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Mini Review

Neonatal Immunization: Challenges and Future Scenario

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Abstract

Infections are one of the greatest toll in early life requiring strong approaches to protect the very young. Here, we review neonatal immunization - the knowledge, its present state, and future scenario.

Keywords: Neonatal Immunization; Infections; HIV

Introduction

Infections are one of the greatest toll in early life requiring strong approaches to protect the very young. Here, we review neonatal immunization - the knowledge, its present state, and future scenario. Neonates and infants suffer a high frequency and severity of microbial infection resulting in millions of deaths worldwide [1]. We are able to reduce the under 5 mortality by 53% from 2000 to 2015 with the success of the Millenium Development Goal, still around 2 million infants under 6 months die annually due to infections [2]. It was found that around 5.9 million children under 5 years of age who died in 2015, 45% were neonate [3]. Most of these deaths are attributed to vaccine preventable illnesses, occurring before protection is afforded by routine immunization. The first dose is usually given at 6-8 weeks of age, the first dose does not provide immediate protection and multiple doses are required for providing complete immunity, hence leading the infants to vulnerability in the first 6 months of life. Neonates (defined as children less than 4 weeks of age) and young infants are less protected against life-threatening diseases due to lack of vaccines or late administration. For instance, developing a flu vaccine that can be given to infants younger than 6 months of age would significantly reduce worldwide morbidity and mortality from the disease. Recent research indicates that neonatal vaccination may be an effective strategy for protecting against early life infections such as influenza, respiratory syncytial virus, and pertussis. Preterm infants are at increased risk of infections in general and from vaccine preventable diseases in particular with increased incidence and severity [4,5]. Consequently, there is a need for timely vaccination of preterm infants, using the same schedules as recommended for full-term infants, without correcting for prematurity and regardless of birth weight [6,7].

The reality, that we rely on immunization occurring early in life, coupled with recent advances in our understanding of neonatal immune responses [8], has led to renewed interest in neonatal immunization as a promising and effective strategy, to reduce morbidity and mortality in young infants. Thus, the topic of early life immunity, and in particular neonatal immunization, is one of tremendous public health relevance. Great strides in vaccine development over the last century have resulted in a number of effective vaccines being given in early life, but only Bacille Calmette-Guérin (BCG), hepatitis B (HBV), and polio vaccine [oral polio vaccine (OPV); or inactivated polio vaccine (IPV)] have been routinely recommended at birth. For some pathogens, including pertussis and tuberculosis (TB), better vaccines are needed, while for others such as human immunodeficiency virus (HIV) and respiratory syncytial virus (RSV), efficacious vaccines have yet to be developed and licensed for any age group. Effective neonatal vaccination would be ideal especially for less-privileged infants, for whom birth is often the only contact with health care systems. Neonatal vaccination therefore has the potential to improve vaccine cover age and confer protection before initial exposure to vaccine-preventable viral and bacterial infections. Alternative, indirect strategies include vaccination of the pregnant mother and/or other family members so as to 'cocoon' the neonate against exposure to pathogens (e.g. expectant mothers in the US are recommended to receive the Tdap and inactivated influenza vaccines [9] [15]), but these strategies have shortcomings.

Potential barriers to neonatal immunization

Safety concerns

Concerns that have been raised regarding vaccination of neonates and infants include: i) doubts about efficacy given the limited

capacity of neonates to respond to many Ag; and ii) potential effects on immune system polarization, including potential for triggering autoimmunity via epitope mimickry or Aj effect [10,11]. From a theoretical perspective, these concerns are in part mitigated by: i) the documented ability of newborns to respond to several vaccines including Bacillus Calmette Guérin (BCG) and hepatitis B vaccine (as outlined below), which serves as proof of concept that neonatal vaccination can be safe and effective and; ii) the presence of extensive immunologic mechanisms for central and peripheral tolerance that eliminates self-reactive T and B cells in newborns, coupled with; iii) evidence that multiple pediatric vaccines, including BCG, are not linked to allergy or autoimmunity [12].

Inadequate immunogenicity of most vaccines at birth

Immunization in early life is a major public health imperative, but remains a challenging field. The neonatal immunological milieu, skewed towards Th2 immunity to prevent recognition of the developing fetus as an allograft by the maternal immune system [13], represents an important obstacle that vaccination during neonatal period must overcome. In addition to the challenge posed by immaturity of the neonatal leukocyte compartment, effective neonatal vaccines, must also overcome the potential inhibitory effect of MatAb [13]. In general, neonates mount impaired responses to T-independent polysaccharide antigens, and their antibody responses to T-dependent protein antigens are short-lived [5]. Accordingly, the 23-valent Streptococcus pneumoniae polysaccharide vaccine (PPV23) is not immunogenic in children younger than 2 years [14]. Although the pneumococcal protein-polysaccharide conjugate vaccine is safe and effective when administered to infants as a four dose series (2, 4, 6, and ≥ 12 months), its efficacy at birth is unknown and currently under investigation [15].

Proof of concept: Routine neonatal vaccines

Bacille calmette-guérin

Bacille Calmette-Guérin is a live-attenuated strain of *Mycobacterium bovis*. Given in areas with high-endemic TB to prevent disseminated TB in infancy, BCG is the most commonly given vaccine with ~4 billion doses administered to date. Although it has been administered for nearly 100 years, several key issues regarding BCG have emerged, including: (a) lack of a clear correlate of protection (CoP); (b) marked heterogeneity between licensed BCG formulations [16]; and (c) growing evidence that BCG has heterologous ("non-specific") beneficial effects, particularly when administered in newborns [17].

