The effect of maternal antibodies on the cellular immune response after infant vaccination: A review

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A B S T R A C T

During the last few decades, maternal immunization as a strategy to protect young infants from infectious diseases has been increasingly recommended, yet some issues have emerged. Studies have shown that for several vaccines, such as live attenuated, toxoid and conjugated vaccines, high maternal antibody titers inhibit the infant’s humoral immune response after infant vaccination. However, it is not clear whether this decreased antibody titer has any clinical impact on the infant’s protection, as the cellular immune responses are often equally important in providing disease protection and may therefore compensate for diminished antibody levels. Reports describing the effect of maternal antibodies on the cellular immune response after infant vaccination are scarce, probably because such studies are expensive, labor intensive and utilize poorly standardized laboratory techniques. Therefore, this review aims to shed light on what is currently known about the cellular immune responses after infant vaccination in the presence of inhibiting Abs both in animal and human studies. Overall, the findings suggest that maternally derived antibodies do not interfere with the cellular immune responses after infant vaccination. However, more research in humans is clearly needed, as most data originate from animal studies.

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1. Introduction

It is well known that children below the age of one year have an elevated risk of developing severe complications after contracting infectious diseases such as pertussis, tetanus, influenza and measles. At this vulnerable age, young children are not yet fully protected by active immunization, as the current vaccination strategies do not offer complete protection to infants under the age of six months [1–3]. To protect this fragile population, vaccination during pregnancy has been implemented in several countries. Similar to other industrialized countries, the Centers for Disease Control and Prevention (CDC) in the US recommends one dose of a tetanus, diphtheria, and acellular pertussis vaccine during every pregnancy [4]. Additionally, one dose of non-live influenza vaccine, when a woman is pregnant during the flu season, is recommended [5]. The administration of other non-live vaccines can be considered, when there is an explicit risk of disease exposure on individual or epidemiological grounds [6]. Furthermore, live attenuated vaccines are generally contraindicated [7]; nonetheless, termination of the pregnancy is not advised when a live vaccine is accidentally administered.

The main objective of immunization during pregnancy is to induce the production of disease-specific maternal antibodies (Abs). These systemic Abs will not only protect the mother from a possible infection, but are transported across the placenta providing protection to the neonate up to several months after birth [8]. The optimal timing of maternal vaccination is therefore essential, because Ab production should be high when the transplacental transport is most efficient [9]. The duration maternal Abs persist in the newborn is dependent on the half-life, which is variable based on the amount of Ab that is transferred, the Ab subclass (IgG1, IgG2...), the vaccination status of the mother, etc. [10].

Although maternal immunization has been proven to be safe and beneficial for the prevention of morbidity and mortality in infants [11,12], some limitations of the strategy have come to light. First, because maternal immunization is often administered during the second or third trimester of pregnancy, preterm infants may not benefit to the same extent as term infants [13]. This concern raises questions regarding the optimal timing of maternal immunization, as preterm infants face no or a shorter period of transplacental transport of Abs [14]. Second, studies have shown that high titers of maternal Abs may inhibit the infant's humoral immune response after infant vaccination. This decreased humoral response, also called the blunting effect, has been demonstrated for several vaccines, such as pertussis, influenza, tetanus, diphtheria, measles and mumps, making blunting a possible concern for future vaccine development and implementation [15–20]. In general, these studies suggest that high maternal Ab titers at the time of infant vaccination increase the risk for insufficient Ab synthesis in infants, resulting in a possible decrease in disease protection. In addition, even if protective Ab levels may be achieved, initially lower Ab titers will inherently fall more rapidly below the protective threshold. This makes blunting a concern for vaccines that do not have a defined correlate of protection, as the infant’s Ab production can unknowingly drop below the protective threshold [20].

