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## REVIEW

# THE INTERFERENCE BY MATERNALLY-DERIVED ANTIBODY WITH ACTIVE IMMUNIZATION OF FARM ANIMALS AGAINST FOOT-AND-MOUTH DISEASE

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## SUMMARY

Foot-and-mouth disease (FMD) is a highly contagious disease affecting ruminants and pigs. In countries in which control of FMD relies predominantly on vaccination, young stock ingest specific anti-FMD virus antibodies in the colostrum. This maternally-derived antibody (MDA) provides immediate protection against infection with FMD virus, but also interferes with the development of active immunity following vaccination. However, susceptibility to infection precedes the ability to respond to vaccination in the presence of MDA. Currently available vaccines cannot overcome this inhibitory effect of MDA, and protection of young stock can only be provided by their isolation from FMD virus.

**KEYWORDS:** Foot-and-mouth disease; maternal immunity; immunization.

## INTRODUCTION

Neonates of all species are born into a hostile environment of physical and biological dangers. The obligate parasites in particular require to infect new susceptible individuals in order to ensure their own survival. The immune system has developed to respond to the various strategies employed by these pathogens to take advantage of their intended host, and consists of a number of different components which reflect the varied and diverse methods of entry and establishment that have evolved. However, not only are the different species of farm animal born with their immune system at different levels of maturity, the different parts of the complete system do not become functional simultaneously.

At birth, the calf can immunologically respond to bluetongue virus (MacLachlan *et al.*, 1984) and foot-and-mouth disease (FMD) virus (Nicholls *et al.*, 1985) by producing neutralizing antibody, but can only partially respond to infection with parainfluenza-3 virus (Thorsen *et al.*, 1969). Experimental infection of the foetal calf has been used to show how the developing immune system

responds to different antigens during its ontogeny (see review by Osburn, 1986). The immune system of the pig is less mature at birth; it can respond to hog cholera vaccination at 1 week of age (Precausta *et al.*, 1983) but not effectively to FMD vaccination until 2 weeks after birth (Francis & Black, 1986). However, despite the development of a functionally competent immune system, there is inevitably a lag period between immunization and the development of active immunity. It is during this period that prevalent viruses can establish themselves in young animals.

Immediate immunity in the newborn pig or ruminant is provided in the colostrum of the dam. All classes of antibody are present, in concentrations greater than those present in the parental blood, together with immunologically active cells. The specificity of this antibody reflects the vaccination and disease history of the dam, and therefore, by boosting the antibody levels to those pathogens associated with neonatal mortality through vaccination, the newborn animal can receive from its mother high levels of specific protection. However, this maternally derived antibody (MDA) is equally effective in preventing the response to active vaccination in the young animal as it is in providing protection against disease.

#### ORIGIN OF MDA

Unlike the situation in primates, transfer of immunoglobulins across the epitheliochorial placenta of farm animals during pregnancy is not possible. Early passive immunity in these species is transferred to the offspring *post-partum* by the absorption of colostrum through the gut mucosa. In the calf and piglet an indiscriminate uptake by the gut epithelium of macromolecules and immunocompetent cells in colostrum is possible for the first 24–36 h of life (Logan *et al.*, 1973). The process is non-selective and is responsible for the rapid increase of IgA, IgG and IgM in the circulation of the suckling neonate, with peak titres occurring at 24–72 h *post-partum*. The persistent detection of MDA in the serum and secretions of the offspring is dependent upon the initial colostrum uptake, which is determined by the immune status of the mother, and the half-life of antibody in the offspring, which is different for each isotype. MDA specific for FMD virus has been found to persist for up to 5 months in calves and 2 months in piglets (Ahl & Wittman, 1987).

Estimations of the half-lives of individual MDA isotypes vary. One set of values for the calf gives figures of 2.8 days for IgA, 4.8 days for IgM and 20 days for IgG (Banks, 1982). The corresponding figures for pigs are 2.1–3.0 days for IgA, 3.6–6.4 days for IgM and 6.6–22 days for IgG (Curtis & Bourne, 1973). Variability in these results is due to the range of methods used for measurement, and whether allowance has been made for the production of antibody by the neonatal immune system and the dilution effect of increasing blood volume during growth. Indeed, Francis and Black (1984) concluded that the decay of serum neutralizing IgG titres during the first 70 days of life in the pig was largely a result of expanding blood volume and not catabolism of the antibody.

