Neonatal Immunization

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Contents

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7.1 Introduction

Neonatal immunization refers to the immunization of newborns during the first 28 postnatal days; however, neonatal immunization may also include vaccines used in the first 2 months of life and immunization practices among high-risk neonates, including preterm newborns.

Neonatal immunization represents a key global strategy in overcoming morbidity and mortality due to infection in early life. Neonatal immunization will provide early protection for neonates and infants, narrowing the critical and vulnerable duration between birth and before routine immunization schedules begin. With neonatal immunization, if an immunogenic response is elicited at this early stage, less vaccine doses may be required, as there may be a general immunomodulatory effect which improves immunity from birth until exposure to pathogens. Neonatal immunization can be easily implemented, considering that birth is a key point of communication with the global health system. Neonatal immunizations have not made the same progress as maternal immunizations, due to certain barriers and risks, including weak immunogenicity, safety concerns, and hypo-responsiveness to either the same antigen or concomitant antigens administered at birth or in subsequent months. The ideal vaccine for neonatal period will be delivered orally rather than via intramuscular or subcutaneous routes at birth (or before 4 weeks of age), safely eliciting a strongly protective response after a single dose with minimal interference with maternal antibodies. As part of the subsequent routine infant immunization schedule, this response will be sustained or easily boosted without developing hyporesponsiveness when confronted with the same or concomitant vaccine antigens.

7.2 Neonatal Immune System and Related Factors

The neonatal immune system is no longer considered immature, but rather precisely adapted for early postnatal life, developing over time through a regulatory process that has not yet been well defined. Mohr and Siegrist described the neonatal immune system as a response to danger signals and antigens characterized by anti-inflammatory rather than pro-inflammatory responses, leading to the preferential differentiation of CD4+ helper T cells (Th) to Th2 cells that antagonize Th1 cells and cytotoxic responses to intracellular pathogens, based on their propensity to differentiate into immunoregulatory cells. Immunological milieu is polarized towards Th2-type immunity with dampening of Th1-type responses and impaired humoral immunity, resulting in quantitatively and qualitatively poorer antibody responses compared to older infants. The efficacy of vaccines against the tuberculosis, hepatitis B, and oral polio is evidence of the concept that neonatal immunization can be used effectively.

The neonatal adaptive immune system is predominantly composed of naive lymphocytes during the intrauterine phase, indicating low exposure to foreign antigens. Dynamic changes in the maternal and fetal immune systems are necessary for a healthy pregnancy. After birth, the newborn and young infant's immune systems develop to meet the challenges of tolerance to commensal and immunity to infectious pathogens. The lack of cells encountered by antigens confers susceptibility to severe pathogens and leaves newborns reliant on their innate immune system. Functional deficiency in antigen-presenting cells is also demonstrated by innate immunity: the expression and signaling of toll-like receptors undergo maturational changes associated with different functional responses. This mechanism is biased against the activation of cytokine polarization of T helper 1 (Th1) cells, which is essential in preventing alloimmune reactions or excess anti-inflammatory reactions between mother and fetus but increases susceptibility to many viral and bacterial pathogens. In order to prevent the identification of the developing fetus as an allograft by the maternal immune system, the neonatal immunological environment is skewed towards T helper 2 (Th2) immunity, which poses a significant obstacle to vaccination during the neonatal era. Responses to

two main threat pathways in neonates, toll-like signaling of the receptor and interleukin (IL)-1/inflammasome pathways, are dampened and fail to induce potent pro-inflammatory responses, including IL-12p70, Th1 master cytokine, and cytotoxic responses. The low responsiveness of neonatal T cells to toll-like receptor and IL-1/inflammasome pathways has an impact on the intrinsic ability of T cells to respond to vaccines and pathogens. B-cell intrinsic and extrinsic features/limitations affect early-life humoral responses, but they are largely regulated by extrinsic factors. After birth, follicular dendritic cells grow slowly, delaying germinal cell formation, and bone marrow stromal cells have inadequate survival factors, such as a proliferation-inducing ligand. A major limiting factor for the growth of early-life germinal complex responses is the expansion of T follicular helper cells.

