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Vaccination against enteric rota and coronaviruses in cattle and pigs: enhancement of lactogenic immunity

C.F. Crouch

Passive immunity against enteric viral infections is dependent upon the continual presence in the gut lumen of a protective level of specific antibodies. This article examines methods currently used to enhance the titre and duration of specific antibody in the mammary secretions of cows and pigs, with particular reference to rotavirus and coronavirus infections. In addition, some of the potential problems to be found in attempting to produce vaccines against these viral infections are outlined.

Keywords: Viruses: rotavirus: coronavirus: cattle: pigs lactogenic immunity

Introduction

Neonatal diarrhoea is a complex disease associated with a number of infectious agents occurring either singly or in combination. In domestic animals economic losses are suffered, as a result of mortality (ranging between 0 and 80%), and also veterinary costs and decreased productivity of the survivors. The viral agents most commonly associated with this syndrome are rotavirus and coronavirus, both of which have been found to be primary pathogens in calves and piglets. These viruses are most frequently isolated during the period from birth to weaning, and animals of this age have been the most intensively studied because of the frequency and severity of these infections. Animals of all ages are, however, susceptible, with subclinical infections apparently common in both adult cows and pigs. In neonatal calves the incidence of rotavirus and coronavirus associated diarrhoea is similar varying between 15 and 76%. The situation in neonatal piglets is less clear, rotavirus infections are apparently common, whilst transmissible gastroenteritis virus (TGEV), the prototype enteric coronavirus in swine, is an example of a seasonal cold-weather disease, probably related to both the thermal sensitivity of the virus and the effect of cold-stress on converting subclinical to clinical infections.

Pathogenesis of infection

The pathogenesis of enteric rotavirus and coronavirus diseases of swine and cattle are similar. In contrast to TGEV, however, rotaviruses appear to be confined to the alimentary tract, predominantly the small intestine, although there is some evidence in both lambs and piglets for infection of the large intestine. The infections are characterized by diarrhoea and dehydration caused by the functional and anatomical loss of the absorptive cells of the intestine. The principal site of virus replication has been shown to be the intestinal villus epithelium. The infected cells are lost from the tips of the villi and are replaced with immature crypt cells. Generally, there is a diminution in the number and size of the villi and a progressive replacement of the epithelium with squamous and cuboidal cells which lack a brush border. Such immature cells have been shown to possess reduced levels of disaccharidases. The loss of the absorptive cells of the intestine is assumed to result in the observed malabsorption syndrome. This is further exacerbated by the decreased ability to utilize dietary lactose, resulting in its accumulation in the large intestine, thereby preventing further absorption of water by exerting an osmotic effect.

Passive immunity in pigs and cows

As a result of the severity of these enteric viral infections during the first few weeks of life, passively acquired antibody is the major source of protection. In calves and pigs there is no selective transfer of immunoglobulins from the maternal to the foetal circulation during the last third of the pregnancy. Instead, during the period immediately following birth, maternal immunoglobulin is acquired from the colostrum which remains in the gut lumen for many hours. In contrast to colostral absorption, highly specific mechanisms operate in the colostrum-forming mammary glands of cattle and pigs causing large amounts of IgG (relative to IgA and
IgM) to concentrate in the colostrum. IgG passively acquired by the neonate from colostrum persists in the serum for several weeks protecting against systemic infection. In TGEV infection of pigs and rotavirus infection of calves circulating antibody has been found to be of little value. Resistance to these infections appears to be mediated instead by local immunity at the epithelial surface of the intestine.

In cattle the selective transfer of IgG, from serum to milk continues throughout lactation, although at a reduced level when compared with colostrum formation. The concentration of all three classes of immunoglobulin in milk is significantly reduced (30 to 60-fold) in milk and in consequence IgG remains the primary immunoglobulin in bovine milk. In contrast, in pigs the concentration of IgG decreases about 30-fold during the first week of lactation, whilst that of secretory IgA declines only about three-fold, leaving it to become the predominant class of immunoglobulin in swine milk. Most adult cattle are seropositive for both rotavirus and coronavirus antibodies. There is a dramatic decline in these colostral antibody titres during the transition to milk, reflecting this reduction in concentration of immunoglobulins. This partially explains the high incidence of antibody decline.

Antigenic variation and cross-protection

Despite the presence of one or more common antigens it has been demonstrated that rotaviruses isolated from different species can differ antigenically from each other. More recently it has been shown that different serotypes exist within isolates obtained from single species. The existence of at least two different serotypes of porcine rotavirus and at least three distinct bovine serotypes have been described. Bridger et al. have suggested the occurrence of intermediate bovine rotavirus types, although more work is essential to clarify this situation.

