

Review

Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants

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Abstract

Several mechanisms have been suggested as mediating the inhibitory influence of maternal antibodies (MatAb) on infant responses. This inhibition is B cell determinant-specific, depends on the ratio between MatAb titers at the time of immunization and the dose of vaccine antigen, and leaves infant T cell responses largely unaffected. Neutralization of vaccine replication or FcγRIIB-mediated inhibitory signalling to infant B cells would not account for these characteristics. In contrast, determinant-specific masking of B cell epitopes and APC uptake of MatAb:vaccine antigen immune complexes, followed by antigen processing and presentation, explain the pattern of pre-clinical and clinical responses to infant vaccines. This allows the definition of the main determinants of the influence of MatAb on infant immunity. © 2003 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The review of clinical studies assessing the influence exerted by antibodies of maternal origin on infant vaccine responses results in a large series of apparently contradicting observations. Significant inhibitory effects on infant antibody responses, reflected by lower seroconversion rates and/or geometric mean antibody titers in infants immunized in the presence of higher compared to lower levels of maternal antibodies (MatAb), were described 25 years ago for measles vaccine [1] and also reported following infant immunization with other live vaccines including oral polio, varicella-zoster, influenza and recently oral human rotavirus vaccines [2–4]. In contrast to initial hypotheses, the inhibitory influence of MatAb on infant antibody responses is not restricted to live vaccines. Inhibitory effects were reported following immunization with tetanus and diphtheria toxoids [5–8], pertussis vaccine [9,10], Hib conjugate vaccines [11,12], hepatitis A vaccine [13–15], i.e. with every infant vaccine administered in the presence of significant titers of MatAb. Remarkably, the suppressive influence of MatAb on infant responses varied significantly from one vaccine to another, and even from one study to another, with other reports assessing infant responses to the very same vaccines

in other clinical settings reporting lack of interference of MatAb on infant responses.

These contradictory reports currently preclude any definition on whether a novel infant vaccine may—or may not—prove capable of escaping from the inhibitory influence of MatAb. They also prevent anticipation of the influence of the implementation of adolescent/adult immunization programmes likely to result in higher Ab titers at the time of pregnancy, and thus in higher MatAb titers at the time of infant immunization, such as adolescent hepatitis B immunization or adolescent/adult acellular pertussis boosting. This would require being able to define whether MatAb may affect infant antibody responses to all types of vaccine antigens and/or all types of delivery systems, and to identify above which titers MatAb mediated inhibition may occur and thus persist and which is the role of the immunization schedule. Recent reports showing that MatAb inhibit infant antibody responses without inhibition of infant T cell responses [16–18] and/or of infant priming [15] have generated additional questions. It is currently difficult to predict, based on these few reports, whether the lack of inhibition of CD4⁺ T cell responses by MatAb will prove a general rule, whether the Th1/Th2 balance of infant responses could be modulated by MatAb or whether infant CD8⁺ cytotoxic responses might be preserved as well as CD4⁺ responses. Finally, researchers currently assessing novel immunization routes have few elements to define whether such injection

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routes (i.e. nasal, oral, transcutaneous, etc.) will prove more or less susceptible to inhibition by MatAb.

To better address these questions, this review follows a “reverse” approach, examining the immune mechanisms by which MatAb might influence the induction of infant immune responses and probing existing clinical and pre-clinical observations to either confirm or deny their suspected role. The identification of the main mechanisms at the basis of MatAb-mediated inhibition of infant responses should indeed allow definition of their essential determinants, and thus of the expected influence of MatAb on infant immunization programmes.

2. Mechanisms hypothesized as mediating the influence of maternal antibodies on infant vaccine responses

2.1. Neutralization of live viral vaccines

The strong and prolonged inhibitory influence of MatAb on infant antibody responses to live viral vaccines resulted in the widely believed hypothesis that MatAb neutralize the viral vaccine inoculum rapidly after injection [1], preventing *in vivo* replication and thus the production of an antigenic load sufficient to prime infant B and T cells. To date, there is no reported data assessing whether viral vaccine replication is affected, or not, when infant immunization is performed in the presence or absence of MatAb. However, recent studies showing induction of normal CD4⁺ T cell responses to measles vaccine despite MatAb-mediated inhibition of infant antibody responses [16–18] indirectly demonstrate that the neutralization of *in vivo* viral replication may not be responsible for the inhibition of infant antibody responses to measles: the initial measles vaccine load is so low that viral replication is indeed considered essential for enough viral antigen to enable the priming of normal infant measles T cell responses.