The quality and quantity of early infant antibody response are determined by several factors, including the stage of infant immune system development, the type of vaccine and its intrinsic immunogenicity, the number of doses and intervals between doses, and the effect of maternal antibodies. Most of the serum immunoglobulins of the newborn are derived from the transfer during the third trimester of pregnancy of maternal immunoglobulin G (IgG) through the placenta. Neonates and infants have a limited antibody repertoire, can produce suboptimal antibody responses to certain polysaccharides and protein antigens, and may demonstrate the limited persistence of these antibodies. The pathway of neonatal B-cell differentiation is skewed towards memory B cells rather than plasma cells. Increasing the placental transfer of maternal antibodies can effectively protect newborns and babies against such diseases, including tetanus, influenza, and pertussis. The amount of antibody transferred depend on several factors, including gestational age, maternal antibody level, type of IgG subclass, and placental characteristics. Maternal antibodies may interfere with infant vaccine responses, and also breast milk antibodies may affect the efficacy of vaccines. Concerns about the use of vaccines during the newborn period include the limited capacity of neonates to respond to many antigens and the potential effects of vaccinations on the immune system polarization during prenatal and early periods after birth. Immune components central to vaccine responses, including antigen-presenting cells, B cells, and T cells, function differently at birth than later in life. The implications of these complex changes on the efficiency of immune responses during pregnancy and soon after birth remain poorly understood. The advent of new technology and computational tolls allowing vast and complex data sets to be combined opens up new ways of understanding the immunobiology of the mother-infant dyad.

Maternal cofactors influencing immune ontogeny and immune responses in early life include chronic maternal infections, nutrition, the microbiome, and the levels and specificity of maternally acquired antibodies. Vaccines currently given at birth provide strong evidence that protective immunity can be induced by vaccination and can also inform on the potential of neonates to develop specific immune responses and on the impact of cofactors. There are three maternal factors that could theoretically influence the effectiveness of neonatal immunization: maternal-fetal antibody transmission, maternal-fetal pathogenic organism transfer, and recurrent maternal infections. Genetic variance between hosts, in addition to maternal influences, plays a key role in the observed variability of early responses to neonatal and infant vaccines. Another factor influencing the quantity and consistency of innate and adaptive responses is prematurity. Neonatal immunity and therefore vaccine responses often vary greatly across various geographical settings. The formation of gut microbiota, considered to be crucial for optimal host immune growth, is influenced by environmental factors combined with host genetics.

7.3 Neonatal Vaccines

The immunization studies have focused on the potential use of existing vaccines during the neonatal period, immunization practices in

premature babies, and new vaccines and adjuvants. The same immune deficiencies that render newborns susceptible to infection also reduce their memory responses to most antigens, thereby potentially frustrating efforts to protect this high-risk population. Some vaccines have been developed and proven safe and effective at birth. Three vaccinations are frequently used in neonates: the Bacillus Calmette-Guérin (BCG) vaccine, hepatitis B vaccines, and the oral polio vaccine (OPV). Recently, the use of neonatal rotavirus vaccines has also seen some promising results. As birth is the most reliable point of health-care contact worldwide and effective vaccination at birth would provide early protection for newborns and infants, expanding and improving the available means of neonatal vaccination are a global health priority.