#### THEORIES OF IMMUNOSUPPRESSION

There is ample evidence that in addition to the protective potential of MDA, it is also responsible for marked antigen-specific immunosuppression in young ani-

mals for periods that exceed the period of protection (Francis & Black, 1986). This is demonstrated *in vivo* by interference with the serum antibody response to vaccination, and *in vitro* by a reduction in the reactivity of lymphocytes upon stimulation with antigen. In this way MDA may interfere with the active immunization of young animals in a reversible fashion. In cattle and pigs, this phenomenon has been demonstrated for several infectious diseases including FMD.

It has long been appreciated that the active immunization of vertebrates early in life is not as effective as in the mature individual. Immaturity of the immune system at birth is partly responsible for this observation, although it has been shown in the domesticated species that good vaccination responses can be generated from the 2nd week of life (Ahl & Wittman, 1987). The greatest suppressive influence on vaccination response in the neonate is MDA. Immediately after birth, there is a short period of generalized suppression of B and T lymphocyte responsiveness, which could be due to the transfer of immunosuppressive factors in colostrum such as cortisol, histamine and cytokines (Clover & Zarkower, 1980). However, it has been clearly shown that the presence of MDA in the offspring correlates with the antigen-specific suppression of antibody responses, an effect that can be mimicked by the passive administration of monoclonal antibodies to neonatal mice (Xiang & Ertl, 1992). The mechanism by which MDA causes this effect is not completely determined for any species. The current hypotheses build upon the proposed mechanisms for regulation of the immune response in adults.

Initially it was thought that MDA interfered with the generation of an antibody response following vaccination of young animals purely by the enhanced removal of inactivated vaccine antigens or by neutralization of attenuated live vaccines. In both instances it was thought that vaccine antigen would be prevented from encountering the immunocompetent cells of the neonatal immune system by the effective 'antigen blockade' provided by MDA to the specific microorganism. More recent evidence suggests that MDA has a direct suppressive effect upon immunocompetent cells via a similar negative feedback system to the one that is thought to regulate the antibody response in mature animals (Katz, 1980). By the cross-linking of membrane-bound immunoglobulin Fc-receptors with surface immunoglobulin, immune complexes comprised of MDA and vaccinal antigen may deliver a negative signal to the B cell. This suppressive signal is antigen-specific and has the potential to be limited to particular MDA isotypes (Uhr & Mohler, 1968). MDA could thus act directly on B lymphocytes to down-regulate the proliferation and differentiation required for antibody production.

Alternatively MDA complexed with vaccinal antigen may act through a regulatory network to either suppress antigen-specific  $T_H$  cells or actively up-regulate the production of an antigen-specific T suppressor cell population (Harte & Playfair, 1983). A third theory of MDA-related immunosuppression makes use of the 'idiotype-anti-idiotype' immunoregulatory network proposed by Jerne (1974). In this antigen-free system MDA would induce antibody in the offspring which recognized its own antigen-binding site, or idiotype. The internal image antibody molecules, or anti-idiotypes, thus created could then interact with antigen receptors on the surface of B and T lymphocytes due to their similarity to the initiating antigen. This leaves the Fc portion of the antibody molecule free to deliver a negative signal to the cell through the Fc receptors. In reality the results of vaccination

trials in young animals do not decisively confirm or refute any one of these theories.

### EXPERIMENTAL EVIDENCE

Suppression of the antibody response to rabies virus vaccination in both the dog (Aghomo *et al.*, 1990) and the mouse (Xiang & Ertl, 1992) has been shown to occur for considerable periods after MDA has fallen below detectable levels. In the mouse system the suppression of *in vitro* T lymphoproliferation responses was more prolonged than the effect on the antibody response. The authors concluded that in this experimental system MDA-induced T suppressor cells were responsible for vaccination failure in these neonatal mice rather than a simple reduction in antigenic load. In addition to the MDA-mediated effects on neonatal immunocompetence in the mouse, Fujii and Yamaguchi (1992) reported that immunization of pregnant mice induced CD4<sup>+</sup> T lymphocytes which were capable of either producing a suppressive factor themselves or stimulating a population of T suppressor cells to secrete such a factor that could cross the placenta and induce specific humoral and cellular immunosuppression in the neonate. One of the authors has also previously reported the induction in mice of suppressor T cells in offspring following maternal immunization (Koshimo *et al.*, 1989). Immunocompetent cells and various factors are absorbed by the gut during the first 36 h of life in the domesticated species and, therefore, it is possible that these may have a regulatory effect on the immature immune system in these species similar to the transplacental factors in mice (Palmerly & Beer, 1977).

