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Maternal antibodies and infant immune responses to vaccines

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ABSTRACT

Infants are born with immature immune systems, making it difficult for them to effectively respond to the infectious pathogens encountered shortly after birth. Maternal antibody is actively transported across the placenta and serves to provide protection to the newborn during the first weeks to months of life. However, maternal antibody has been shown repeatedly to inhibit the immune responses of young children to vaccines. The mechanisms for this inhibition are presented and the impact on ultimate immune responses is discussed.

Infants are born with immature immune systems, making it difficult for them to effectively respond to the infectious pathogens encountered shortly after birth. However, maternal antibody is actively transported across the placenta beginning at the end of the second trimester and serves to provide protection to the infant during the first weeks to months of life [1]. Most maternal antibodies are of the IgG isotype and are metabolized over time. However, even low-titer, non-protective levels of maternal antibodies have still been shown to inhibit infant immune responses to vaccination. Immune responses to all types of vaccines, including live-attenuated, inactivated, and subunit vaccines, have been reported to be inhibited by the presence of maternal antibody [2]. Specific antibodies elicited by vaccination, including IgA, IgM and IgG isotypes, are secreted into human colostrum and milk, with secretory IgA the predominant antibody class. During breastfeeding these ingested antibodies provide mucosal protection by inhibiting the adhesion and invasion of both commensal and pathogenic organisms and by promoting their exclusion and neutralization [3].

In this review, we will use measles vaccine as a model to highlight the effect of maternal antibody on the immune responses in young children since it has been extensively studied, although many of these studies were performed several decades earlier. In addition, we will also summarize data where maternal antibodies inhibit the generation of infant antibody after other routinely administered vaccines. Finally, we will present new insights into the mechanisms of inhibition by maternal antibody and focus on potential ways to circumvent this inhibition. These new insights were comprehensively reviewed in an excellent overview on this topic [2].

Measles vaccine: Measles vaccine is the best studied example of the effect of maternal antibody on infant responses to immunization. The original measles vaccine virus, the Edmonston strain, was developed by attenuating wild-type measles through successive laboratory passages. Vaccination with the attenuated strain induces neutralizing antibodies against the two major glycoproteins, hemagglutinin and fusion protein [4]. During their first year of life, children are protected from measles by neutralizing antibodies provided through transplacentally acquired antibody. However, over time, these antibody titers wane and no longer provide protection against wild-type infection [5]. In clinical studies, immunization in the presence of maternal antibodies leads to reduction in mortality [6] and morbidity [7]. However, solid lasting immunity, including protective B cell responses, and the absence of clinical symptoms after infection is not established after immunization in the presence of maternal antibodies.

In marked contrast to poor antibody responses after measles vaccination in young children with maternal antibody, specific T cell responses are induced and are measurable after immunization in the presence of maternal antibodies [8]. In addition, measles vaccination in the presence of maternal antibodies leads to priming of B cells such that when children are given a booster dose of measles vaccine, enhanced immune responses are noted [9]. Yet, other studies have shown that children immunized with measles vaccine in the presence of maternal antibodies have lower overall antibody titers after boosting when compared to children who were seronegative at the time of initial measles immunization and then boosted [10].

In an effort to circumvent the effect of maternal antibody on the primary immune response to measles vaccine in young children,

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high titer measles vaccines were developed and studied. In a trial conducted in the Gambia, infants were randomized to receive either high titer Edmonston-Zagreb (EZ) measles vaccine at 4 months of age or lower titer conventional Schwarz measles vaccine at 9 months age [11]. Measles developed in 2 of 119 children who received the high titer EZ vaccine and in 7 of 120 children who received the lower dose Schwarz vaccine. Serological responses measured at 5 months after vaccination and at 18 months of age were satisfactory in both groups, although antibody levels were on average 2-fold higher in the Schwarz group than in the EZ group. The frequencies of fever, cough, vomiting, and diarrhea were no higher in the EZ vaccine recipients in the 3 weeks following vaccination than in age-matched non-immunized controls. Long-term morbidity as assessed by clinic attendance and weight at 18 months of age was much the same in the two groups [11]. However, subsequent studies of the high titer measles vaccine demonstrated that it was associated with increased mortality in female vaccine recipients [12,13]. Although maternal antibody titers were reported to be lower in girls than in boys, the reason for the increase in adverse events after the high titer vaccine in females remains unclear [14]. However, given the adverse mortality outcomes in females, further studies of the high titer EZ vaccines were not pursued.