7.4 BCG Vaccine

The BCG vaccine (see also ▶ Chap. 17) is a live attenuated *Mycobacterium bovis* vaccine that is usually administered intradermally within the first few days of life in most low- and middle-income countries to prevent tuberculous meningitis and miliary tuberculosis. Most infants receive the BCG vaccine at birth in accordance with World Health Organization (WHO) recommendations. The BCG vaccine is one of the most commonly used vaccines globally, with more than three billion people having received this vaccine, and the BCG vaccine exhibits an excellent safety profile. The protective efficacy of the neonatal BCG vaccine is 64–73% against meningitis and 77–78% against miliary tuberculosis. The effectiveness differs between countries, particularly against military tuberculosis and meningitis of tuberculosis, reflecting differential exposure to environmental mycobacteria, variations of the strain used in the BCG preparations, genetic or nutritional differences, and environmental factors such as exposure to sunlight and poor maintenance of the cold chain. The greatest benefit of BCG immunization has been observed in regions where both the risk of tuberculosis and the rates of vaccine coverage are highest.

The effectiveness of neonatal BCG vaccine administration has been linked to its ability to effectively induce neonatal immune responses that are polarized by anti-mycobacterial CD4+ T-cell Th1. BCG does not contain any exogenous adjuvant but is inherently "self-adjuvanted" because *Mycobacteria* induce immune responses via TLR2, TLR4, and TLR8. BCG vaccination at birth results in neonatal IFN-γ production against mycobacterial antigens, and the levels of secreted IFN-γ are comparable with adult levels. Notably, in early childhood, BCG also influences the immune response to unrelated antigens, enhancing both Th1- and Th2-type responses to other antigens (e.g., HBV and oral polio vaccines), possibly due to its effect on the maturation of dendritic cells (DC). Th1 responses are characterized by CD4+ T-cell interferon (IFN)-γ production. For combating infections with intracellular pathogens and toxin-producing species, enhanced neonatal Th1-polarized immune responses will be beneficial. Neonatal BCG vaccinations have demonstrated non-specific or heterologous effects against other unrelated infections, and it has also been reported to reduce neonatal and infant mortalities resulting from unrelated diseases. A meta-analysis of three BCG vaccine trials showed that early use of the BCG vaccine reduced mortality by 38% within the neonatal period and 16% by age 12 months. Cellular immunity measured at 10 weeks after BCG immunization was similar in infants administered BCG at birth and in those administered BCG at 2 months of age. These results suggest that delaying BCG immunization might not confer any immunological advantage in cellular immunity. Early administration of the BCG vaccine in low birth weight infants is also related to substantial reductions in mortality rates. The non-specific beneficial effects can also include reduction of atopic diseases (see ▶ Chap. 17). Although the underlying immunological mechanisms were not thoroughly elucidated, for these non-specific results, two theories were proposed: "trained innate immunity" and "heterologous immunity." The capacity of the innate immune system to produce immunological memory is defined by "trained innate immunity" and

thus trained to provide partial defense against subsequent infections, independent of classical T- and B-cell adaptive immunity.

Disseminated BCG infections are a major concern regarding the use of the BCG vaccine at birth. A disseminated BCG infection is a rare complication, occurring in less than one per million individuals, mainly those with congenital immune deficiencies. BCG vaccination at birth is no longer recommended in HIV-positive infants because of the risk of disseminated BCG disease, in approximately 1%, and the limited vaccine efficacy in HIV-infected infants.

The BCG vaccine is routinely recommended in Bulgaria, Hungary, Ireland, Latvia, and Lithuania at 48 h after birth without tests. In Poland, the BCG vaccine is administered within 24 h of birth. In Croatia, vaccination is ideally given at the time of hospital delivery; otherwise it should be given before 1 year of age. Vaccines in Cyprus and Luxembourg are administered only for particular indications at birth. In the Czech Republic, the BCG vaccine is given to babies in at-risk groups from the fourth day until 6 weeks after birth. In Estonia, BCG administration is recommended 1 to 5 days after birth. In Finland, France, Greece, and Malta, BCG vaccines are only given to specific groups at risk. In Romania, BCG vaccination is recommended 2 to 7 days after delivery. In Slovenia, vaccination is recommended for newborn infants of immigrant families who moved to Slovenia from countries with a high prevalence of tuberculosis in the last 5 years. Vaccination is recommended in the UK for infants and children who are particularly likely to come into contact with tuberculosis (see also ► Chap. 17).