Although neutralization of live vaccines and inhibition of *in vivo* viral replication is therefore not the mechanism that mediates the inhibition of MatAb on infant responses to measles vaccine, and obviously not the one responsible for inhibition of Ab responses to non-live vaccines, it could occur under certain conditions. As an example, pre-clinical murine studies have shown that MatAb could inhibit viral replication of live attenuated RSV in the lower respiratory tract [19], possibly reflecting the weaker relative replicating capacity of human RSV in mice. Taking this possibility into account, it is suggested here that the neutralization of live viral vaccines by MatAb depends upon the relative ratio of MatAb titers at the time of immunization and of viral vaccine load/replicating capacity (Fig. 1). Under conditions of MatAb excess and/or low viral load/replicating capacity, inhibition of viral replication, and thus possibly of both B and T cell infant responses, could occur. In contrast, under conditions of lower MatAb concentration or of viral load increase above certain thresholds (as observed with high titer

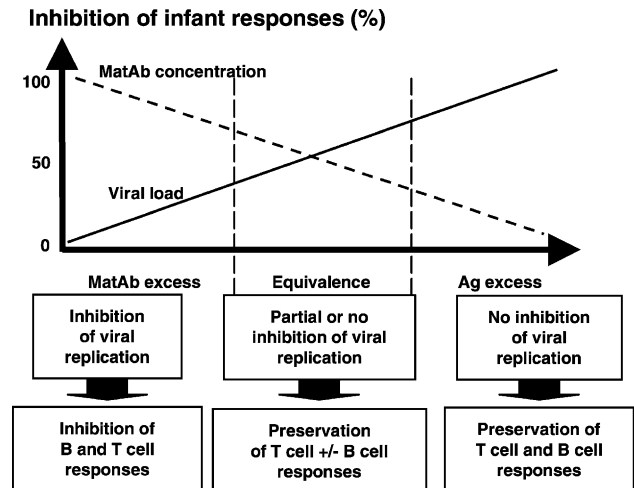


Fig. 1. Expected influence of maternal antibodies on infant responses to live viral vaccines.

measles vaccines), viral replication, and B and T cell responses remain unaffected. At intermediate conditions, viral replication apparently remains largely unaffected, such that the influence exerted by MatAb is essentially similar for live and non-live vaccines, predominantly affecting antibody responses.

2.2. Inhibition of infant B cell activation by Fcγ-receptor mediated signals

An hypothesis frequently put forward is that MatAb: vaccine antigen immune complexes inhibit B cell activation by inducing a colligation at the B cell level of the B cell receptor (BCR) and of FcγRIIB, a negative regulator mediating inhibitory signals [20]. Several recent observations however indicate that this mechanism may not explain the inhibition of vaccine antibody responses by MatAb: (1) IgG-mediated inhibition of Ab responses occurs equally well (99% suppression) in FcγRIIB-deficient and wild-type mice [21]; (2) increasing the dose of vaccine antigen is sufficient to circumvent MatAb-mediated inhibition of infant Ab responses (see below), whereas it would be expected to also increase FcγRIIB-mediated inhibitory signals; (3) the inhibition of antibody responses is determinant-specific [22], which is not compatible with an Fc-mediated signal. Thus, although FcγRIIB-mediated inhibitory signals to B cells do provide feedback suppression mechanisms which set the upper level of Ab responses, the inhibition pattern of infant responses elicited in the presence of MatAb is not compatible with FcγRIIB-mediated mechanisms.