Overall, protection against a disease has mostly been defined by the development of serum Abs in response to immunization or natural infection. However, protection may not only be defined by humoral immunity, as cell-mediated immune (CMI) responses also play important roles in providing disease protection. Therefore, a lowered Ab titer, caused by the blunting effect, does not necessarily imply reduced protection [21,22]. To fully understand the impact of high maternal Ab titers at birth on the immune development of the child, it is critical to study both the humoral and cellular immune responses. Unfortunately, CMI responses are less extensively studied compared to humoral immune responses because the correlates of protection are often defined by antibody levels, and studies therefore focus on humoral immune responses as the key element of host-mediated protection [3]. Furthermore, most studies refrain from reporting on cellular immunity because it is more challenging, costly, and labor intensive, and large amounts of blood are needed, which are often not available. In addition, CMI responses are commonly analyzed with complicated assays, such as lymphocyte proliferation tests evaluating thymidine incorporation within blast cells, chromium (Cr)51 release assays analyzing the cytotoxic response or other assays measuring the cytokine concentrations. Unfortunately, all these techniques remain poorly standardized, making comparisons between different studies quite difficult. Over the years, these limitations have resulted in only a few publications reporting the CMI responses in the presence of maternal Abs, creating an extensive knowledge gap compared to the number of reports on the humoral immune response. This review will provide an initial insight into the literature concerning CMI responses after infant vaccination in the presence of high maternal Ab titers, aiming to give a more comprehensive overview on the distinct effects of high maternal Abs on the infant’s vaccine response.

2. Methods

To establish a better understanding of the effect of maternal Abs on the CMI responses, a literature search was performed (4/ JAN/2018) in the PubMed, Web of Science, Medline and Cochrane databases. Both human and animal studies were included in the search, as only a few studies have investigated the effect on the CMI response, and the majority of them were performed in animals. Search terms included “cellular immune response”, “cell-mediated immunity”, “T cell response”, “lymphocyte response”, “cellular response” or “T cell” and these were combined with the terms “maternal antibodies”, “maternal antibody titers”, “maternal immunity”, “maternal vaccination”, “maternal immunization”, “vaccination during pregnancy” and with the terms “vaccine response”, “vaccination”, “vaccine” or “immunization”. Only papers published after 1990 were selected (n = 889). After the removal of duplicates, the relevant papers were identified based on the titles and abstracts. The relevant papers were combined with internal references found therein (n = 19) for a total of 30 papers, of which 16 were used for the data synthesis (Fig. 1).

3. Results and discussion

3.1. Cellular immune response after vaccination in the presence of inhibiting Abs

3.1.1. Animal studies

Eleven animal studies reported the CMI responses after infant vaccination in the presence of high Ab titers. Of these studies, nine demonstrated that CMI responses were not affected in the presence of passive (maternal) Abs after active infant immunization. Van Binnendijk et al. [23] and Siegrist et al. [24] were the first to investigate the effect of high Ab titers on the CMI response after primary vaccination in animals (Table 1). In the former study, in which rhesus macaques were injected with measles neutralizing Abs 48 h before primary measles vaccination, specific T cell and cytotoxic responses were detected even in the presence of these high measles Ab titers. Furthermore, one year after vaccination, all vaccinated monkeys were completely or partially protected from intra-tracheal challenge with the measles virus, even when they had reduced or absent measles-specific IgG and IgM at that
Table 1
Animal studies reporting the immune response after infant vaccination in the presence of high (maternal) Ab titers.