7.5 Hepatitis B Vaccine

Primary prevention through immunization remains the most effective strategy for controlling the spread of the hepatitis B virus (HBV). One dose provides ~30–50 percent protection in healthy infants, two doses provide 50–75 percent protection, and three doses provide >90 percent infection protection from HBV. In the absence of antigen exposure/booster immunization, immunity elicited by neonatal/infant HBV immunization continues during life (see ► Chap. 13). Regardless of endemicity, the WHO recommends that the hepatitis B vaccine be given uniformly within 24 h of birth, followed by two or three additional doses of the vaccine. The first dose must be given within 7 days. The recommended birth dose schedule of the vaccine can eliminate most perinatally acquired infections and provide early protection against horizontal transmission. The hepatitis B vaccine induces at least equivalent antibody responses in newborns and adults; this suggests that the capacity of the newborn to develop antibody responses depends on the nature of the immune stimulus. The success of the HBV vaccine schedule confirms that, regardless of the primary antibody response, vaccination at birth can elicit potent memory B-cell responses that promote the immunogenicity of subsequent vaccine booster doses. It has been shown that the T-cell responses elicited by the HBV vaccine differ between newborns and adults; there are lower interferon-γ production (reflective of Th1 immunity) but higher Th2 memory responses compared to adults in those vaccinated at birth. In Europe, the first dose of the hepatitis B vaccine is recommended at 12 to 24 h after birth in Bulgaria, Poland, Portugal, Romania, and Turkey. Hepatitis B vaccination concurrently with hepatitis B immunoglobulin is recommended at birth for babies born to a mother infected with hepatitis B, and initial vaccination is given at birth. In 2017, the Advisory Committee on the Immunization Practices (ACIP) of the USA added monovalent hepatitis B vaccinations to all newborns within 24 h of birth. ACIP recommends the hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth for infants born to hepatitis B surface antigen (HBsAg)-positive mothers. The guidelines of the ACIP include the administration of the hepatitis B vaccine, irrespective of birth weight, if the status of the mother with HBsAg is uncertain.

7.6 Oral Poliovirus Vaccine (OPV)

An oral polio vaccine (OPV) is also recommended at birth as part of routine immunization in certain countries. The WHO also recommends an OPV dose at birth (called the "zero" dose) in polio-endemic countries and in areas at high risk for importation and eventual spread, followed by a primary sequence of three OPV doses with at least one IPV dose. OPV remains the first mucosal vaccine received by most newborns. Until April 2016, a trivalent OPV formulation was used worldwide, at which point it was substituted during a global coordinated switch with bivalent type 1 and type 3 OPV (see ► Chap 8).

7.7 Rotavirus Vaccine

A rotavirus vaccine provided at birth may provide early protection and could maximize the opportunity to complete a full vaccine schedule. In the early phase of the development of rotavirus vaccine, the use of a neonatal dose was investigated but was not followed due to concerns regarding legal issues related to safety.

The oral human neonatal rotavirus vaccine (RV3-BB) has been developed from the human neonatal rotavirus (RV3) strain (G3P[6]) found in the stools of infants with asymptomatic infections. In a phase 2a trial in New Zealand, when administered according to a neonatal or infant plan, RV3-BB was immunogenic and no safety issues were found. In Indonesia, a randomized, double-blind, placebo-controlled trial of RV3-BB found that healthy newborns received three doses (neonatal 0–5 days, 8 weeks, and 14 weeks of age) and the efficacy of the vaccine was 75%, compared with 51% in the child and 63% in the neonatal and infant combination groups, respectively. RV3-BB has been shown to have a vaccine efficacy of 94% at 12 months of age and 75% at 18 months of age when administered according to the neonatal schedule, findings that support the administration of RV3-BB starting from the time of birth.