2.3. Effective elimination of MatAb-coated Ag via Fc-dependent phagocytosis

Many textbooks and reviews state for a fact that the inhibition of infant antibody responses by passive antibodies is mediated by Fc-dependent phagocytosis and elimination of

immune complexes. However, studies recently performed in a panel of knockout mice reported similar inhibition of Ab responses in mice lacking Fc γ R as in wild-type mice [23], demonstrating the existence of Fc γ R-independent inhibitory mechanisms. Whether the same is true following infant immunization with vaccine antigens can obviously not be directly assessed. It is now understood that MatAb:antigen complexes are readily internalized by antigen-presenting-cells (APC), via Fc γ R or other scavenger receptors, as immune complexes are efficiently targeted to APC. This uptake is followed by Ag processing and peptide presentation at the APC surface, such that internalization of MatAb:antigen complex uptake would indeed result in the inhibition of infant B cell but not T cell responses observed both in human and infant mice. Interestingly, under certain conditions which remain to be defined, this mechanism should even result in enhanced T cell responses in infants immunized in the presence rather than in the absence of MatAb. However, the APC uptake of MatAb:Ag immune complexes may not account for the determinant-specificity of MatAb influence on infant antibody responses, indicating the contribution of another immune mechanism.

2.4. Epitope masking by MatAb, preventing antigen binding by infant B cells

The demonstration of the existence of Fc γ R-independent mechanisms led to the hypothesis of epitope-specific masking, i.e. of “suppressive” MatAb simply hiding antigenic epitopes from infant B cells. This hypothesis, demonstrated in mice for responses to erythrocyte antigens [24], is indeed compatible with pre-clinical and clinical observations of responses to infant vaccines including lack of inhibition of T cell priming, correlation between the inhibitory influence of Ab and their titers at the time of immunization, the capacity of circumventing the inhibition by increasing the dose of vaccine antigen and the epitope-specificity of such inhibition.

As an example of this epitope-specificity, MatAb elicited to the HIV-1 V3 loop inhibited induction of Ab responses to V3 but not to other epitopes of GP120 [25]. Thus, the epitope-specific masking of immunodominant Ag epitopes prevents recognition/binding by corresponding infant B cells without preventing binding by B cells specific for non-immunodominant epitopes. This epitope specificity may not be absolute, as steric hindrance could result in non-epitope specific inhibition at high MatAb:antigen ratios. This epitope-specificity of MatAb-mediated inhibition has not yet been assessed/reported in infants. It should be stressed, however, that antibody detection assays which simultaneously detect antibodies to all determinants of a given antigen (i.e. virtually all assays) would be unable to identify fine changes in epitope specificities. This may indeed be worth considering, as if certain immunodominant epitopes carry the functional Ab capacity (i.e. toxin binding sites), their epitope-specific inhibition by MatAb may not

be functionally compensated for by the induction of infant Ab to sub-immunodominant epitopes.

Evidence in favour of determinant-specific masking by MatAb in human infants is however provided by the evaluation of the influence of MatAb on responses to HIB-conjugate vaccines. MatAb to carrier proteins (i.e. MatAb to tetanus toxoid (TT)) do mediate a specific inhibitory influence on infant responses to TT, but do not inhibit Ab responses to the HIB polysaccharide moiety [26–28]. As the APC uptake of MatAb:Ag immune complexes would inhibit responses to both HIB and TT determinants, these observations do reflect the specific masking of TT but not of HIB antigenic determinants to infant B cells.

Thus, specific masking of B cell determinants and APC uptake of MatAb:Ag complexes emerge as the two essential immune mechanisms mediating the influence of MatAb on infant vaccine responses.

3. Essential determinants of the influence of maternal antibodies on infant responses

If APC uptake of MatAb:Ag complexes and epitope-specific masking of B cell determinants are responsible for the shaping of infant responses elicited in the presence of MatAb, one should expect (a) the lack of inhibition of infant T cell responses to be observed with all infant vaccines and to significantly impact on infant Ab responses, and (b) the ratio of MatAb to vaccine Ag to be the essential determinant of infant Ab responses.

