB,138, 151 Hib 151 and IPV type 3151 vaccination at 2 years of ageLower responses to HepB 151 and pertussis152 vaccination at 5 years of age |

BCG – Bacille Calmette-Guérin

HepB – hepatitis B

Hib – *Haemophilus influenzae* type b

IL – interleukin

IFN – interferon

IPV – inactivated polio

MenC – meningococcus C

OPV – oral polio vaccine

TNF – tumour necrosis factor