The implementation of the rotavirus vaccine with a birth dose requires co-administration with other vaccines where available in newborn immunization schedules. Cowley and colleagues evaluated the co-administration of the RV3-BB and OPV, which are administered at birth in many developing countries. The two vaccines are oral vaccines, both of which replicating in the gut. Cowley and colleagues found that the responses of the poliovirus serum antibody and serum antibody titers to poliovirus 1, 2, and 3 were similar in newborns receiving RV3-BB co-administered with the OPV. The use of RV3-BB in a birth dose strategy is novel and has been shown to be effective in developing countries, but not yet adopted in practice.

7.8 Monovalent Acellular Pertussis Vaccine

In developed countries, the majority of deaths due to whooping cough occur in the first 2 months of life. The first clinical trial of the neonatal pertussis vaccine started in the 1940s but did not proceed due to subsequent concerns regarding immune tolerance and reduced responses in the presence of maternal antibody. A good safety profile was previously demonstrated by immunization within 24 h of life with whole cell pertussis or combined with diphtheria and tetanus vaccines; however, the serological response was suboptimal and a decreased response to pertussis boosters was recorded in 75 percent of study subjects up to 5 months of age, regardless of the low maternal antibody titer. Some studies have shown decreased responses to vaccines given concomitantly with the second dose of the pertussis vaccine. The activation of Th2-polarized cellular immune responses can be another disadvantage of pertussis immunization at birth. Immunization of neonatal pertussis may be suggested in babies born to mothers with low levels of Ab, decreased reaction to pertussis vaccine, or decreased transfer of maternal antibodies. In a randomized clinical trial in Australia, immunogenicity and safety from the birth dose of the monovalent acel-

lular pertussis (aP) vaccine were assessed between 2010 and 2013 in 440 healthy term infants of less than 5 days of age at recruitment. Of the babies receiving the aP vaccine at birth, 93.2 percent had detectable antibodies to both PT and pertactin at 10 weeks, while 50.8 percent had these antibodies in the control group.

To conclude, a birth dose aP vaccine is safe and well-tolerated and results in only nonsignificant decreases in antibody responses to some concomitantly administered vaccine antigens. Acellular pertussis vaccine administration at birth has the potential to decrease severe morbidity due to potential of pertussis infection in the first 3 months of life, especially in infants of mothers who have not received a pertussis vaccine during pregnancy. At this time, the neonatal pertussis vaccine is an alternative strategy for infants when their mothers have not been vaccinated, although maternal vaccination would be a better choice (see ► Chap. 6).

7.9 Pneumococcal Vaccine

There are limited studies about the use of pneumococcal conjugated vaccines with a birth dose. In Kenya, the use of the seven-valent conjugate vaccine (PCV7) at birth (with 10 and 14 weeks) appears to be safe, and there was no substantial difference in the proportion of IgG above the protective threshold for each serotype at 18 and 36 weeks compared to the routine infant regimen, whereas the geometric mean concentrations for some serotypes in the birth dose group were lower. Response to 36-week boosters and vaccine-type/non-vaccine-type carriage prevalence were comparable between groups, suggesting absence of immunological tolerance after schedule including birth dose. PCV7 was administered in Papua New Guinea on a 0–1-2-month (neonatal) cycle with a 23-valent pneumococcal polysaccharide vaccine booster at the age of 9 months. Although all antibody responses to vaccine forms in the birth dose group were not lower than those in the infant group at 2 months of age, the infant-immunized group typically had higher antibody levels over time than the neonatal-immunized group. There is also no birth dose tolerance for PCV7 in this research. However there are no routine recommendations for birth dose for PCVs.