3.1. Preservation of infant T cell responses elicited in presence of maternal antibodies

Human T cell responses to infant vaccines elicited in the presence of concentrations of MatAb which inhibit Ab responses have so far only been directly reported for measles vaccine. However, indirect evidence indeed suggests that it is a general phenomenon. First, use of infant vaccines in infant mice demonstrated a lack of MatAb-mediated inhibition of CD4⁺ and CD8⁺ T cell responses to all infant vaccines tested [29–32]. Second, clinical studies demonstrated that MatAb-mediated inhibition of primary antibody responses did not prevent infant priming, i.e. induction of secondary responses to booster immunization. Thus, the lack of inhibition of T cell priming by MatAb appears as a general phenomenon allowing induction of infant T cell responses to take place under the “umbrella” of MatAb. The potential contribution of such responses to disease attenuation in case of early exposure depends upon the pathogen-specific protective immunity.

3.2. Main determinant of infant Ab responses: the MatAb:vaccine antigen ratio

The direct influence of the concentration of MatAb at the time of immunization on infant Ab responses to live

vaccines has long been recognized [1]. This is also true for responses to non-live vaccines, as demonstrated recently in an elegant study by Dagan and coworkers where Israeli infants were immunized with hepatitis A vaccine at 2, 4 and 6 months and bled immediately before each vaccine dose and at 7 months of age [15]. The first vaccine dose only induced detectable infant responses in those immunized in the absence of detectable MatAb. The second vaccine dose induced detectable infant responses in those primed in the presence of MatAb < 1999 mIU/ml, and the third dose in those primed in the presence of MatAb < 3999 mIU/ml. Remarkably, the induction of infant responses was observed in each study group as soon as MatAb reached a threshold of 300–400 mIU/ml, whether this was reached at the time of administration of the first, the second or the third dose, or only at administration of the 12-month boosting in infants with MatAb > 4000 mIU/ml at the time of priming [15]. Thus, Ab responses may *only* be elicited when MatAb have fallen below a specific threshold, and secondary responses can be elicited *as soon as* this threshold is reached, as a reflection of unaffected T cell priming. This infant response threshold can presently only be defined experimentally and requires infants to be stratified by MatAb titers at the time of priming and randomised for bleeding after each vaccine dose.

How is this essential infant response threshold defined? Rather than simply reflecting a given concentration of MatAb at the time of immunization, this threshold is determined by the ratio of MatAb concentration to the dose of vaccine antigen. This was clearly demonstrated in infant mice, where TT elicited similar antibody responses in control pups immunized with 0.5, 2 or 6 Lf, (Fig. 2). Infant pups from TT-immune mothers failed to raise antibody response to 0.5 Lf of TT, as a result of the inhibitory influence of TT-specific MatAb. However, antibody responses were only transiently inhibited in infant mice immunized with 2 Lf of TT, whereas no inhibition was observed following immunization with 6 Lf (Fig. 2). Thus, increasing the dose of vaccine antigen was sufficient to circumvent

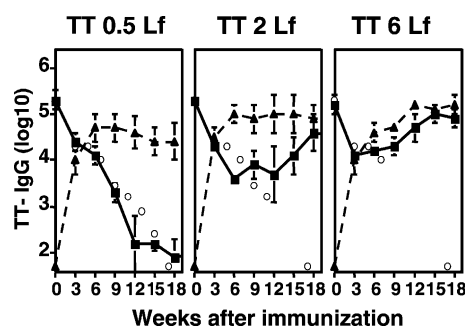


Fig. 2. Influence of the dose of vaccine antigen on antibody responses elicited to tetanus toxoid (TT) in 2-week-old BALB/c pups from control (dashed line) or immune mothers. Mice were bled at the time of immunization with 0.5, 2 or 6 Lf of alum-adsorbed TT and bled at regular intervals for detection of TT-specific IgG by ELISA.

inhibition by MatAb, presumably by providing additional antigenic epitopes which remained free of MatAb, and thus accessible to infant B cells.

The same MatAb:vaccine antigen ratio also defines the outcome of human infant immunization. As an example, a two-fold increase of the dose of a hepatitis A vaccine (from 720 to 1440 U) was sufficient to circumvent the MatAb-mediated inhibition of infant responses [33]. Similarly, high titered measles vaccines resulted in the expected enhanced sero-conversion/sero-responses in infants immunized in the presence of MatAb [34], although high doses of live measles vaccine unfortunately resulted in an excess unspecific mortality [35]. This understanding that the optimal infant dose may differ when immunization is performed in either the absence or presence of MatAb should be taken into consideration during clinical vaccine development, as a cost-driven selection of the lowest vaccine dose in seronegative infants may eventually prove insufficient in the presence of higher titers of MatAb.

