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Review

Challenges in vaccination of neonates, infants and young children

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ABSTRACT

All neonates, infants and young children receive multiple priming doses and booster vaccinations in the 1st and 2nd year of life to prevent infections by viral and bacterial pathogens. Despite high vaccine compliance, outbreaks of vaccine-preventable infections are occurring worldwide. These data strongly argue for an improved understanding of the immune responses of neonates, infants and young children to vaccine antigens and further study of the exploitable mechanisms to achieve more robust and prolonged immunity with fewer primary and booster vaccinations in the pediatric population. This review will focus on our recent work involving infant and young child immunity following routine recommended vaccinations. The discussion will address vaccine responses with respect to four areas: (1) systemic antibody responses, (2) memory B-cell generation, (3) CD4 T-cell responses, and (4) APC function.

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1. Introduction

One of the biggest challenges facing vaccinations is that 19.3 million infants and children throughout the world do not receive the multiple recommended doses of vaccines required to achieve optimal immunity [1–6]. Aside from the many issues facing worldwide vaccination programs, there are environmental and genetic factors that affect the development of the immune system that also contribute to high mortality especially in neonates, infants and young children [3]. We are focusing on the mechanisms involved in the vaccine responses in these youngest of pediatric populations. This review will mainly focus on the work being done in our lab to address this important issue.

Maternal antibody and poor generation of T-cell and B-cell memory in neonates and infants are known to result in inadequate adaptive immunity from vaccinating this population compared to older children and adults [7–20]. Our group has recently identified a subset of infants and young children that fail to generate protective antibody levels to diphtheria (DT), tetanus (TT), pertussis (PT) toxoid, pertussis filamentous hemagglutinin (FHA), and pertussis pertactin (PRN) in DTaP vaccinations, polio serotype 3, and *Streptococcus pneumoniae* conjugated polysaccharide 23F (Prevnar-CRM) and produce lower geometric mean titers to polio serotypes 1 and 2 and, *Streptococcus pneumoniae* serotype 14 [21]. However, we did not observe an increase incidence of infections caused by diphtheria, pertussis, tetanus, etc. and reasoned that this could be due to limited-exposure and/or herd immunity. Therefore, we elected to study seasonal influenza infections since they occur as widespread annual community-wide outbreaks. We found that

Abbreviations: DT, diphtheria; TT, tetanus; PT, pertussis; FHA, toxoid pertussis filamentous hemagglutinin; PRN, pertussis pertactin; pDC, plasmacytoid DC; mDC, myeloid DC; sOP, stringent otitis prone; LVR, low vaccine responder; NOP, non-otitis prone; APC, antigen presenting cell; PBMC, peripheral blood mononuclear cells.

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otitis prone, OP, children show inadequate immune responses to influenza vaccination and therefore 10-fold more influenza infections (Verhoeven et al., Vaccine 2014, submitted for publication). These same children have $CD4^+$ T-cell memory recall responses to PT, FHA and PRN that are significantly inferior in quality as compared to adult responses [22]. We are calling these children "low vaccine responders" (LVR), as compared to "normal vaccine responders" (NVR), and have observed that they have features resembling a neonate's immune system [21–26].

We serendipitously discovered this group of low vaccine responders during our work involving infants and young children prone to recurrent middle ear infections [27–30]. In that research we identified a cohort of young children, 15 (5.9%) of 254, that experienced frequent recurrent middle ear infections, despite individualized care that included tympanocentesis drainage of acute otitis media (AOM) episodes and modification of antibiotic therapy as needed according to the otopathogen isolated and its antibiotic susceptibility [31]. We called these children stringent otitis prone (sOP) due to the stringent requirement of tympanocentesis-proven middle ear infections. Subsequently, we now have over 40 children out of 700 in our prospective study cohort who meet the sOP criteria. We hypothesized and showed that the propensity to recurrent AOM could be attributed to poor adaptive immune responses following infection by the dominant otopathogens *Streptococcus pneumoniae* and *Haemophilus influenzae*. Specifically we found low or absent antibody and cellular responses to vaccine candidate antigens PhtD, PhtE, Ply and LytB but less so to PcpA of *Streptococcus pneumoniae* [24,27] and to protein D and OMP26 but less so to P6 of *Haemophilus influenzae* [28,29]. Also, the children exhibited poor antigen-specific memory T-cell responses to *Streptococcus pneumoniae* and *Haemophilus influenzae* antigens, although they responded normally to Staphylococcal enterotoxin B, suggesting the primary immune defect might involve multiple factors such as poor antigen presenting cell (APC) function, altered innate responses or lower toll-like receptor expression [22,23,26,32,33].