Some recent isolates possessing the distinctive morphology of rotaviruses have been found to lack the common group antigen. To date, these atypical rotaviruses have been isolated from humans, birds, calves, lambs and pigs. In pigs, preliminary results using two previously characterized atypical isolates have indicated that these are distinct and do not share a common group antigen. These observations have been extended by Snodgrass et al. who suggest the occurrence of at least four distinct groups of rotaviruses based on their group antigen.

The significance of the serotype differences observed between rotaviruses in vitro still needs to be fully assessed in vivo. Orbiviruses (also members of the Reoviridae) possess many serotypes and require the use of multivalent vaccines.

Many of the cross-protection studies carried out using different rotavirus serotypes are contradictory and the data inconclusive. For example, in vivo vaccination of calves with a bovine rotavirus was found to protect against diarrhea caused by challenge with human rotavirus serotype 2. Although challenge virus was still shed. In contrast, one out of three calves was protected against a bovine rotavirus challenge after vaccination with a human serotype 2 or an equine rotavirus and this animal shed no detectable virus. Furthermore, pigs vaccinated with human rotavirus and challenged with porcine rotavirus were protected against the clinical disease but shed virus. Using a more defined challenge system, evidence has been obtained indicating that rotavirus isolates from different animal species and of different serotypes show poor cross-protective properties in vivo. This observation has been confirmed and extended by studies in gnotobiotic calves and piglets showing that cross-protection only occurred between rotaviruses of the same serotype, and that even a minor serotype difference could be sufficient to affect cross-protection. Further evidence for a lack of cross-protection between rotavirus serotypes can be obtained from studies of sequential infections, where subsequent rotavirus infections were found to be associated with different serotypes.

The situation with coronaviruses is simpler. To date, the coronaviruses isolated from mammals and birds have been grouped into four antigenic classes, where little or no cross-reactivity can be demonstrated between classes. TGEV is antigenically distinct from bovine enteric coronavirus as well as from another as yet unclassified coronavirus causing diarrhoea in pigs.

Vaccination against rotavirus and coronavirus infection in cattle

Two approaches have been used in an attempt to provide calves with protection against rotavirus and coronavirus infections. The first approach involves oral vaccination with live attenuated virus in order to stimulate active immunity in the calf. The incidence of diarrhoea in neonatal calves orally vaccinated with attenuated rotavirus was found to be reduced, but the vaccine was not proven to be effective in blind field trials. There are a number of limitations associated with this approach. These include the potential of the vaccine to regain virulence; a high incidence of seropositive adult animals, leading to the possibility of interference with vaccine virus replication by maternally derived (milk) antibodies; and the relative immaturity of the neonate's immune system. The second approach utilizes passive protection produced through lactogenic immunity, stimulated by maternal vaccination. Attempts to vaccinate dams using an attenuated live vaccine (Calf Guard, Norden Laboratories) have failed to significantly enhance milk antibody titres. Table 1, whilst in-vivo enhancement of lactogenic immunity: C.F. Crouch

| Immunogen | Vaccine | Adjuvant | Whv antibody titre (VN) |
|-----------|---------|----------|-----------------------|
| Formaldehyde inactivated rotavirus | Formaldehyde inactivated rotavirus | FICA | 800 | 13004 |
| Formaldehyde inactivated rotavirus | Formaldehyde inactivated rotavirus | FICA | 200 | 32768 |
| Formaldehyde inactivated rotavirus | Formaldehyde inactivated rotavirus | AlPO₄ | 800 | 13004 |
| Formaldehyde inactivated rotavirus | Formaldehyde inactivated rotavirus | AlPO₄ | 200 | 4598 |
| None | None | FICA | 813 | 9 |
| Calf Guard | Calf Guard | FICA | 4096 | 13 |

*FICA, Freund's incomplete adjuvant

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Table 2. Enhancement of rotavirus neutralizing antibody in cows following different vaccination protocols