Identifying the MatAb:vaccine antigen ratio and the lack of inhibition of T cell priming as the main determinants of the influence of MatAb on infant antibody responses explains the contradictory clinical observations reported using infant vaccines at various doses, with various immunization schedules, in populations characterized by distinct levels of MatAb. Conditions of MatAb excess or use of a low vaccine dose results in inhibition of antibody responses, which are in contrast preserved when MatAb decline or when the vaccine dose increases above certain thresholds (Fig. 3). At conditions of equivalence, partial masking of B cell epitopes occurs and may result in distinct outcomes in terms of infant antibody titers and epitope-specificity, depending upon the distribution of MatAb concentrations and the relative vaccine immunogenicity in a given population.

As an example, 60% of Nigerian infants were born with TT-specific MatAb < 0.3 IU/ml, as compared to only 12%

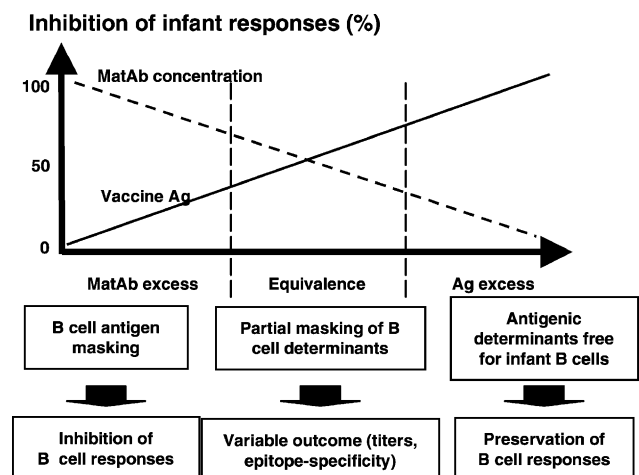


Fig. 3. Expected influence of maternal antibodies on infant antibody responses to subunit vaccines.

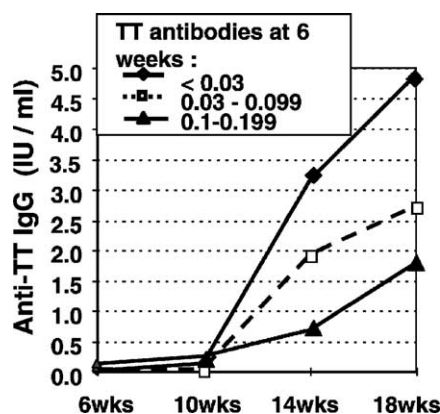


Fig. 4. Anti-tetanus IgG elicited by immunization in the presence of maternal antibodies. Infants were immunized at 6, 10 and 14 weeks with alum-adsorbed TT and bled at repeat intervals for detection of TT-specific IgG by ELISA.

of Finnish infants, whereas TT maternal immunization programmes resulted in 20% of Nigerian infants with MatAb titers > 2.99 IU/ml, which was never observed in Finland [26]. Comparison of the influence of MatAb on TT infant responses in these two populations inevitably leads to distinct and contradictory observations, but this does not imply differences in the immune mechanisms mediating the influence of MatAb in Nigerian and Finnish infants. It is important to recognize that even modest changes in MatAb titers at the time of immunization may significantly impact on infant responses. When Nigerian infants were immunized with DTP and HIB vaccines at 6, 10 and 14 weeks of age [36], even minute TT-specific MatAb concentrations (0.03–0.099 IU) at the time of priming exerted an inhibitory influence on infant TT responses (Fig. 4). Thus, the influence of MatAb on infant antibody responses cannot be directly extrapolated from one population to another and should be defined in the target population. Furthermore, changes in the distribution of infant MatAb as a result of the implementation of adolescent/adult immunization programmes, and their possible influence on infant responses, should be anticipated. For example, the induction of high hepatitis B titers by adolescent/young adult immunization will definitely result into enhanced MatAb titers in infants. Whether this will be associated with enhanced MatAb inhibition of infant responses will depend upon vaccine immunogenicity/vaccine antigen content and should be assessed. In contrast, it is unlikely that adolescent acellular pertussis boosting will have an impact on infant pertussis responses, as pertussis-specific antibodies unfortunately return to baseline within a few years following adult boosting. Similarly, maternal immunization with any vaccine resulting in the decline of infant MatAb titers to baseline titers prior to the age of completion of the infant immunization schedule should not be expected to significantly inhibit infant antibody responses.