7.10 Immunization of Premature Infants

It is generally recommended that premature infants should follow the same vaccination schedule that is generally used for full-term infants, without correcting for prematurity and regardless of birth weight. The routine immunization of premature infants, however, is frequently delayed because many clinicians suspect that these infants' compromised immune systems could substantially suppress responses to vaccine antigens and minimize the vaccination's protective effects. Preterm infants have lower than normal maternal IgG concentrations, resulting in increased susceptibility to infection, including pertussis, pneumococcus, rotavirus, influenza, and RSV. This is in part also due to reduced cellular immune responses and lower lymphocyte counts, as well as lower levels of maternal antibodies. Preterm infants are frequently excluded from new vaccine prelicensing trials, effectiveness studies are almost non-existent, and immunogenicity studies contain small numbers, different schedules, and different populations with differing requirements for inclusion and exclusion, posing a barrier for this group in evidence-based decision-making. Preterm infants typically have lower antibody concentrations after primary vaccinations than full-term infants, but proportions achieving protective concentrations may be equivalent for vaccines for which correlates of protection have been described. In these infants, booster doses are particularly important. Potential post-immunization adverse events, such as apnea and major cardiorespiratory events, occur more often in preterm infants than in full-term infants, but, overall, vaccinations are safe in preterm infants who should be immunized in accordance with their chrono-

logical age rather than their adjusted gestational age.

Numerous differences in vaccine responses between premature and full-term newborns have been observed. Less than sufficient amounts of peptides are secreted by skin, lung, and epithelial cells, such as defensins, which can alter gene expression, act as chemokines and/or induce chemokine production, inhibit the production of pro-inflammatory cytokine-induced lipopolysaccharides, and modulate the responses of dendritic cells and adaptive immune response cells. For premature newborns, an impaired innate system is another important factor for immunization via antigen-presenting cell dysfunction resulting from suboptimal vaccine responses. Adaptive cellular and humoral immunity is also less efficient in premature newborns, including the suboptimal functioning of Th1 and Th2 polarized responses with the relative impairment of Th1 activity, significantly reduced T-cell repertoire limiting the recognition of the peptides, less IL-2 production, decreased cytolytic activity, and abnormal cytokine production associated. Premature infants predominantly respond with IgM, and there is a slow or no switch to IgG. Maternal antibodies are lower in premature babies than in infants, which could potentially enhance vaccine responses. Clinical studies have shown that premature infants seroconvert in response to the hepatitis B vaccine by 30 days of age, regardless of gestational age and birth weight, suggesting that prematurity per se rather than gestational age or birth weight might be more predictive of a decreased antibody response.

Babies born at under 32 weeks of gestation or with a birth weight of under 2000 g are advised to receive their hepatitis B vaccines at 0, 2, 4, and 6 months of age followed by either a test for hepatitis B antibodies at 7 months of age and a booster at 12 months of age if the titer of the antibody is <10 mUnits/mL or give a booster at 12 months without measuring the titer of the antibody. Recent systematic review evaluated the immunogenicity and the safety of BCG vaccine in preterm and/or low birth weight neonates which were vaccinated in the first 7 days. There is no difference in the incidence of death, systemic disease, scar formation, and immunogenicity. Based on their findings, they recommended early BCG vaccination in stable infants who are preterm and/or have low birth weight to improve uptake. The immunogenicity of the meningococcal C-conjugated vaccine in premature infants is not different from that of full-term infants. Most studies on the *Haemophilus influenzae* type b vaccine reported only marginal differences between premature and full-term infants. This finding clearly indicates that most premature infants, particularly those at a gestational age > 32 weeks, remain protected, even after the primary series. Premature infants are at an increased risk for invasive pneumococcal disease compared with term infants and are more likely to have lower vaccine responses compared with term infants. A recent clinical study that included 210 premature newborns showed that after primary PCV13 vaccination, 75%, 88%, and 97% of participants had protective antibody concentrations for at least one-half of the PCV13 serotypes for the reduced, accelerated, and extended schedules, respectively. After the booster vaccination, nearly all participants, regardless of schedule or serotype, had seroprotective IgG concentrations. A reduced priming schedule for PCV13 resulted in higher post-booster IgG concentrations, but lower post-primary concentrations. Preterm infants are vulnerable to severe rotavirus infection resulting in hospitalization. Rotavirus vaccines are immunogenic and safe and have been demonstrated to have similar effects in preterm infants to term infants when given according to calendar age. However, preterm newborns are usually not given rotavirus vaccine at birth but only at a calendar age of 6–8 weeks.