Display of similar immune dysfunction in neonates, infants and young children following vaccination suggests the possibility of involvement of common cell types and mechanisms. Through studying dynamic differences in immune responses over time a better understanding of the state of flux of the immune response should be attainable as neonates and infants rapidly mature from the neonatal regulated state to a metered inflammatory phenotype to protect from disease but limit immunopathology.

2. Systemic antibody responses

Vaccination produces protective benefits primarily by induction of systemic antibodies [34–38]. Neonates, infants and young children produce lower vaccine-specific IgG serum titers than older children or adults to most vaccines [39].

In Fig. 1 changes in pediatric vaccine antibody titers over time for 68 age-matched infants and young children from age 6 to 30 months is shown. LVRs (red) selected from a cohort of sOP children and normal vaccine responders (black) selected from a cohort of non-otitis prone children are shown. The nadir of low titers at age 9–15 months old is seen, with improvement after first boosters (measured at 24 months), varying among vaccines. From the results we established an operational classification of children as normal vaccine responder when protective antibody levels to >80% of recommended vaccine antigens tested is achieved. A LVR would be an infant/child with below protective antibody titers to >50% of recommended vaccines tested [40].

We have also analyzed differences in immune response to influenza vaccination and occurrence of infection in LVRs. In that study we found plasma IgG responses to purified hemagglutinin HA1 or HA3 did not correlate with failure to protect against influenza infection. Instead it was the quality of the antibody as determined by hemagglutination inhibition titers and viral neutralizing antibody titers that identified bona fide LVRs who more frequently contracted influenza infection (Verhoeven et al. Vaccine 2014, submitted We have also studied immune responses to RSV. sOP children who are LVR, experience higher RSV viral burdens, lower RSV-specific IgG and neutralizing antibody levels that correlate with diminished T-cell responses to RSV. (Verhoeven et al. Clin Inf Dis 2014, revision submitted). In addition, these LVR children infected with RSV show lower expression of TLR7 on isolated APCs and lower level of activated HLA-DR expression on B-cells infected with RSV.

3. Memory B-cell generation

The ability of B-cells to proliferate and differentiate into memory and plasma cells influences the levels of protective antibodies. Infants and young children can elicit adult-like antibody avidity profiles after early-life immunization with protein vaccines [41]. But the underdeveloped B-cell repertoire and the absence of previous antigenic exposure lead to lower level of protective antibody [42].

We have recently studied antigen-specific memory B-cells [24] to provide a more precise understanding of dysfunctional mechanism(s) leading to reduced B-cell maturation to IgG- secreting plasma cells in infants and young children. We found that B-cell frequencies in the peripheral circulation correlated with serum levels of antigen-specific Ig responses of sOP infants and young children who were LVRs (Fig. 2) resembled B-cells of neonates. Immaturity in the neonatal B-cell repertoire may include a reduced strength of B-cell receptor (BCR) signaling, under-expressed co-stimulatory receptors and lower activation signals [43,44].

Two mechanisms in B cells likely account for much of the immune dysfunction in neonatal, infant and young children: inadequate B-cell receptor (BCR) signaling and lower levels of MHC class II (MHC II) expression (Fig. 3). CD22 is a surface exposed molecule that affects apoptosis and BCR signaling [44,45]. Neonatal B cells or cord blood lymphocytes show differential expression of CD22 depending upon antigen stimulation compared to adult B cells, resulting in either apoptosis or impaired B cell activation and differentiation [44]. Expression of MHC II molecules and their ability to present processed antigenic peptides to T helper cells play an important role in B-cell activation, proliferation, Ig isotype switching and somatic hypermutation [46,47]. Neonatal B-cells express lower levels of MHC II are less effective in antigen processing and presentation to T-cells. CD40 is another important receptor on B cells that interact with CD154 (CD40L), a co-stimulatory molecule on T cells that also regulates B-cell function [48]. The neonatal immune system has showed an immaturity at CD40-CD40L in the T-cell interaction with B cells and monocytes [49]. Lower levels of CD154 on T-cells also results in lower expression of signaling cascade proteins and lower expression of cytokine genes [50].

Follicular T-helper, Tfh, cell is another T-helper subset to help B cells differentiate into plasma cells and memory cells [51]. We are interested in the B-cell memory percentages in normal and low vaccine responding infants and whether peripheral blood levels of Tfh cells may reflect the vaccine responses. Preliminary data in our laboratory suggests that circulating blood levels of TFH cells in 6-month and 12-month old infants are significantly lower compared to older children and adults. We also found that the quantity of TFH cells in tonsils increases with age, as would be expected with "outgrowing" the immunological delay of CD4 T-cell activation (unpublished results). Importantly, lower percentages of TFH

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