Another approach to circumvent the effect of maternal antibody on immune responses to measles vaccine in young children was to attempt to determine the earliest possible time where the maternal antibody titer would be low enough to permit successful vaccination. Borras and colleagues attempted to determine this time by carefully monitoring the decline in maternal antibody during the first months of life in young infants and determining their measles antibody titers at ages 9–14 months both before and 28 days after their vaccination [15]. Seroconversion was defined as the presence of antibodies after vaccination in subjects without antibodies before vaccination. In this study maternal antibodies were still present in 45% of children at age 9 months. However, in those children who were actually seronegative prior to vaccination, 61% of the children seroconverted after measles vaccination. Borras et al. suggested that changing the first dose of measles vaccine from age 15 months to age 12 months would be the optimal vaccination time [15].

Gans and colleagues attempted to provide greater precision in determining the optimal time for measles vaccination in young children. They evaluated neutralizing antibody responses in 6-, 9- and 12-month-old infants given measles or mumps vaccine. They demonstrated that 6-month-old infants had diminished humoral immune responses associated with passive maternal antibody effects, but also reported that they had an intrinsic deficiency in antiviral antibody production, which was independent of the effects of passive antibody. In contrast, lower neutralizing antibody titers in 9-month-olds were related only to passive antibody effects and not to intrinsic deficiencies in antibody production. In further contrast, measles and mumps-specific T-cell proliferation and interferon-gamma production were induced by vaccination at 6, 9 or 12 months of age, regardless of the presence of passive neutralizing antibodies or the age of the child [16]. These observations suggested that the sensitization of antiviral T-cells occurred in the presence of passive antibodies and was seen in infants who did not develop active humoral immunity. When a second dose of measles vaccine was given at 12–15 months of age, an enhanced antiviral T-cell response to measles was noted in the infants who were vaccinated at either 6 or 9 months of age, and higher seroconversion rates were also noted. Since T-cell immunity is elicited under the cover of passive antibodies, the youngest infants benefit from the synergistic protection mediated by maternal antibodies and their own capacity to develop sensitized antiviral T-cells [16].

The presence of measles antibody in breast milk has also been assessed in a study reported from Nigeria. Maternal and cord blood samples were collected from 33 Nigerian mother-infant pairs and tested for measles-specific IgG. All these samples had protective measles antibodies at the time of delivery. Determination of the rate of waning of these antibodies revealed that 58 per cent of these children had lost the protective maternal antibody by the age of 4 months and only 3 per cent of the children had protective antibody between the ages of 6–9 months. Fifty-five colostrum samples from the same mothers and 347 breastmilk samples collected at various periods during breastfeeding also showed that anti-measles IgA had dropped below the protective cut-off within the first 2 weeks of birth [17]. Thus, these data indicated that Nigerian infants were born with anti-measles antibody but that the rate of waning of both serum and breast milk antibody left many of the infants unprotected before the first dose of the vaccine.

Differences in the actual amounts of maternal antibody transplacentally provided to the infant exist due to a number of factors, including whether the maternal antibodies were a result of wild-type measles infection versus administration of live attenuated vaccine. Maternal antibody levels in children of vaccinated mothers are lower and decline faster than in children from naturally infected mothers [18]. Gans and Maldonado recently discussed the effect of lower maternal antibody levels resulting from vaccine-induced immunity when they highlighted that measles outbreaks in countries with high measles vaccine coverage have been seen primarily in infants [19]. Further, they speculated that the number of susceptible infants is expected to increase among highly vaccinated populations as the majority of women in child-bearing years have vaccine-induced immunity to measles. Recent studies show that 99% of infants born to vaccinated mothers lack detectable measles antibodies by 6 months of age [20,21]. Many of the studies with measles were conducted at the time of the circulation of natural measles infection and the widespread use of measles vaccine for many years has resulted in lower antibody levels in mothers. Continued assessment of the effect of decreased maternal antibody and the optimal timing for measles vaccination will be needed.