In the case of FMD vaccination in pigs, Francis and Black (1986) concluded that the complete immunological unresponsiveness seen in the first 2 weeks of life was due to immaturity of the immune system and antigen blockade by high titre MDA, and as this titre declined an active suppression of T and/or B cells occurred to variable degrees. The degree of inhibition of the antibody response in these piglets was directly proportional to the MDA titre at the time of vaccination. This was reflected in the outcome of the challenge experiment which showed that whereas partial protection was achieved by vaccination at 8 weeks old, earlier vaccination conferred no protection to FMDV challenge after 6 months. In this same study it was possible to elicit a primary antibody response, consisting of IgM, at an age when IgA and IgG responses were totally suppressed. This observation supports the view that a period of T lymphocyte immunosuppression follows the initial state of unresponsiveness, and that this interferes with the generation of secondary antibody responses. In this case the suppression acts after the initial stage of antigen-processing and recognition by B cells, and affects the regulation of the evolution of the antibody response by interference with clonal expansion and antibody isotype-switching, both of which are necessary for a secondary response and the generation of 'immunological memory', and thus long-term protection.

Similar results have been reported from studies on the effects of MDA on vaccination of calves against several viral diseases (Marshall & Frank, 1975; Kimman *et al.*, 1988). Vaccination of calves with high MDA titres at 1-week-old inhibited the active production of antibody to bovine coronavirus (Heckert *et al.*, 1991). Again

the IgM response was least susceptible to the suppressive effects of MDA in these calves, whereas both the serum IgG<sub>1</sub> and secretory IgA responses were markedly depressed. However, it is notable that the degree of suppression to the different coronavirus proteins was not uniform, and the authors suggest that the more immunogenic viral proteins may be able to elicit antibody responses at MDA titres that inhibit the response to other proteins. The reported success of oil-emulsion vaccines in the face of high MDA titres may also be due to improved immunogenicity (Morgan & McKercher, 1977). This suggests that the duration of the interference of MDA with antibody responses to vaccines may be specific to individual protein sub-units or even epitopes (van Maanen *et al.*, 1992), which emphasizes the importance of vaccine potency in a situation where high MDA titres are present. In support of this hypothesis that interference by MDA could be specific to particular antigens are the results of Kit *et al.* (1993) who were able to partially overcome the MDA to pseudorabies with a live glycoprotein gIII-deleted marker vaccine.

### FMD

In many of the FMD endemic regions of the world cattle, and sometimes also pigs, are vaccinated between one and four times a year, against the prevalent serotypes of FMD virus. The half-life of MDA to FMD virus in the calf is approximately 22 days (Nicholls *et al.*, 1984) and 21 days in the pig (Francis & Black, 1984), although in the pig the decline in concentration was considered to be due more to the increase in body weight than degradation or excretion of the MDA. The initial blood level of MDA and its subsequent persistence relates directly to its level in the colostrum and the efficiency with which it is adsorbed. Heifers tend to have lower levels of specific anti-FMD virus antibody in their colostrum than adult cows, and consequently their calves receive lower quantities of specific antibody than the calves of second or third lactation cows. This can result in an earlier susceptibility to FMD infection in endemic situations, and makes it more difficult to formulate vaccination schedules.

In South America, Nicholls *et al.* (1984) showed that MDA against FMD was likely to persist for 4–5 months, and that calves with MDA vaccinated against FMD not only failed to respond, but that vaccination depressed the serum titre of specific FMD virus antibody in these animals. They recommended that calves receive their primary vaccination at 5–6 months of age.

