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Protection of Newborn Animals through Maternal Immunization

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Summary

Providing protective immunity to neonatal animals in early life is associated with numerous challenges regarding vaccine safety and efficacy. A much simpler approach is maternal vaccination, either before or during pregnancy, to provide the neonate with passively transferred immunity. In humans, the medical, societal and legal risks of immunizing pregnant women are important considerations in undertaking this approach. By contrast, maternal vaccination has been successfully employed in the animal health industry for decades. These veterinary vaccines have proven to be safe and efficient. Although only passively transferred antibodies have been extensively studied, other immunological mechanisms may be equally important in providing maternally derived immunity.

Keywords: maternal immunization; neonatal immunity; passive transfer

Introduction

The period immediately after birth is critical for the health and development of animals. The high susceptibility to infectious disease during this period is related to a variety of factors including immaturity of the immune system and susceptibility to tolerogenic signals (Barrios *et al.*, 1996). In particular, suboptimal interactions between antigen-presenting cells and T cells, and the inability of these cells to secrete some cytokines, may result in responses that are qualitatively different from those in adults, with decreased cytotoxic effector cell function and B-cell help (Upham *et al.*, 2002). An alternative strategy to provide early life protection against infectious disease is maternal vaccination. In humans, the medical, societal and legal risks of immunizing pregnant women pose important barriers to this process (Brent, 2003). By contrast, active maternal vaccination of various animal species has been practiced for a long time and provides a good level of safety and protection against some pathogens.

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Placental Structure and Classification

The placentae of all eutherian (placental) mammals share common structural and functional features, but there are also striking differences between species in the gross and microscopical structure of the placenta. Two characteristics form the basis for classification of placental types: the shape and area of contact between fetal and maternal tissue, and the number of layers of tissue between the maternal and fetal vascular systems. These differences in the structure of the placental interface determine the nature of molecular transport across the placenta. In primates and rodents, there is substantial transfer of immunoglobulin (Ig) G from the maternal to the fetal circulation prior to birth. By contrast, there is no transplacental transfer of immunoglobulin in animals like cattle, sheep, horses and pigs. In these species, the neonate is essentially devoid of circulating antibodies until it absorbs them from colostrum. Antibodies contained in the colostrum reach the neonatal vascular circulation through the intestine which is permeable to immunoglobulin for a few hours following birth. In dogs, in addition to postnatal

transfer of maternal IgG through colostrum, some passive immunity is conferred to the fetus during the last third of pregnancy (Stoffel *et al.*, 2000). Whatever the placental structure and transport mechanisms involved, successful maternal vaccination programmes are employed in various domestic animal species. Some examples of maternal vaccines used in cattle, dogs and pigs will be discussed in this overview.

Prevention of Intestinal Disease in Neonatal Calves

Diarrhoea is common in newborn calves. The acute disease is characterized by progressive dehydration and death, sometimes in as little as 12 h. In the subacute form, diarrhoea may persist for several days and result in malnutrition and emaciation. Several enteropathogens are associated with neonatal diarrhoea, but the most prevalent in most areas are *Escherichia coli*, rotavirus, coronavirus and *Cryptosporidium parvum*. In North America and Europe, various maternal vaccines against calf diarrhoea have been developed. Both modified-live and inactivated vaccines have been shown to enhance antibody titres in the colostrum and milk of vaccinated cows. In most cases, two primary injections are given several weeks before calving, followed by an annual booster injection just before subsequent calvings. The safety and efficacy for the pregnant cow and new born calves is well established in the field.

Studies have been conducted to determine the amount of transferred IgG required to provide protection against newborn calf infections (Tyler *et al.*, 1999). In order to be fully protective, these maternal antibodies must cross the permeable intestinal barrier during the first 24 h of neonatal life (Moore *et al.*, 2005). Efficient uptake of colostrum will depend on several factors including: the genetic background of the cow, alimentation, sanitary status and calving conditions. A more controlled method of ensuring good passive transfer is to feed calves a concentrate of specific antibodies, such as those in the commercial product Locatim® (Biokema Anstalt, Furstentum, Liechtenstein) which confers good protection against neonatal enteritis.