4. Influence of maternal antibodies on infant responses to novel immunization strategies

The hypothesis that MatAb-mediated inhibition on infant responses was essentially mediated by neutralization of in vivo replication of live vaccines led to the assumption that mucosal immunization should be resistant to MatAb-mediated inhibition, as a result of significantly lower IgG concentrations on mucosal surfaces. Clinical observations however, do not support this hypothesis, as mucosally administered live infant vaccines, such as oral polio or rotavirus vaccines, remain susceptible to MatAb inhibition [2–4]. This may essentially reflect the fact that B cell responses are not elicited directly at mucosal surfaces but within draining lymphoid tissue, implying exposure of vaccine Ag to systemic MatAb concentrations, and thus to epitope-masking and APC uptake of immune complexes regardless of the injection route.

Similarly, as MatAb are unable to bind to DNA vaccines, it was hoped that DNA vaccines would easily escape even from high titers of MatAb-mediated inhibition. However, APC transfection by DNA vaccines is followed by in vivo Ag production and migration into draining lymph nodes. This again exposes vaccine Ag to systemic concentrations of MatAb and thus possibly to inhibition of infant responses, depending upon the MatAb:vaccine Ag ratio (reviewed in [37]). Thus, DNA vaccines may not prove more resistant to MatAb than corresponding subunit/live vaccines, unless they result in sufficiently prolonged in vivo Ag production for MatAb titers to decline below the infant response threshold. Novel vaccine formulations capable of avoiding MatAb-mediated inhibition, even at high MatAb titers, thus remain to be identified.

5. Conclusions

Understanding that the influence of MatAb on infant responses does not result from neutralization of in vivo vaccine replication or from FcγR-mediated inhibition of infant B cell activation, but essentially depends upon the MatAb:vaccine antigen ratio at the time of immunization, allows better definition of the potential influence of immunization strategies resulting in enhanced MatAb titers in infants. First, inhibition of infant responses will not occur if enhanced MatAb titers do not persist until completion of the infant immunization schedule, as is the case for most current vaccines. However, more immunogenic vaccines, such as TT or hepatitis A/B vaccines, may induce enhanced titers of MatAb throughout the first year of life, calling for a careful evaluation of the impact of adolescent/adult immunization programmes on infant antibody responses. Second, as MatAb do not prevent T cell priming, subsequent vaccine doses will induce infant antibody response as soon as MatAb titers decline below the infant response threshold. Maternal antibodies, therefore, represent a difficult challenge for

single dose infant vaccines, which are rare as immune immaturity limits infant antibody responses in an age-dependent manner [37]. Third, the influence of MatAb titers on infant responses will depend upon the relative distribution of MatAb titers in a given population at a given time, and upon the relative vaccine dose/immunogenicity. As such, maternal immunization programmes with strongly immunogenic vaccines could possibly reveal the need for more immunogenic infant vaccine/schedules, in terms of antigen content and/or number of vaccine doses. If identified, these obstacles could indeed be circumvented, such that the fear of suppressing infant responses should not hamper the development of adult/maternal immunization strategies against pathogens causing severe infections within the first weeks of life.