<table>
<thead>
<tr>
<th>Maternal/passive Abs</th>
<th>Disease/vaccine</th>
<th>Species</th>
<th>Number of animals</th>
<th>Effect of high maternal/passive Ab titers on the:</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive Abs</td>
<td>Measles</td>
<td>Rhesus macaques</td>
<td>16</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of proliferative and cytotoxic T cell responses</td>
</tr>
<tr>
<td>Passive Abs</td>
<td>Tetanus</td>
<td>Mice</td>
<td>6–8 (per group)</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of T cell responses</td>
</tr>
<tr>
<td>Passive Abs</td>
<td>RSV</td>
<td>Mice</td>
<td>6 (per group)</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition CD4+ and CD8+ T cells.</td>
</tr>
<tr>
<td>Pre-existing maternal Abs*</td>
<td>BVDV</td>
<td>Calves</td>
<td>Unknown</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of CD4+, CD8+ and γδ T cell responses</td>
</tr>
<tr>
<td>Maternal vaccination</td>
<td>Measles</td>
<td>Mice</td>
<td>6–8 (per group)</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of T cell responses</td>
</tr>
<tr>
<td>Maternal vaccination</td>
<td>Hepatitis B</td>
<td>Mice</td>
<td>5–12 (per group)</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of CTL responses</td>
</tr>
<tr>
<td>Maternal vaccination</td>
<td>Sendai virus</td>
<td>Mice</td>
<td>Unknown</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of T cell responses</td>
</tr>
<tr>
<td>Maternal vaccination</td>
<td>PRV</td>
<td>Pigs</td>
<td>82</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of T cell responses</td>
</tr>
<tr>
<td>Maternal vaccination</td>
<td>Dengue</td>
<td>Mice</td>
<td>5–8 (per group)</td>
<td>Inhibition of Ab responses</td>
<td>No inhibition of CD8+ T responses</td>
</tr>
<tr>
<td>Passive Abs</td>
<td>Measles</td>
<td>Macaques</td>
<td>13</td>
<td>Inhibition of Ab responses</td>
<td>Inhibition of T cell responses</td>
</tr>
<tr>
<td>Maternal vaccination</td>
<td>PRV</td>
<td>Pigs</td>
<td>30</td>
<td>Inhibition of Ab responses</td>
<td>Reduction of T cell responses</td>
</tr>
</tbody>
</table>

**Note:**
Overall of the reported animal studies. Administration of passive Abs is performed with serum from immunized animals. NA: Not applicable; Abs = Antibodies; RSV: respiratory syncytial virus; PRV: pseudorabies virus; BVDV: bovine viral diarrhea virus; HBsAg = hepatitis B surface antigen; CTL: cytotoxic T lymphocyte.

* Pre-existing maternal Abs = antibodies that were not induced by maternal vaccination.
moment [23]. This observation suggests that T cell memory was induced and conferred disease protection even if the humoral vaccine response was inhibited. Additionally, a latter study in mice showed that T cell responses were not inhibited after tetanus toxoid (TT) vaccination in the presence of high serum anti-TT Abs (administered 48 h before vaccination). Here, specific TT-induced lymphocytes and TT-induced cytokine secretions were detected, despite the total inhibition of the anti-TT Ab responses [24].

Over the years, similar results have been demonstrated in several animal models for different vaccines (Table 1). Another mouse study showed that respiratory syncytial virus (RSV) vaccination was protective against RSV by generating both specific CD4+ and CD8+ T cells, even though the primary Ab response in these mice was suppressed by the administration of passive Abs [25]. Similar results were observed in a study on calves vaccinated against the bovine viral diarrhea virus, in which no inhibition of T cell responses by pre-existing maternal Abs was detected [26]. This indicates that despite humoral blunting by the passively acquired Abs, the induced cellular responses after vaccination are not affected and are capable of conferring disease protection.

Similar conclusions were reported when primary vaccination was given in the presence of high Ab titers induced by maternal vaccination. A study in mice reported that normal T cell responses were observed after measles vaccination despite the inhibited Ab production [27]. Analogous results were demonstrated in mouse studies on hepatitis B and Sendai viruses, both of which used non-live vaccines [28,29]. Furthermore, in a study on pigs immunized against pseudorabies virus (live vaccine), no inhibition of T cell responses by maternal Abs was detected [30]. More recently, it has been shown that vaccinating mice against dengue in the presence of maternal Abs offered full protection against dengue virus challenge, which was mediated by specific CD8+ T cells. This again supports the role of T cells in vaccine protection when interfering maternal Abs induced by vaccination during pregnancy are present [31]. In general, all these observations suggest that high maternal Ab titers still allow sufficient priming of the CMI responses, which might imply that the blunting effect is not as alarming as previously thought.