Other vaccines administered to young children: The effect of maternal antibody on infant immune responses has been shown with a number of other vaccines and these are summarized in Table 1 [22–30]. Vaccine responses are inhibited in the presence of maternal antibody for many vaccine antigens. Jones et al. recently reported on the relationship between the concentration of specific antibody to *Bordetella pertussis*, *Haemophilus influenzae* type b (Hib), tetanus toxoid and pneumococcal antigens at birth and after primary immunization at 2, 3, and 4 months of age to assess the effect of maternal antibody levels on infant immune responses [22]. Sera were obtained from the infants at birth and at 5 months

Table 1
Inhibition of immune responses to vaccines in young children by maternal antibody.*

Vaccine antigen	Type of vaccine	Reference numbers
Tetanus	Combination protein vaccine	[20]
Diphtheria	Combination protein vaccine	[20]
Haemophilus influenza, type b	Protein conjugate vaccine	[20]
Pertussis	Acellular and whole cell vaccines	[21]
Measles	Live-attenuated	[3–9,15]
Mumps	Live-attenuated	[15]
Hepatitis A	Inactivated virus	[22]
Hepatitis B	Protein vaccine	[23]
Rotavirus	Live-attenuated	[24]
Poliovirus	Inactivated	[25]
	Live-attenuated	[26]
Pneumococcal	Protein conjugate vaccine	[20,27]
Influenza Virus	Inactivated vaccine	[28]

* Modified from Ref. [2].

of age and specific antibody concentrations were determined. Following primary immunization, 97% of infants had specific antibody concentrations associated with protection against Hib, 89% against pertussis and 100% against tetanus. Concentrations of all specific antibodies after vaccination were significantly higher than at birth ($p < 0.0001$), except for antibody titers against tetanus toxoid. There was an inverse correlation between infant antibody concentrations at birth and fold-increases in antibody concentration post-immunization for tetanus, pneumococcus, pertussis, and Hib. The highest concentrations of specific IgG at birth were associated with lower post-immunization titers for tetanus and pneumococcus, but this association was not observed for Hib or pertussis. The authors concluded that "[h]igher antibody concentrations at birth appeared to inhibit the response to infant immunization for tetanus and pneumococcus, but the effect was less marked for Hib and pertussis, and supports that maternal immunization does not inhibit infant immunization responses in a clinically relevant manner."

One particularly interesting observation was made about the effect of maternal antibody on the infant immune response to either conventional whole cell pertussis (DTP) or acellular pertussis vaccines when combined with diphtheria and tetanus toxoids (DTaP) in studies conducted in the 1990s [23]. A total of 2342 infants were randomized to receive one of 13 different DTaP made by different manufacturers and containing different concentrations of antigens or 2 licensed DTP vaccines containing whole cell pertussis antigens at 2, 4, and 6 months of age. The correlations between pre-immunization and post-immunization antibody titers after three doses of vaccine were modeled by linear regression. Remarkably, after DTP but not DTaP, higher levels of pre-existing antibody were associated with substantial (28–56%) reductions in the antibody responses to pertussis toxin (PT). For other pertussis antibodies, modest inverse correlations were also seen between pre-existing antibody concentrations and post-immunization antibody responses (resulting in 8% to 18% reductions in post-immunization antibody titers) for both DTP and DTaP. These data are particularly relevant in light of the current recommendation that all pregnant women in the United States receive tetanus and diphtheria toxoids with acellular pertussis antigens (Tdap) with each pregnancy. The earlier data suggest that the use of Tdap in pregnancy would be unlikely to adversely affect pertussis antibody responses after DTaP given to infants born to mothers with high antibody levels. However, studies to assess the effect of maternal Tdap on infant immune responses to routinely administered infant vaccines are ongoing.

Another recently published study suggests that maternal immunization could have adverse implications for immune responses of infants to conjugate pneumococcal vaccines [30]. In this randomized trial, pregnant women were given either an investigational 9-valent pneumococcal conjugate vaccine (PCV-9) or placebo during the last trimester of pregnancy with the goal of reducing early infant otitis media. Then all infants received 7-valent pneumococcal conjugate vaccine at 2, 4, 6, and 12 months of age. Results suggested that immunizing pregnant women with PCV-9 increased the infants' risk of acute OM in the first 6 months of life, and this correlated with decreased infant antibody responses to several of the *Streptococcus pneumoniae* vaccine serotypes. Explanations for these results included dampening of infant antibody production by high levels of passively acquired maternal pneumococcal antibodies and/or altered B lymphocyte immune responses in infants exposed to these specific polysaccharide antigens in utero. Additional studies are needed to affirm or refute these results.