Prevention of Herpes Virus-Induced Disease in Neonatal Puppies

Canine herpesvirus-1 (CHV-1) is enzootic in dog populations all over the word. Infection is associated with an acute and usually fatal disease in puppies during the first weeks of life. The pups become infected oronasally during whelping or in their first day of life from the bitch or their littermates. In adult dogs, the virus causes only a mild infection of the upper respiratory or genital tracts, but infection of the pregnant bitch may induce stillbirth, abortion or neonatal mortality. This virus is also strongly suspected to cause infertility. As a result of its different pathogenic roles, CHV-1 may cause severe reproductive problems and high economic losses in breeding units. Because CHV may infect puppies very early in life, vaccination of the bitch represents the only option for actively preventing the disease. An inactivated CHV-1 vaccine is available (Poulet *et al.*, 2001) and in both laboratory and field studies this vaccine has been shown to be safe for the pregnant bitch with no adverse effects on reproductive performance. In all cases, vaccination resulted in uniform seroconversion and high neutralizing antibody titres in the bitches. No cases of CHV disease were recorded in the puppies produced by vaccinated bitches. Moreover, the results of field trials provided strong evidence of the efficacy of the vaccine against other effects, such as infertility, induced by the virus.

Prevention of Post-Weaning Multisystemic Syndrome in Neonatal Piglets

The porcine circovirus type 2 (PCV2) is now accepted as the major infectious agent involved in post-weaning multisystemic syndrome (PWMS). PWMS affects pigs during the first weeks of life. Clinical signs include progressive weight loss, dyspnoea, tachypnoea, anaemia, diarrhoea and jaundice. PWMS is now endemic in many swine-producing countries, causing an economic impact on the swine industry worldwide. The effects of PCV2 on the pig immune system are not fully understood but several studies have suggested that PCV2 might cause immunosuppression (Shibahara *et al.*, 2000; Segales *et al.*, 2001; Vincent *et al.*, 2007). Moreover, it has been reported that experimentally induced immune stimulation (e.g. by vaccination) early in life can induce the disease (Grasland *et al.*, 2005). Because of these features, maternal vaccination is regarded as the most favourable option to provide protection from PWMS.

Piglets born from sows with high antibody titres to PCV2 were well-protected from a severe PCV2 challenge. By contrast, piglets of the same age but born from sows with low PCV2 antibody titres had higher viral load in lymph nodes, more serious clinical signs and lesions, and some of them developed PWMS. A killed PCV2 vaccine has been developed recently. Experiments conducted in a specific pathogen-free model evaluated the effect of maternal protection against a virulent PCV2 challenge. Piglets born to vaccinated gilts expressed significantly fewer clinical signs and lesions, and had significantly lower viral load in serum, faeces and lymph nodes, compared with piglets born to non-vaccinated gilts. Field studies reported a significant decrease of PWMS and global mortality in both neonatal and finishing pigs, suggesting that passive immunity could confer long-term protection. It is

hypothesized that mild PCV2 exposure, in the face of maternally derived immunity, enables piglets to build efficient active immunity specific to the virus.

Conclusions

Many other examples of maternal vaccination of animals exist, for example the vaccination of sows has been widely used in the field to protect piglets and pigs from neonatal colibacillosis, necrotizing diarrhoea, erysipelas, atrophic rhinitis, swine influenza and Aujesky's disease. In all cases these vaccinations have proven to be safe and efficient.

The protective effect of passive vaccination has always been related to the presence of antigen-specific antibodies in the vaccinated mother and colostrum. However, other mechanisms whereby maternal immunity confers protection may exist. Numerous other constituents of colostrum, in addition to antibodies, are thought to potentially contribute to passive immunity. These include innate defence factors such as lysozyme, lactoferrin, peroxidase, complex oligosaccharides, mucins, cytokines, chemokines and leucocytes (Kelleher and Lonnerdal, 2001). It has been established that colostrum-derived lymphocytes can migrate from the gut into the circulation and lymphoid organs of neonates (Tuboly and Bernath, 2002). Transferred lymphocytes could represent a source of cytokines and chemokines that exert regulatory effects on neonatal antigen-presenting cells and Tcells, or be a source of specific armed cells able to fight early infection. Although maternally derived antibodies are generally considered to impair neonatal responsiveness to active vaccination, at least at the B-cell level, their potential positive effects on the generation of specific T-cell responses requires further detailed investigation (Rowe *et al.*, 2004).

The rational design of the most appropriate maternal vaccination programmes and strategies is linked to a better understanding of the different mechanisms by which maternal immunity confers protection to the newborn. Veterinary models could help to address these fundamental questions for the benefit of human vaccination.

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