To the best of our knowledge, only two animal studies reported a reduced CMI response in the presence of maternal Abs (Table 1). Prenemenko-Lanier et al. described a complete inhibition of the CMI responses in macaques after the administration of a live attenuated measles vaccine at birth in the presence of passive Abs [32]. In addition, Bouma et al. reported a reduced proliferative T cell response after the vaccination of pigs with pseudorabies virus in the presence of maternal Abs [33]. It is extremely difficult to pinpoint the causes behind these contradictory results, as there are several factors including viral virulence, the type of immunoglobulin transported to the neonate, the timing of vaccination, the type of vaccine (live-attenuated, inactivated, toxoid...), and species-specific differences, among others, that can influence the observed results. Furthermore, Bouma et al. reported in the same study that different routes of vaccine administration in the presence of Abs were associated with either the induction or inhibition of CMI responses, whereas the humoral immune responses were inhibited in both cases. Second, that study also suggested that the level of vaccine potency might influence the CMI response [33]. Moreover, it is also possible that the priming of the CMI response was simply not detected due to limitations of the proliferation assays that were used.

### 3.1.2. Human studies

Given the results in animals, validation of whether CMI responses are induced in humans despite the presence of humoral blunting by the passively acquired Abs is necessary. Unfortunately, very few human studies investigating the effect of maternal Abs on the CMI response could be found. However, the few publications that do report the CMI responses seem to confirm that there is no detected cellular blunting in infants after primary vaccination (Table 2). Pabst et al. [34] and Gans et al. [35] were the first to illustrate prominent T cell responses (both proliferation and cytokine secretions) in infants after primary vaccination, despite the presence of passive maternal measles Abs [34,35]. In addition, a subsequent study by Gans et al. confirmed these results by demonstrating specific CMI responses after measles and mumps vaccination, even with passive Abs present at the time of immunization [36]. Moreover, the long-term follow-up study by Gans et al. showed that T cell responses to the measles vaccine were robust and persisted up to 10 years of age, even when the first vaccine dose was given in the presence of high passively acquired Ab titers [37]. Another study by Bertley et al. showed that the maternal Ab titer at the time of initial measles vaccination was strongly correlated with the lymphoproliferative response against the measles vaccine at 5 years of age, suggesting that maternal Abs

### Table 2

Human studies reporting the immune response after infant vaccination in the presence of high maternal titers.

<table>
<thead>
<tr>
<th>Maternal/passive Abs</th>
<th>Disease/vaccine</th>
<th>Number of participants</th>
<th>Effect of high maternal/passive Ab titers on the:</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing maternal Abs*</td>
<td>Measles</td>
<td>300</td>
<td>Inhibition of Ab responses</td>
<td>H. F. Pabst et al. [34]</td>
</tr>
<tr>
<td>Pre-existing maternal Abs*</td>
<td>Measles</td>
<td>162</td>
<td>Inhibition of Ab responses</td>
<td>H. A. Gans et al. [35]</td>
</tr>
<tr>
<td>Pre-existing maternal Abs*</td>
<td>Measles and mumps</td>
<td>210 (measles) 97 (mumps)</td>
<td>Inhibition of Ab responses</td>
<td>H. Gans et al. [36]</td>
</tr>
<tr>
<td>Pre-existing maternal Abs*</td>
<td>Tetanus</td>
<td>132</td>
<td>Inhibition of Ab responses</td>
<td>j. rowe et al. [39]</td>
</tr>
<tr>
<td>Pre-existing maternal Abs*</td>
<td>Measles</td>
<td>193</td>
<td>Inhibition of Ab responses</td>
<td>F. M. Bertley et al. [38]</td>
</tr>
</tbody>
</table>

Overview of the reported human studies. MMR = measles, mumps and rubella; DTaP = diphtheria, tetanus and acellular pertussis.

* Pre-existing maternal Abs = antibodies that were not induced by maternal vaccination.
might even promote a stronger CMI response after vaccination [38]. Finally, in a study focusing on infant TT vaccination, specific T cell responses appeared to be boosted in the presence of TT maternal Abs, even though the humoral immune response was suppressed [39]. All these results correlate well with those from animal studies and suggest that although the presence of maternal Abs inhibits humoral immunity, they do not interfere with the CMI response. In addition, some publications even suggest that maternal Abs prime the body for a more robust CMI response that persists until booster vaccination and confers possible protection throughout the child’s life [37,38]. However, to reach a clear conclusion, more research in humans is needed.