| Dose per cow | No. of doses | Route* | Adjuvant# | Immunogen* | Colostral antibody titre | Ref. |
|-------------|-------------|--------|-----------|------------|-------------------------|------|
| 10^8.1      | 2           | i.m.   | FICA      | Formaldehyde inactivated rotavirus | 20452# | 89 |
| 10^8.8      | 2           | nr     | Al(OH)_2 + oil | Formaldehyde inactivated rotavirus | 1580# | 90 |
| 10^6.0      | 2           | i.m.   | Al(OH)_2 + oil | None | 320# | 90 |
| 10^5.5      | 1           | i.m.   | Oil       | Formaldehyde inactivated rotavirus | 11481# | 88 |
| 10^4.9      | 1           | i.m.   | Oil       | Formaldehyde inactivated rotavirus | 9120# | 88 |
| nr          | 1           | s.c.   | Oil       | BPL inactivated rotavirus | 645# | 88 |
| nr          | 2           | s.c.   | Oil       | BPL inactivated rotavirus | 1995# | 91 |
| 10^6.4      | 2           | i.m.   | FICA      | None | 795# | 91 |
| 10^6.4      | 2           | i.m.   | FICA      | BEI inactivated rotavirus | 24401# | 53 |
|             |             |        |           | BPL inactivated rotavirus | 2374# | 53 |
|             |             |        |           | None | 2685# | 53 |

nr, not reported: *i.m., intramuscular; s.c., subcutaneous. #FICA, Freund's incomplete adjuvant. $BPL, \beta$-propriolactone; BEI, binary ethylenimine.

activated, adjuvanted rotavirus preparations have been found to enhance levels of specific antibody in colostrum and milk (Tables 1 and 2).

A number of parameters need to be considered in attempting to optimize the enhancement of antibody production in mammary secretions.

**Dose and form of vaccine.** In considering inactivated vaccines, it is to be expected that relatively large amounts are necessary to achieve a satisfactory response. Further, the process of inactivation may decrease the immunogenicity of some viral polypeptides. Table 2 shows that no significant differences in milk antibody titres were obtained following vaccination of cows with rotavirus preparations containing either 200 or 800 ELISA units (after inactivation) emulsified in Freund's incomplete adjuvant. In contrast, if the same preparations were used, but adjuvanted with aluminium phosphate, the higher dose resulted in a greater antibody response. A similar result using an oil adjuvanted rotavirus vaccine has been previously reported.

Formaldehyde inactivated rotavirus vaccines have been used to successfully enhance milk antibody titres as compared with controls.\(^{98-90}\). Other workers have reported increased antibody responses using \(\beta\)-propriolactone as the inactivating agent\(^{61}\), although Saif et al. found that antibody titres in mammary secretions were at least tenfold greater from cows vaccinated with binary ethylenimine inactivated rotavirus compared with those vaccinated with \(\beta\)-propriolactone inactivated rotavirus\(^{53}\).

**Adjuvant.** Snodgrass et al.\(^{88}\) found that oil-based adjuvants were more effective than hydrogel for the enhancement of rotavirus antibody titres in mammary secretions. This concurs with the data presented in Table 1. Most workers have demonstrated a satisfactory immune response following vaccination using oil-based adjuvants, generally Freund's incomplete adjuvant (Table 2).

**Route and timing of vaccination.** To some extent the route and timing of vaccination are dependent upon the type of cattle being farmed. Thus the intramammary route used successfully by Saif et al.\(^{93}\), whilst applicable to dairy cattle, may not be practical in beef cows. Similarly, from an administrative viewpoint a single vaccination would be preferable to a regime utilizing several doses. The majority of studies have reported a significant increase in rotavirus antibody titres in mammary secretions using either subcutaneous or intramuscular injection of oil-adjuvanted vaccines. All such vaccines have also proved to be effective when administered as either single or double doses injected prior to or at parturition\(^{53,88-92}\) (Table 1).

The efficacy of immune milk as a mechanism for providing passive immunity against rotavirus challenge has been examined by a number of workers (Table 3). The
Table 3: Passive protection against rotavirus challenge of calves fed immune milk

| Origin | Amount | Method of feeding | Challenge | No. of calves | Virus shedding | Diarrhoea |
|--------|--------|-------------------|-----------|---------------|---------------|-----------|
| Vacc   | --     | Suckling          | Exp       | 7             | 100           | 5.2       | 71        | Ref. 89 |
| Cont   | --     | Suckling          | Exp       | 9             | 100           | 2.0       | 100       | Ref. 89 |
| Vacc   | --     | Suckling          | Field     | 402           | --            | nr        | 93        | Ref. 92 |
| Cont   | --     | Suckling          | Field     | 174           | --            | nr        | 90        | Ref. 92 |
| Vacc   | 21 2x  | Supp              | Exp       | 7             | --            | nr        | 88        | 92       |
| Cont   | 21 2x  | Supp              | Exp       | 5             | --            | nr        | 100       | 6.0      |
| Vacc   | 10%    | Supp              | Field     | 10            | 40            | nr        | 40        | 6.0      |
| Normal | 10%    | Supp              | Field     | 11            | 36            | nr        | 73        | 4.1      |
| Cont   | --     | --                | Field     | 21            | 76            | nr        | 76        | 3.9      |
| Vacc   | --     | Suckling          | Field     | 77            | 10            | nr        | 8         | nr       |
| Cont   | --     | --                | Field     | 64            | 29            | nr        | 27        | nr       |
| Vacc   | nr     | Supp              | Exp       | 3             | nr            | 6.0       | 0         | nr       |
| Cont   | nr     | Supp              | Exp       | 2             | 100           | 1.0       | 0         | nr       |
| Vacc   | 1%     | Supp              | Exp       | 8             | 0             | --        | 25        | 3.0      |
| Vacc   | 0.1%   | Supp              | Exp       | 6             | 66            | 3.8       | 83        | 3.7      |
| Vacc   | 1%     | Supp              | Exp       | 6             | 100           | 1.8       | 100       | 1.6      |
| Normal | 1%     | Supp              | Exp       | 6             | 100           | 1.8       | 100       | 1.7      |
| Cont   | --     | --                | Exp       | 8             | 100           | 1.1       | 100       | 1.1      |