Overall, premature infants should follow the same vaccination schedule as that generally used for full-term infants, without correcting for prematurity and regardless of birth weight. Even though an impaired immune response can reduce antibody production and cell-mediated immunity, antibody production is high enough to ensure short- and long-term protection in most premature infants. Maternal immunization is a crucial mechanism by which these highly vul-

nerable infants may be covered, given that vaccination takes place in the second trimester and that a significant transfer of antibodies is accomplished prior to birth, although this benefit will not carry for extremely vulnerable preterm infants.

7.11 The Need for Novel Approaches to Enhancing Neonatal Vaccination

There are three innovative approaches to neonatal immunization: new types of vaccine configurations (both modes of action and antigen-adjuvant formulations vary), new types of delivery for vaccines, and new types of strategies for infant immunization. Adjuvants boost infant immunity via multiple mechanisms: triggering inherent immune responses; increasing the half-life of the vaccine antigen by producing a "depot effect"; assembling and directing antigens to antigen-presenting cells (APCs) and then activating them; generating stronger mucosal responses; and fostering cell-mediated immunity by improving the role of cytotoxic or Th-1 form T cells. Adjuvants strengthen neonatal vaccine immunogenicity through innate activation and through the enhancement of multiple aspects of adaptive immunity. Adjuvants, such as monocytes and dendritic cells, can activate APCs and increase the development of cytokine and co-stimulatory marker expression, which enhances the priming of naive CD4+ T cells. CD4+ T cells can differentiate into T follicular helper cells after activation and antigen presentation, which are essential in the germinal center reaction to assist B cells in generating effective antibodies. Improvement in memory and plasma B cells increases the identification and neutralization of antigens by increasing the production of antibodies of high affinity.

Novel adjuvants are an exciting area of neonatal immunizations. Much interest has focused on specifically stimulating TLR3, TLR7, TLR8, and TLR9 receptors, which are located within endosomes and display robust responses to stimulation in neonates. It has been shown that pertussis toxoid-specific antibody secretion has been increased by CpG DNA, a TLR9 ligand. Similarly, TLR8 agonists, such as some synthetic imidazoquinolines and single-stranded viral RNA, are especially effective in stimulating in vitro human neonatal APCs, eliciting secretion of TNF and IL12p40/70 and promoting upregulation of the CD40 co-stimulatory molecule. Recently, TLR8 agonist nanoparticles (polymersomes) mimic immunomodulatory mechanisms with higher IL12p70 secretion seen after BCG administration. In particular, the ability to concurrently stimulate multiple TLRs has a synergistic effect, with a recent emphasis on combined stimulation of TLR7/TLR8 to bypass impairment of APC responses in newborns. Simultaneously ligating both TLR7 and TLR8 receptors, R848 is especially effective in activating human neonatal APC in vitro, resulting in more pronounced TNF alpha and IL-1β production than when individually stimulated at these sites. When administered to rhesus macaques on the first day of life, a lipidized TLR7/8 agonist has been reported to enhance B-cell responses to a polysaccharide pneumococcal vaccine. Some combinations of STING and TLR agonists function in synergy to cause Th1-polarizing responses from human neonatal antigen-presenting cells, indicating that STING agonists may be candidate adjuvants for early life immunization, alone or in combination with alum and/or TLR agonists. There are limited studies on the effects of TLR adjuvants, with most neonatal data still coming from neonatal animal models on novel adjuvants, with uncertainty as to how well the situation in human neonates could reflect this. Recently, sugar-like structures have been shown to prime the adaptive immune system for infants to respond to vaccines, possibly being more successful than conventional adjuvants. In neonatal vaccine models, sugar-based compounds with beneficial adjuvant effects include delta inulin and curdlan. Such compounds, either used alone or in conjunction with conventional innate immune adjuvants, make potential neonatal adjuvant candidates.