3.2. Possible mechanism of priming of the cellular immune response in the presence of Abs

As humoral blunting might be caused by either the masking of antigen epitopes or the inhibition of the antigen-specific B cell activation via the Fcγ-receptor IIB [20], it has been suggested that T cell responses are not inhibited because they can originate from maternal Ab-vaccine antigen complexes that are taken up by macrophages and dendritic cells. Subsequently, these antigen-presenting cells will display the vaccine antigen peptides at their surface, making binding and recognition of the disease antigens by T cells possible [40]. These powerful immunogenic complexes will allow the infant to develop T cell responses after immunization in the presence of maternal Abs. Furthermore, it is also possible that the high-affinity maternal Abs may stimulate the infant to respond to a variety of epitopes, leading to a more diverse and robust T and B cell repertoire [19,40,41]. Some studies even imply that maternal Abs might exert other important effects on the neonate's immune system. Fink et al. reported that maternal Abs shape the specific Ab repertoire and peripheral B cell development in the offspring of mice, which might suggest that high maternal Ab titers have long-lasting effects on the infant’s immune system [42]. Additionally, the study by Bentley et al. (mentioned above) showed that robust lymphoproliferative responses at 5 years of age were strongly correlated with high maternal Ab titers at the time of vaccination [38]. This suggests that maternal Abs might promote the induction of stronger T memory responses after vaccination. Moreover, in the study by Aaby et al., the overall mortality rate of infants was reduced when the first dose of measles vaccine was given in the presence of high measles-maternal Ab titers, compared to infants with no maternal Abs present [41]. These findings indicate that although humoral immunity is a vital element, as high Ab titers often correlate with protection, cell-mediated immunity is essential for the clearance, recovery and persistence of long-term immunity against the pathogen. Furthermore, it should be noted that not only Abs but also immune cells (lymphocytes) can be transported to the fetus during pregnancy (study in mice) [43]. Previous studies have even shown that maternal cells persist in several organ sites, such as the liver, spleen, thymus, lymph nodes, bone marrow and blood; however, the exact function of these maternally derived cells is still unknown [43,44]. Overall, maternal Abs help vulnerable infants safely transition from maternally derived immunity to long-lasting acquired immunity. A review article even indicated that infection or vaccination during pregnancy may alter the infant’s susceptibility to diseases and the response to future vaccinations, with an overall impact on the immunological development [45]. It is, therefore, presumed that the immune status of the mother is an important influencer of immune maturation in the infant; however, evidence is lacking on the exact underlying mechanism and influences of maternal Abs on infant T cells.

3.3. T cell polarization after vaccination in the presence of maternal Abs

During the first months of life, the T cell repertoire diversifies enormously and experiences different developmental impulses from its environment. In particular, the maternal environment is suggested to have a large impact on T cell polarization and might program the infant’s immune system against future challenges [21]. To produce a successful immune response, a good balance between effective intracellular and extracellular killing of the pathogen and immune suppressive responses to prevent overreaction is imperative. Any alterations in this balance, also referred to as the Th1/Th2 balance, is known to leave the individual more vulnerable to diseases [46]. Furthermore, it should be noted that the Th1/Th2 balance is dependent on the interplay between effector cells and regulatory T cells, as antigen-specific immunity is mediated by effector T cells (Th1- or Th2-mediated) whereas regulatory T cells are capable of hampering these specific CMI responses. It is well known that during infancy, the proportion of regulatory T cells is higher compared to that found in adults [47,48]. Moreover, the neonatal T cells, although immunocompetent, are more likely to differentiate towards a Th2 response [21,29]. This temporary imbalance, which is directed towards more immune suppression, might leave the infants vulnerable up until their subsequent booster vaccination [21].

To determine whether maternal Abs might influence these balances, the abovementioned articles were also reviewed for such a possible impact. Of all 16 studies, only 1 animal study reported the effector T cell responses in the presence of high maternal Ab titers [31], whereas no studies reported possible influences on the regulatory T cell population. The study by Lam et al. described weakened effector CD4+ and CD8+ T cell responses in the presence of maternal Abs, even though CD8+ responses remained protective against dengue virus challenge. This suggest a possible influence of maternal Abs on the CMI responses, however the extend of this effect is questionable because the total CD4 population and viral protection remained unaffected.