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References

- [1] Albrecht P, Ennis FA, Saltzman EJ, Krugman S. Persistence of maternal antibody in infants beyond 12 months: mechanism of measles vaccine failure. *J Pediatr* 1977;91(5):715–8.
- [2] Perkins FT, Yetts R, Gaisford W. A comparison of the responses of 100 infants to primary poliomyelitis immunization with two and with three doses of vaccine. *Br Med J* 1959;11083–6.
- [3] Karron RA, Steinhoff MC, Subbarao EK, et al. Safety and immunogenicity of a cold-adapted influenza A (H1N1) reassortant virus vaccine administered to infants less than 6 months of age. *Pediatr Infect Dis J* 1995;14(1):10–6.
- [4] Ruiz-Palacios GM. Impact of maternal antibodies on the immune response to an oral human rotavirus vaccine in Mexican infants. In: *Proceedings of the 3rd World Congress of Pediatric Infectious Diseases*. Chile: Santiago; 19–23 November 2002.
- [5] Booy R, Aitken SJ, Taylor S, et al. Immunogenicity of combined diphtheria, tetanus, and pertussis vaccine given at 2, 3 and 4 months versus 3, 5 and 9 months of age [see comments]. *Lancet* 1992;339(8792):507–10.
- [6] Sarvas H, Kurikka S, Seppala IJ, Makela PH, Makela O. Maternal antibodies partly inhibit an active antibody response to routine tetanus toxoid immunization in infants [letter]. *J Infect Dis* 1992;165(5):977–9.
- [7] Barr M, Glenny AT, Randall KJ. Diphtheria immunisation in young babies. A study of some factors involved. *Lancet* 1950;6593:6–10.
- [8] Bjorkholm B, Granstrom M, Taranger J, Wahl M, Hagberg L. Influence of high titers of maternal antibody on the serologic response of infants to diphtheria vaccination at 3, 5 and 12 months of age. *Pediatr Infect Dis J* 1995;14(10):846–50.
- [9] Burstyn DG, Baraff LJ, Peppler MS, Leake RD, St. Geme Jr J, Manclark CR. Serological response to filamentous hemagglutinin and lymphocytosis-promoting toxin of *Bordetella pertussis*. *Infect Immun* 1983;41(3):1150–6.
- [10] Englund JA, Anderson EL, Reed GF, et al. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. *Pediatrics* 1995;96(3 Pt 2):580–4.
- [11] Claesson BA, Schneerson R, Robbins JB, et al. Protective levels of serum antibodies stimulated in infants by two injections of *Haemophilus influenzae* type b capsular polysaccharide-tetanus toxoid conjugate. *J Pediatr* 1989;114(1):97–100.
- [12] Daum RS, Siber GR, Ballanco GA, Sood SK. Serum anticapsular antibody response in the first week after immunization of adults and infants with the *Haemophilus influenzae* type b–*Neisseria meningitidis* outer membrane protein complex conjugate vaccine. *J Infect Dis* 1991;164(6):1154–9.
- [13] Kanra G, Yalcin SS, Ceyhan M, Yurdakok K. Clinical trial to evaluate immunogenicity and safety of inactivated hepatitis A vaccination starting at 2-month-old children. *Turk J Pediatr* 2000;42(2):105–8.
- [14] Troisi CL, Hollinger FB, Krause DS, Pickering LK. Immunization of seronegative infants with hepatitis A vaccine (HAVRIX SKB): a comparative study of two dosing schedules. *Vaccine* 1997;15(15):1613–7.
- [15] Dagan R, Amir J, Mijalovsky A, et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. *Pediatr Infect Dis J* 2000;19(11):1045–52.
- [16] Gans HA, Maldonado Y, Yasukawa LL, et al. IL-12 IFN-gamma, and T cell proliferation to measles in immunized infants. *J Immunol* 1999;162(9):5569–75.
- [17] Pabst HF, Spady DW, Carson MM, Krezolek MP, Barreto L, Wittes RC. Cell-mediated and antibody immune responses to AIK-C and Connaught monovalent measles vaccine given to 6 month old infants. *Vaccine* 1999;17(15–16):1910–8.
- [18] Gans HA, Arvin AM, Galinus J, Logan L, DeHovitz R, Maldonado Y. Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *JAMA* 1998;280(6):527–32.
- [19] Crowe Jr JE, Firestone CY, Murphy BR. Passively acquired antibodies suppress humoral but not cell-mediated immunity in mice immunized with live attenuated respiratory syncytial virus vaccines. *J Immunol* 2001;167(7):3910–8.
- [20] Daeron M. Fc receptor biology. *Annu Rev Immunol* 1997;15:203–34.
- [21] Heyman B, Dahlstrom J, De Stahl TD, Getahun A, Wernersson S, Karlsson MC. No evidence for a role of FcgammaRIIB in suppression of in vivo antibody responses to erythrocytes by passively administered IgG. *Scand J Immunol* 2001;53(4):331–4; discussion 339–45.
- [22] Moller G. Antibody-mediated suppression of the immune response is determinant specific. *Eur J Immunol* 1985;15(4):409–12.
- [23] Karlsson MC, Wernersson S, Diaz de Stahl T, Gustavsson S, Heyman B. Efficient IgG-mediated suppression of primary antibody responses in Fcgamma receptor-deficient mice. *Proc Natl Acad Sci USA* 1999;96(5):2244–9.
- [24] Heyman B. Functions of antibodies in the regulation of B cell responses in vivo. *Springer Semin Immunopathol* 2001;23(4):421–32.
- [25] Jelonek MT, Maskrey JL, Steimer KS, Potts BJ, Higgins KW, Keller MA. Maternal monoclonal antibody to the V3 loop alters specificity of the response to a human immunodeficiency virus vaccine. *J Infect Dis* 1996;174(4):866–9.
- [26] Kurikka S, Olander RM, Eskola J, Kayhty H. Passively acquired anti-tetanus and anti-*Haemophilus* antibodies and the response to *Haemophilus influenzae* type b-tetanus toxoid conjugate vaccine in infancy. *Pediatr Infect Dis J* 1996;15(6):530–5.
- [27] Nohynek H, Gustafsson L, Capeding MR, et al. Effect of transplacentally acquired tetanus antibodies on the antibody responses to *Haemophilus influenzae* type b-tetanus toxoid conjugate and tetanus toxoid vaccines in Filipino infants. *Pediatr Infect Dis J* 1999;18(1):25–30.
- [28] Panpitpat C, Thisyakorn U, Chotpitayusunondh T, et al. Elevated levels of maternal anti-tetanus toxin antibodies do not suppress the immune response to a *Haemophilus influenzae* type b polyribosylphosphate-tetanus toxoid conjugate vaccine. *Bull World Health Org* 2000;78(3):364–71.