Experimental studies have indicated that antigen entry into the cytoplasm of APCs is a crucial condition for the induction of an efficient neonatal adaptive response. Neonatal immune responses can be enhanced by the cytoplasmic delivery of antigens. An attenuated strain of the intracellular pathogenic bacterium *Listeria monocytogenes* has used a novel approach to neonatal vaccination to transmit antigens to the APC cytoplasm. Another approach is fostering the robust response of T cells, including transferring polarization to immunity of type Th1. In mediating DC-directed T-cell differentiation to TFH, interleukin-12 is essential and co-administration of IL12 and influenza subunit vaccine to newborn mice has resulted in the improved protective efficacy of antiviral immunization.

Administration of neonatal vaccines through the mucosal route will be an option for increasing their efficacy. Experimental studies on intranasal administration of the candidate RSV vaccine at birth can, even in the presence of high RSV-specific maternal antibody titers, elicit systemic humoral immune responses and elevated IFNγ secretion. In order to improve immune responses to homologous or heterologous boosters in later childhood, there are also several hybrid methods, such as using neonatal vaccines as primers.

7.12 COVID-19

Concerns about the risk of vertical or perinatal transmission of SARS-CoV-2 and the impact of the infection on the pregnant woman, the fetus, or the infant have been posed during the current COVID-19 pandemic. In newborns, the incidence and complications of COVID-19 tend to be relatively mild. A recent systematic analysis of neonatal COVID-19 infections showed that 71% were confirmed/probably postnatally acquired, 3.3% were intrapartum acquired (with an additional 14% likely/possibly intrapartum acquired), and 5.7% were confirmed congenital cases (with an additional 6.5% likely/possibly congenital). There is no current clinical trial of the proposed newborn COVID-19 vaccine and no evidence on the normal use of these candidates in infants. Due to the potential for non-specific (heterologous) immunomodulatory effects resulting in defense against a variety of infections, BCG remains a significant interest, as postulated for COVID-19, but there is no routine recommendation for the BCG vaccine for the potential prevention of COVID-19. WHO recommended that the existing evidence was insufficient to prompt a revision of immunization policy including the prevention of COVID-19.

There are tremendous scientific activities underway to achieve safe and efficient vaccines and new immunization methods, including mRNA vaccines, adenovirus vector-based vaccines, or protein subunit vaccines, and these have been reported with encouraging results. Experience with these technologies and lessons learned from COVID-19 vaccine would be an option for potential neonatal vaccines. The evaluation of vaccine-preventable disease epidemiology and routine neonatal immunization records should be a priority for all countries during and after the pandemic.

7.13 Conclusion

Maternal and neonatal immunization is an effective key strategy in reducing death and significant morbidity from infectious diseases globally. A significant goal of global interaction with health care is the production of early life vaccinations, including vaccines that are safe when administered at birth. Even in the presence of maternal antibodies, an ideal vaccine for neonatal period would induce a rapid immune response and would have an optimal safety profile. Despite the difficulties inherent in the production of vaccines for newborns, there is a clear reason for continued vaccine development for this population, including the fact that birth is the most secure point of contact with health care. Newborn vaccines are also a valuable and secure probe for neonatal immunity that create a more

thorough understanding of protective mechanisms in early life by allowing the controlled delivery of a well-defined immune challenge to the naive newborn immune system. There is a common practice of neonatal immunization against tuberculosis, hepatitis B, oral polio virus vaccine, and some promising recent rotavirus vaccine findings. Considering the potentially significant benefit of vaccinating at birth, the availability of a broader range of more effective neonatal vaccines is an unmet medical need and a public health priority. In future studies, lessons from early immune ontogeny must be incorporated, and focus must be on the creation of vaccine types with novel mechanisms of action that associate with the distinctive neonatal immune profile. Innovative neonatal vaccines must also undergo both comprehensive safety tests and human clinical trials.

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