Possible influence of maternal Abs on Th1 or Th2 cytokine responses, characterized by either measuring the cytokine concentrations released in cell culture supernatants with ELISA or by counting the numbers of cytokine-producing cells with an ELISPOT analysis, were also reviewed (Table 3). Out of the 11 animal studies, only 5 studies reported the cytokine levels in the presence of Abs, of which 2 studies described unchanged IFN-γ and IL-5 levels [24,27], suggesting that both Th1 and Th2 responses remained unaffected by high Ab titers. However, the three other animal studies did report a significant decline in IFN-γ production or in the numbers of IFN-γ-producing cells in neonates when high Ab titers were present at the time of primary vaccination [31,32]. This suggests that maternal Abs might influence the Th1-Th2 balance; however, more detailed information on other cytokines in these studies was lacking.

Most human studies demonstrated similar IFN-γ levels in neonates from vaccinated and unvaccinated mothers [34–36,39]. Nonetheless, the study by Gans et al. (1999) showed higher IL-12 production after vaccination in the presence of passive Abs [35], suggesting for the first time in humans that maternal Abs might influence the Th1-Th2 balance in favor of a dominant Th1 response. Only two human studies reported the effect of Abs on Th2-related cytokine responses. Pabst et al. described unchanged IL-10 cytokine production in the presence of high serum anti-measles Ab titers [34]. In contrast, Rowe et al. found that higher levels of anti-TT IgG titers at 2 months of age were associated with higher IL-4, IL-5 and IL-13 cytokine responses, suggesting a boosting of Th2 responses caused by the pre-existing maternal Abs [39].
The above studies indicate that maternal Abs might modulate the Th1/Th2 cytokine balance and influence the effector T cells. These modulations might have serious implications for the neonate. If maternal immunization would stimulate the neonate to produce a more Th1-oriented T cell response, this could be beneficial because Th1-polarization could eventually lead to more robust cellular immune responses. A more Th1-directed immune response would make the neonate less susceptible to partially intra-cellular pathogens and thus result in better disease protection later in life [21,49]. This polarization could even have substantial implications for preterm infants. High maternal Ab titters could offer them better protection against diseases during the first months of life but could also help prepare their immune system, making them less susceptible to disease later in life. In contrast, if maternal Abs would shift the Th1/Th2 cytokine balance to a more prolonged Th2-polarized immune response, this could lead to several negative consequences, such as becoming more susceptible to infections and even becoming at risk of developing atopy [49]. However, Th1/Th2 cytokine polarization might also vary depending on the vaccine that is used to induce maternal Abs, suggesting that the vaccine formulation can also have an effect on this polarization. In general, due to the limited findings of this review, it is complicated to predict whether maternal Abs shift the Th1/Th2 balance to a more Th1- or Th2-polarized response. Furthermore, it is difficult to reflect on the possible impact of maternal Abs on the effector and regulatory T cells, as only 1 study in animals described alterations in the effector T cell responses. How-ever, as the first 6 months of life are characterized by vital immunological changes, such as Th1-Th2 cytokine and effector/regulatory T cell stasis refinement [21,48,49], there is no doubt that future research should include extensive analyses of the CMI responses at young age.

