readily elicited at an early stage, but that early immunization is associated with lower IFN-γ responses (and higher IL-4, IL-5, and IL-13 responses) to most conventional vaccines (reviewed in Ref. 14). Altogether, these observations suggest a preferential differentiation of early-life T-cell responses to viral/protein vaccines toward the Th2 pathway, as a ''default'' developmental pathway (reviewed in Ref. 49) reflecting suboptimal APC-T cell interactions. Evidence that neonatal APC function may be immature has indeed been provided in mice and humans (reviewed in Refs. 50 and 51). Available data suggest limited responses to most but not all (52) TLR ligands. Limitations in the capacity to release IL-12/IFN-γ persist during the first year of life (53), and deficiencies in the numbers of APC and their functional competence limit the capacity to express effector memory responses (54). Future studies are expected to better define the relative influence of the immaturity of neonatal APC, neonatal T cells, and/or of the microenvironment in which APC/T-cell interactions take place, to indicate potentially effective immunomodulation strategies.

Influence of Maternal Antibodies on Neonatal $CD4^+$ and $CD8^+$ Vaccine Responses

In contrast to the inhibiting influence of MatAb on infant antibody responses, MatAb may leave $CD4^+$ and $CD8^+$ T cell responses largely unaffected. This was first observed in mice, under experimental conditions in which high titers of MatAb completely abrogated antibody responses but did not affect either $CD4^+$ T cell proliferative and cytokine responses (31,32) nor CTL responses (32,55,56). In human infants with MatAb who are immunized with measles and mumps vaccines, $CD4^+$ T cell proliferative and INF-γ responses remain unaffected, whereas antibody responses are inhibited (11,13,40). Accordingly, measles-specific T-cell responses were recorded in 86.8% of six-month old infants immunized in the presence of MatAb, whereas antibody responses were observed in only 36.7% (57). This inhibition of B-cell but not T-cell responses is best explained by the efficient uptake of antigen-antibody immune complexes by APC. Following processing, vaccine-derived antigenic peptides are thus presented at the APC cell surface, allowing priming of $CD4^+$ and $CD8^+$ T cells to occur independently of the inhibition of B cell responses. This early T-cell priming is likely to explain the reduced measles morbidity and mortality observed in vaccinated infants who failed to seroconvert due to the presence of maternal antibodies. It could also significantly facilitate early prime–later boost strategies in early human life, as shown in mice (32). To note, measles immunization of newborn macaques inhibited both B- and T-cell responses, suggesting that very high maternal antibody titers may totally prevent viral replication and subsequent responses (58).

Perspectives for Enhancement of Early-Life $CD4^+$ and $CD8^+$ Vaccine Responses

Studies in mice have clearly demonstrated that adultlike T-cell responses may be induced even in the neonatal period if novel delivery systems and/or adjuvants are employed. This has been repeatedly achieved by DNA immunization against a panel of vaccine antigens (reviewed in Ref. 34), and the induction of adultlike $CD4^+$ and $CD8^+$ T-cell responses appears as a generic property of most DNA vaccines. In part, this could result from prolonged antigenic exposure, allowing both prolonged immune stimulation and ongoing immune maturation to occur. However, induction of adultlike neonatal Th1 and CTL responses were also achieved by certain adjuvants, including by oligonucleotides containing immunostimulating CpG-motifs (59,60), which are present in DNA plasmids, as well as by certain nonpersistent novel delivery systems.

The current understanding is that neonatal T cells may have greater requirements than adult T cells for costimulatory signals, such that the induction of Th1 and CTL neonatal responses essentially reflects the relative capacity of vaccines to activate neonatal APCs to thresholds sufficient, or not, for optimal T-cell activation to occur. In mice, mimicking (IL-12 supplementation) or triggering (CD40) optimal APC activation is sufficient to induce adultlike IFN-γ and CTL neonatal responses. Recently, the novel MF-59 adjuvant was reported as increasing human lymphoproliferative responses to recombinant HIV gp120 following immunization at birth, two weeks, two months, and five months of age (61), and ongoing studies with adjuvanted influenza vaccines are promising. It thus seems reasonable to expect that certain adjuvant formulations or delivery systems may prove capable of significantly enhancing early-life Th1/Th17 responses, representing a major progress in the control of early infections with intracellular pathogens. That these formulations may not be selected based on adult studies represents a significant challenge calling for specific early-life studies.

CONCLUSION AND PERSPECTIVES

The rapid induction of strong and sustained antibody responses in very early life is yet an unmet challenge calling for a better understanding of the determinants of these important limitations. However, immune immaturity may not prevent early induction of memory B cells, which may be recalled by subsequent boosting. The limited capacity for early-life INF-γ and CTL responses appears to result essentially from suboptimal APC/T-cell interactions and thus might be overcome by use of specific adjuvants or delivery systems enhancing such interactions. As the optimal immunogenicity/reactogenicity balance of these new vaccine formulations will have to be defined in very young populations, attention must be directed to address the specific ethical and regulatory considerations of carrying out clinical trials in this age group.

ACKNOWLEDGMENTS

The author is most grateful to the support provided by the Fondation Mérieux and to all who participated in or supported the studies performed in the WHO Collaborating Center for Neonatal Vaccinology.

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