- [29] Siegrist CA, Barrios C, Martinez X, et al. Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allows successful early prime-boost strategies in mice. *Eur J Immunol* 1998;28(12):4138–48.
- [30] Siegrist CA, Cordova M, Brandt C, et al. Determinants of infant responses to vaccines in presence of maternal antibodies. *Vaccine* 1998;16(14–15):1409–14.
- [31] Martinez X, Brandt C, Saddallah F, et al. DNA immunization circumvents deficient induction of T helper type 1 and cytotoxic T lymphocyte responses in neonates and during early life. *Proc Natl Acad Sci USA* 1997;94(16):8726–31.
- [32] Martinez X, Li X, Kovarik J, Klein M, Lambert PH, Siegrist CA. Combining DNA and protein vaccines for early life immunization against respiratory syncytial virus in mice. *Eur J Immunol* 1999;29(10):3390–400.
- [33] Dagan R, Ashkenazi S, Amir J, et al. High-dose inactivated Hepatitis A vaccine (HD-HAV-VAC) in infants: comparison of response in the presence versus absence of maternally-derived antibodies (MatAb). In: *Proceedings of the 38th Annual ICAAC 1998*. San Diego, California.
- [34] Cutts FT, Nyandu B, Markowitz LE, et al. Immunogenicity of high-titer AIK-C or Edmonston-Zagreb vaccines in 3.5-month-old infants, and of medium- or high-titer Edmonston-Zagreb vaccine in 6-month-old infants, in Kinshasa, Zaire. *Vaccine* 1994;12(14):1311–6.
- [35] Knudsen KM, Aaby P, Whittle H, et al. Child mortality following standard, medium or high titer measles immunization in West Africa. *Int J Epidemiol* 1996;25(3):665–73.
- [36] Campagne G, Garba A, Schuchat A, et al. Response to conjugate *Haemophilus influenzae* B vaccine among infants in Niamey Niger. *Am J Trop Med Hyg* 1998;59(5):837–42.
- [37] Siegrist C. Neonatal and early life vaccinology. *Vaccine* 2001;19(25–26):3331–46.