### Table 3

<table>
<thead>
<tr>
<th>Refs.</th>
<th>Animal</th>
<th>Human</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>C. A. Siegrist et al. [24]</td>
<td>H. F. Pabst et al. [34]</td>
</tr>
<tr>
<td></td>
<td>G. A. Blomqvist et al. [29]</td>
<td>H. A. Gans et al. [35]</td>
</tr>
<tr>
<td></td>
<td>J. H. Lam et al. [31]</td>
<td>H. Gans et al. [36]</td>
</tr>
<tr>
<td></td>
<td>M. Premenko-Lanier et al. [32]</td>
<td>J. Rowe et al. [39]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Th1 response</th>
<th>Th2 response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ *</td>
<td>IL-5 *</td>
<td>IFN-γ and IL-5 cytokine productions levels by TT-specific T cells were similar in pups immunized either in the absence or in the presence of high levels of maternal Abs. P-values or means not mentioned. Similarly, IFN-γ and IL-5 cytokine levels were found in the absence or the presence of maternal Abs. P-values or means not mentioned. Results were expressed as IFN-γ/IL-5 ratio’s. Significantly lower mean IFN-γ/IL-5 ratio found at 4–5 weeks and 8 weeks in immunized pups born of immunized mothers (0.02 ≤ p ≤ 0.5). IFN-γ CD8+ T cells in pups born to immunized dams was significantly lower (p ≤ 0.01). Significantly fewer IFN-γ-producing cells after immunization in the presence of maternal Abs. P-values or means not mentioned.</td>
</tr>
<tr>
<td>IFN-γ *</td>
<td>IL-5 *</td>
<td>IFN-γ and IL-10 production levels were elevated for all groups after vaccination with the measles vaccine.</td>
</tr>
<tr>
<td>IFN-γ *</td>
<td>NA</td>
<td>IFN-γ production not significantly affected by passive Abs after immunization (p = 0.2). Higher IL-12 concentration in infants who had passive Abs compared to infants who had none (p = 0.03).</td>
</tr>
<tr>
<td>IFN-γ *</td>
<td>NA</td>
<td>IFN-γ production not significantly affected by passive Abs after immunization (p = 0.2). Higher IL-12 concentration in infants who had passive Abs compared to infants who had none (p = 0.03).</td>
</tr>
<tr>
<td>IFN-γ *</td>
<td>IL-4; *</td>
<td>No significant associations between anti-TT IgG titers at 2 months and subsequent TT-specific IL-4 responses at 12 and 18 months (p = 0.904; p = 0.263). TT-specific IL-4 responses at 12 and 18 months (p = 0.002; p = 0.047) and IL-5 and IL-13 responses at 18 months (p = 0.048; p = 0.028) were associated with higher levels of anti-TT at 2 months. TT-specific cytokine responses at 12 and 18 months were classified as positive or negative (positive response = a two-fold increase above the control production level).</td>
</tr>
<tr>
<td>IFN-γ *</td>
<td>IL-5; *</td>
<td>IFN-γ responses at 12 or 18 months (p = 0.048; p = 0.028) were associated with higher levels of anti-TT at 2 months. TT-specific cytokine responses at 12 and 18 months were classified as positive or negative (positive response = a two-fold increase above the control production level).</td>
</tr>
<tr>
<td>IFN-γ *</td>
<td>IL-13; *</td>
<td>No significant associations between anti-TT IgG titers at 2 months and subsequent TT-specific IL-13 responses at 12 and 18 months (p = 0.904; p = 0.263). TT-specific IL-4 responses at 12 and 18 months (p = 0.002; p = 0.047) and IL-5 and IL-13 responses at 18 months (p = 0.048; p = 0.028) were associated with higher levels of anti-TT at 2 months. TT-specific cytokine responses at 12 and 18 months were classified as positive or negative (positive response = a two-fold increase above the control production level).</td>
</tr>
<tr>
<td>IFN-γ; IL-5; IL-10; IL-4</td>
<td>NA</td>
<td>IFN-γ; IL-5; IL-10; IL-4 cytokine productions levels by TT-specific T cells were similar in pups immunized either in the absence or in the presence of high levels of maternal Abs. P-values or means not mentioned. Similar to TT-primed mice and TT-challenged mice, significantly higher cytokine production compared between groups; =: equal cytokine production compared between groups; ∨: significantly higher cytokine production compared between groups;</td>
</tr>
</tbody>
</table>
3.4. Limitations when measuring T cell responses