A similar situation exists in the large dairy herds in the Middle East (Kitching, unpublished observations). High yielding dairy cows have been imported from Europe and North America into a hostile climate and an environment in which previously unencountered disease such as FMD and rinderpest are endemic. Clinical FMD is kept under control by three or four times a year vaccination, but frequently it is the 6–18 month age group which develops disease in spite of this vaccination regime. Many farm managers had become frustrated by the apparent ineffectiveness of the FMD vaccine, whereby they had been using a variety of calf-hood vaccination protocols, almost all of which initiated vaccination before 3 months of age, and in some instances as early as 1 day old. The reason for the vac-

cine failure was the same as had been shown in South America a decade earlier, except in the Middle East the cows were being vaccinated far more frequently and efficiently and the MDA in their calves was at a very high level. The calves were reaching the age of 5 or 6 months, by which time they had received at least two ineffective vaccinations because of the MDA, and were then becoming susceptible to infection with FMD virus. To compound the problem, if the calves developed clinical FMD, the environmental shedding of virus from these calves was frequently sufficient to overcome the immunity of other animals on the farm, resulting in a major outbreak and loss of production from the milking herd.

A study was undertaken in which a number of the larger dairy herds participated, to examine different calthood vaccination programmes. The results of this previously unpublished study support many of the conclusions reached by Nicholls *et al.*, (1984, 1985), but in addition addressed some of the problems more relevant to the Middle East situation.

Assuming the level of management was sufficient to ensure that all calves received adequate colostrum, preferably pooled colostrum to include colostrum from older cows, vaccination at 1 day old or 1 month of age, even if it was followed by a booster vaccination at 21 days old or 2 months of age, respectively, was ineffective. It could not be shown, however, that vaccination at these ages reduced the level of circulating antibody against FMD virus in calves, as there was no statistically significant difference between antibody levels in the vaccinated groups and unvaccinated control groups.

When calves which had previously failed to respond to vaccination because of MDA were revaccinated at an age at which MDA no longer interfered with the response (i.e. at 5 or 6 months of age), there was no evidence that these calves had been primed by the first vaccination. They showed a similar response to vaccination as totally naive calves. This is contrary to the results of Nicholls *et al.* (1984), although it is acknowledged that comparisons between free ranging South American cattle and zero-grazed intensively-reared dairy animals in the Middle East may not apply.

Calves with waning MDA could become clinically infected with FMD virus prior to being able to respond to FMD vaccination. Calves with antibody titres below 1:100, measured using the liquid phase enzyme-linked immunosorbent assay (Hamblin *et al.*, 1987), became susceptible to infection, depending on the level of FMD virus challenge. However, calves with titres greater than 1:45 failed to respond to vaccination. This situation accounted for the persistence of FMD on one large farm, where the 5-month-old age group would become infected, maintain infection in the group for approximately 1 month and then pass infection to the next, 1 month younger group with which it was in contact and which was just developing susceptibility to infection, in spite of this younger group receiving vaccination.

At all times during the study the strain of FMD virus causing the outbreaks was monitored for changes in antigenic characteristics which could modify the interpretation of the results. Surprisingly, the virus remained antigenically stable over the 4-year period of the study, even though the pressure to mutate in order to evade vaccinal immunity was very great.

The conclusion of the study was that together with a number of management

recommendations, the most effective vaccination programme for calves of well vaccinated dams, was vaccination of all calves at 4, 5 and 6 months of age, to ensure that all calves had good levels of protection.

Vaccination of pigs against FMD is less widely practised due to the rapid turnover in the pig population. In addition, the immaturity of the immune response of the young pig makes vaccination of the sow during pregnancy a more effective method by which to protect the litter. Some response to vaccination in 8-week-old pigs in the presence of MDA was shown by Francis and Black (1986). However, it was the recommendation of Francis that vaccination of pigs from immune sows be delayed until 10–12 weeks of age, although additional vaccination at 2–4 weeks of age could be justified in order to protect those piglets which had received insufficient MDA (Francis, 1986). Francis and Black (1984) found no evidence in the pig that vaccination in the presence of MDA depressed the specific antibody to FMD virus.

The vaccines used in cattle outside of South America against FMD use a saponin and aluminium hydroxide adjuvant. These vaccines are less effective in pigs, and an oil adjuvant is used in pig FMD vaccines. However, in South America, oil adjuvanted FMD vaccines are used in cattle, and it is claimed that these vaccines overcome the depressive effects of MDA (Sadir *et al.*, 1988). Experimental results showed that calves over 30 days of age, but still with MDA, responded as well as adult cattle to the oil-emulsified FMD vaccine. However, there was a 30–60 day delayed response in MDA free calves under 7 days of age vaccinated with this vaccine, which was suggested to be due to high levels of cortical hormones (Sadir *et al.*, 1988).