Siegrist, in her excellent review of the mechanisms responsible for inhibition by maternal antibody on infant vaccine responses, hypothesized four specific mechanisms; (1) neutralization of live viral vaccines by maternal antibody, (2) epitope masking by maternal antibody, thus preventing antigen binding by infant B cells and limiting their priming, (3) inhibition of infant B cell activation by Fcγ-receptor mediated signaling, and (4) elimination of maternal antibody-coated vaccine antigens through Fc-dependent phagocytosis [31]. These mechanisms were further pursued in the comprehensive discussion by Niewiesk [2]. Although viral neutralization of live attenuated vaccines is often suggested to be the explanation for poor immune responses in the face of maternal antibody, this explanation does not address why maternal antibodies suppress both live and inactivated vaccines and non-neutralizing antibodies also efficiently block vaccine responses [2]. Another common mechanism espoused to explain the inhibition is epitope masking. However, high concentrations of some antibodies can be less inhibitory than lower concentrations of others. Further, the inhibition of maternal antibody is often not specific for that epitope [2]. One of the most attractive mechanisms hypothesized for the role of maternal antibody on inhibition of vaccine responses in the infant is the actual inhibition of B cell activation by the physical cross-linking of the B cell receptor, which recognizes the maternal antibody, and the Fc receptor which binds the IgG molecule on the surface of the B cells. This cross-linking results in a negative signal that inhibits both B cell proliferation and antibody secretion (Fig. 1). This mechanism is further supported by the work of Kim et al. who demonstrated in cotton rats immunized with live attenuated measles vaccine, that passively transferred measles-specific IgG inhibited B-cell responses through cross-linking of the B-cell receptor with the Fc receptor for IgG. The extent of inhibition increased with the number of antibodies engaging the Fc receptor [32]. These authors also showed that this inhibition could be partially overcome by administration of measles vaccine-specific monoclonal IgM antibody. The IgM stimulated the B-cell directly through cross-linking the B-cell receptor via complement protein 3d and antigen to the complement receptor 2 signaling complex. These data convincingly demonstrated that maternal antibodies inhibit B-cell responses through interactions with the Fc receptor and not through epitope masking. Finally,

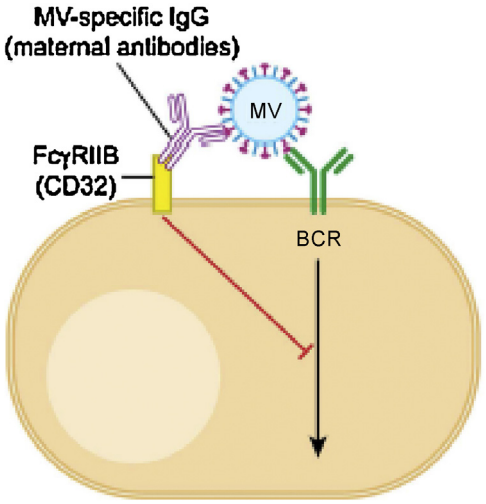

Fig. 1. In the presence of measles virus (MV)-specific maternal antibodies (IgG), the first signal is down-regulated by a cross-link between B cell receptor (BCR) and FcγRIIB. If MV-specific IgG binds to MV, the constant region is bound by the receptor for the constant region (Fc) of IgG (which is FcγRIIB). FcγRIIB is the only Fc-receptor on B cells and does not bind other immunoglobulins like IgM or IgA. After juxtaposition of the BCR and FcγRIIB, the tyrosine-based inhibitory motif of FcγRIIB is in close proximity to the tyrosine-based activation motif of BCR and delivers a negative signal, as shown by the red line. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Source: Figure modified from Ref. [2].

the potential for elimination of maternal antibody coated vaccine antigens through Fc-dependent phagocytosis has been brought into question by studies in knockout mice lacking FC receptors [33].

In summary, the inhibition by maternal antibody of infant vaccine responses has been documented for multiple vaccine antigens. In contrast, the T cell responses are largely not affected. For most vaccines, priming occurs in the presence of maternal antibody, but the extent and magnitude of the booster response may vary. Maternal immunization appears to have an important role in preventing disease in young infants, and the effect on infant responses will require continued evaluation. However, concern over suppression of immune responses to infant vaccination should not impede further development and study of maternal immunization programs against important neonatal pathogens.

Conflict of interest

I have served on a Data Safety and Monitoring Committee for an unrelated product in children for Novartis and my university has received funding from Novartis to conduct a study of Group B Streptococcal Vaccines in Pregnant Women.

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