In most of the reported studies, T cell activation was evaluated through in vitro proliferation in short-term cultures in the presence of specific antigens (Table 4). The in vitro T cell differentiation and division, also referred to as blast transformation, is commonly measured by the amount of \(^{3}H\)-labeled thymidine incorporated into the replicating DNA of cultured cells. The rate of DNA synthesis is usually directly proportional to the rate of cell division. In general, the results are expressed as the stimulation index (SI), which is calculated as the ratio between the measured radioactive counts per minute obtained in response to specific antigen stimulation and those obtained in the unstimulated condition. Unfortunately, the results of these cell cultures are easily influenced by several parameters that remain poorly standardized between laboratories, so the comparison of the results remains difficult. Other studies also used cytokine secretion assays to measure the concentrations of secreted cytokines in cell-cultured supernatants by ELISA or counted the numbers of cytokine-secreting cells by ELISPOT. This approach allows for the detection of Th1- and Th2-produced cytokines. However, it remains challenging to obtain a precise and reproducible evaluation of this Th1/Th2 balance due to different affinities of the anti-cytokine Abs and several technical aspects that are difficult to standardize [50]. Recently, more advanced flow cytometric techniques were developed, allowing the identification of several T lymphocyte subpopulations characterized by their surface phenotype and by the intracellular cytokines they produce. However, also these techniques remain very difficult to standardize, and are labor intensive and extremely costly [50]. Finally, some studies have assessed the cytolytic functions of antigen-specific T lymphocytes by measuring their capacity to lyse antigen-containing \(^{51}Cr\)-labeled, target cells. This technique is also labor intensive because it requires both the use of incremental ratios between the numbers of effector and target cells and radioactive labelled cells. Overall, the assessment of cellular immunity is extremely complicated, expensive and most of all labor intensive. Furthermore, most of these tests require large volumes of blood, which makes a clinical study on neonates nearly impossible because only a limited amount of blood can be drawn. Therefore, the development of novel and inexpensive techniques together with the rising concern regarding the effect of maternal Abs, should provide new motivation to include T cell assays in vaccine research.

4. Conclusion

It is well known that maternal Abs offer a unique protection to newborns until they mount their own effective immune response after receiving their primary vaccination series. This makes maternal immunization an effective strategy for protecting infants from infections [22]. However, following the implementation of
maternal immunization, several studies reported blunting of the humoral immune response after the infant’s primary vaccinations, suggesting a possible disadvantageous effect of maternal Abs. Although this inhibitory effect is reversible as maternal Abs decline and a booster vaccination is given, there still exists a considerable window during which the vaccine efficacy is supposedly compromised [51,52]. To gain more insight into the extent of this blunting effect, further investigation into the CMI response after infant vaccination should be performed. It should be noted that most laboratory tests designed to evaluate in vitro CMI responses are still poorly standardized, which makes the results obtained in different studies difficult to compare. Despite this limitation, the majority of the studies reported significant induction of the CMI responses in infants after vaccination, suggesting that priming of the CMI responses still occurs in the presence of high Ab titers. This was the case after vaccination against measles, mumps, tetanus, RSV, hepatitis B, Sendai virus, bovine viral diarrhea virus, pseudorabies virus or dengue virus in both animal and human research [23–31,34–39]. However, two animal studies dispute these findings. Bouma et al. and Premenko-Lanier et al. [32,33] reported reduced CMI responses after stimulation with vaccine-specific antigens in animals. Nevertheless, as most of the studies reported no blunting effect of the CMI responses, it is likely that those discrepancies are due to differences in the study protocol. Even with the general lack of animal and, in particular, human studies, it is safe to assume that maternal Abs do allow priming of the CMI response after infant vaccination. Together with the growing evidence that blunting maybe short-lived and longer-term protection is not compromised after active immunization in infants, these results imply that there might be no clinical impact of humoral blunting [53,54]. This would therefore suggest that there is no need to delay primary vaccination when high maternal Ab titers are present at the time of vaccination. Furthermore, maternal Abs could even stimulate a more robust CMI response, as observed in the studies by Rowe et al. and Bertley et al. which might indicate a secondary beneficial effect of maternal immunization [38,39]. In addition, the effect of a vaccine should not only be assessed based on Ab levels; the most important criteria should be the overall effect on child health and survival. Especially for vulnerable populations, such as preterm born infants, an extra effort should be made to determine the optimal timing for both maternal and infant immunization. Future research should therefore focus on all the different aspects of immunization. New efforts will lead to a better understanding of the effect of maternal Abs on the neonatal immune system and help with future vaccine development, vaccine implementation and recommendations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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