In summary, it has been shown for several of the domesticated species that MDA can have a marked antigen-specific suppressive effect upon active antibody production in the young, the degree and duration of which is directly related to MDA titres shortly after birth. There is a gradual recovery of immune function in which the individual can become partially responsive prior to the acquisition of full immunocompetence. The precise point or points in the immune system of the offspring at which maternally-derived factors interfere is not defined. Some authors have described generalized cellular responsiveness (Clover & Zarkower, 1980), and others describe antigen-specific reduction in both primary and secondary antibody responses (Husband & Lascelles, 1975). However, it appears that individual lymphocyte subsets may be more or less susceptible to the effects of MDA.

Wittman and Ohlinger (1987) found that MDA titres which interfered with the cytolytic T lymphocyte response to Aujeszky's disease vaccination in piglets did not prevent the sensitization of lymphocytes for antibody production. Interestingly, it has also been shown that high titres of MDA in piglets suppressed the generation of 'memory cells' following vaccination against Aujeszky's disease (Kuiper *et al.*, 1984) whereas lower MDA titres that still suppressed the formation of antibody permitted the generation of immunological memory, which was apparent from the production of a secondary-type antibody response upon subsequent virus challenge (van Oirschot & de Leeuw, 1985). It is also possible that anatomical compartments within the immune system are affected variously by MDA, as has been shown to be the case for the mucosal immune response to respiratory syncytial virus vaccination in calves (Kimman *et al.*, 1989). This study showed that a protec-



tive mucosal antibody response could be effectively primed by the local application of attenuated virus in the face of MDA titres that inhibited all primary antibody responses and the generation of systemic antibody memory. Thus, by taking advantage of these observed qualitative and quantitative variations in the degree of immunosuppression induced by MDA, it may be possible to design vaccination strategies that offer better protection against infectious diseases of young livestock.

### NEW VACCINES

Control of FMD by vaccination has benefitted little from the recent advances in vaccine technology (see review by Kitching, 1992). Improvements in antigen production and concentration techniques have not resulted in significantly better vaccines, and FMD remains a disease that cannot be controlled by vaccination alone. The interference by MDA in the active immunization of young stock merely makes control of the disease even more difficult.

Calves with declining MDA become susceptible to infection with live virus before they are able to respond to an inactivated vaccine. This observation suggests that they would also respond to a live vaccine at a higher serum level of MDA than they would using a dead vaccine. However, previous attempts to develop a live attenuated FMD vaccine were unsuccessful as the virus quickly reverted to virulence. The genome sequences associated with virulence of FMD virus are not known, but stocks of the original attenuated vaccine still exist. If it was possible to fix the mutations responsible for attenuation of FMD virus, vaccination with live virus could again become an option, although the reputation that live FMD vaccines have acquired may exclude their use under any circumstances.

If a live vaccine can partially overcome interference by MDA, an alternative approach might be to insert FMD virus genes into a live vector. The glycoprotein gene of rabies virus has been placed in the vaccinia virus genome (Pastoret *et al.*, 1992) and the F and H genes of rinderpest virus have been placed in the genomes of vaccinia virus (Yilma *et al.*, 1988) and capripoxvirus (Romero *et al.*, 1993) to produce effective live vaccines against rabies and rinderpest, respectively. These recombinant vaccines will replicate in the presence of MDA to rabies or rinderpest as there will be no inhibition of the pox virus vector. Initial attempts to do the same for FMD virus have so far been unsuccessful.

Similarly, peptide vaccines have not replaced conventional FMD vaccines in spite of considerable research effort. This has in part been blamed on their failure to stimulate appropriate B and T cell populations. If, as has been suggested, MDA selectively suppresses antigen-specific responses, there would be little potential for peptide vaccines to overcome MDA. However, Lipford *et al.* (1994) have recently reported the development of immunostimulating complexes (ISCOMs) containing lipids and the saponin Quil A, which induce antigen-specific cytolytic T cells. The incorporation of FMD virus antigens into an ISCOM could improve peptide immunogenicity.

There is at present no completely effective strategy to protect young stock against FMD by vaccination in situations in which FMD is endemic. Only by isolating them completely from challenge with field virus until their MDA has declined

sufficiently for them to respond to conventional vaccines can disease be prevented, but such an approach in many countries may be too expensive to contemplate.

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