Hepatitis B vaccine

Hepatitis B vaccine is an alum-adjuvant vaccine containing hepatitis B surface antigen (HBsAg). The alum-adjuvanted HBV is given within the EPI and also in Australia, Europe, and United States, where a birth dose is recommended [18]. With respect to innate immune activation, while the Alum adjuvant present in HBV may engage the inflammation, HBsAg also interacts with CD14 to activate dendritic cells [19].

Polio

A birth dose of OPV has been recommended by the World Health Organization since -\P+[1984. It is hypothesized that a birth dose of OPV may induce mucosal protection prior to colonization or infection with enteric organisms which may interfere with the immune response to doses given later in life. Data on sero conversion following this individual dose of trivalent OPV (tOPV) vary greatly, from 10 to 15% in India to 76% in South Africa, however, the positive impact on levels of neutralizing Abs and sero conversion rates on completion of the routine immunization schedule are undisputed [20]. Some groups have advocated a shift to using IPV because (a) tOPV has been associated with rare cases of vaccine-associated paralytic poliomyelitis (~2-4 cases/million), (b) concerns about the use of live vaccines in immunocompromised individuals, including those with HIV infection, and (c) potential risk of strain reversion. Of note, however, some studies have suggested that similarly to BCG vaccine, a birth dose of live OPV may induce heterologous ("non- specific") beneficial effects.

Clinical studies of novel early life vaccines

Malaria is a leading global health problem against which no effective vaccine has yet been introduced in clinical practice. The RTS,S/AS02D candidate malaria vaccine was found to be safe, well tolerated, and immunogenic in infants up to 18 weeks old living in a highly endemic area of Mozambique [21]. It is a hybrid recombinant protein consisting of tandem repeats from a Plasmodium falciparum protein and the S antigen of HBV, formulated with the adjuvant system AS02 (a mixture of the Toll-like receptor (TLR) agonist monophosphoryl lipid A (the active moiety of lipopolysaccharide/endotoxin) and monophosphoryl lipid A (the active moiety of lipopolysaccharide/endotoxin) and the detergent saponin QS21). Candidate HIV vaccines capable of generating robust immunologic responses in breastfeeding infants are also being developed [22]. Other novel early life vaccines current being studied include vaccines against Salmonella typhi, RSV, influenza, and parainfluenza. Additional studies are assessing co-administration at birth of hepatitis B vaccine in combination with hepatitis A or BCG, that may modify responses to other vaccines [23].

Need for novel approaches to enhance neonatal vaccination

The ability of certain vaccines such as BCG and HBV vaccine to exhibit some efficacy at birth provides proof of concept that despite generally impaired APC function and Th1 responses, neonatal vaccination is possible. The medical advantages inherent to neonatal vaccines effective at birth include: i) early protection that would close the window of vulnerability inherent to vaccination schedules that start later in life (e.g. 2 months), ii) the practicality of birth being a global point of contact with healthcare systems, and ii) potential advantages of novel vaccines that may require fewer doses to achieve efficacy. In this context, we review recent approaches to the development of neonatal animal models and recent *in vitro* work with human neonatal cells.

Current research on early life immunization

Enhancing current vaccines

One approach to developing enhanced neonatal vaccines focuses on improving existing vaccines such as the live "self- adjuvanted" BCG vaccine. For example, the BCG-derivative VPM1002 expresses listeriolysin from *Listeria monocytogenes* designed to enhance MHC-I responses (60). In a phase II open label study comparison with conventional BCG-SSI in South African newborns (n = 48), VPM1002 demonstrated safety and immunogenicity with an increased proportion of CD8+ IL-17+ cells at 6 months post-vaccine. The authors speculate that although the significance of such cells is unknown, it is possible that they could contribute to more robust protection against TB and that larger studies are needed to assess this possibility.

Development of adjuvants for early life immunization

Another approach to enhancing vaccine responses in infants with "age-appropriate" immunity is the addition of adjuvantation systems to enhance vaccine immunogenicity and efficacy. PRR agonists such as mono-phosphoryl lipid A that activates TLR4, have been employed as vaccine adjuvants but the translational path for this approach must take into account that responses to PRR stimulation vary markedly with the age of a given individual (6). In developing adjuvant systems optimized to early life, there may be lessons to learn from live-attenuated vaccines currently in use.

Conclusion

Overall, neonatal immunization is a common practice across the globe, yet much can be done to optimize its beneficial impact. Taking advantage of pivotal opportunities to enhance this approach will require engagement with stakeholders, including government, funding agencies, and the general public, on: (a) the need for greater precision in our understanding of how current neonatal vaccines protect, the potential impact of the exact timing of administration in the neonatal period (i.e., first 28 days of life) and of vaccine-vaccine interactions, (b) assessing how maternal and neonatal immunization can be best integrated, and (c) leveraging modern tools including systems biology and human *in vitro* modeling to study the impact of immune ontogeny on vaccine responses thereby informing development of novel vaccines for use in early life against pathogens for which currently vaccines are in adequate (e.g., pertussis, TB, and influenza) or do not yet exist (e.g., RSV, HIV).

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