* Lactogenic antibody originated from either vaccinated (vacc), control (cont) or normal cows (normal). aCalves were either suckled naturally (suckled) or fed a supplemented diet containing antibody (supp). cCalves were either challenged experimentally (exp) or naturally exposed under field conditions (field). d Days after challenge. e Days after birth. f Days after start of experiment. g Cows vaccinated with commercial vaccine. nr, not reported.

Table 4: Efficacy of different vaccination protocols for the stimulation of lactogenic immunity for the passive protection of newborn pigs against challenge by TGEV

| Immunogen | Route | Challenge | Protection | Class of major immunoglobulin in milk | Ref. |
|-----------|-------|-----------|------------|---------------------------------------|------|
| Live-attenuated TGEV | i.m. | Experimental | Moderate | IgG | 97 |
| Live-attenuated TGEV | i.mm. | Experimental | Good | IgG | 97 |
| Live-attenuated TGEV | i.m. | Experimental | Poor | IgG | 111 |
| Live-attenuated TGEV | Oral | Experimental | Poor | IgG | 110 |
| Live-attenuated TGEV | Oral | Experimental | Poor | IgG | 100 |
| Live FIPV | Oral | Experimental | Poor | IgG | 109 |
| Live-attenuated TGEV | Oral | Experimental | Poor | IgA | 109 |

* i.m., intramuscular; i.mm., intramammary.

Results, however, are difficult to compare, due to variations in the feeding regime used for the immune milk and also the challenge systems used. The amount and the timing of the feeding of lactogenic antibody and the dose, virulence and serotype of the virus challenge strain used will all affect the apparent susceptibility of the calf to infection. Further, in situations where a field challenge has been used, failure of protection may be due to infection by rotavirus serotypes other than those used in the vaccine, or possibly by other agents capable of causing diarrhoea. Generally, these investigators reported either a reduced incidence of rotavirus shedding or diarrhoea or both. In only one study did the feeding of lactogenic antibody fail to significantly affect the incidence or onset of diarrhoea. The majority of animals receiving passive immunity appear to be capable of developing active immunity during this period, consequently vaccination should lead to elimination of clinical disease rather than a delay in its onset. Investigation of the immunoglobulin isotypes associated with this protective antibody induced by vaccination in bovine milk and colostrum suggests that IgG, plays the major role. These observations are in agreement with those discussed earlier concerning passive immunity in the bovine.

Vaccination against rotavirus and coronavirus infection in pigs

In contrast to the bovine system, evidence suggests that milk or colostral immunoglobulin of the IgA isotype is more effective than those of the IgG isotypes at protecting piglets against infection by TGEV. High persisting levels of IgG may, however, provide some degree of
protection against virus challenge\(^\text{28}\). As a result of these observations, most studies have examined methods for optimising the stimulation of secretory IgA antibodies in milk. The origin of TGEV-specific IgA found in mammary secretions remains somewhat obscure, although there is a good correlation with the presence of an infection in the intestinal tract\(^{9,99,100,101}\). Secretory IgA in porcine milk is almost certainly locally produced in the mammary gland\(^{85-94}\). In order to explain this phenomenon, it has been suggested that specifically-sensitized IgA-secreting lymphocytes may migrate to the mammary gland following initial sensitization in the intestine\(^{9-10}\). Such an inter-relationship between the intestinal and the mammary immune systems has also been proposed in rabbits\(^{103}\) and humans\(^{94}\). Direct evidence for such migration, under the influence of pregnancy-associated hormones, has been obtained in mice\(^{104}\).

A summary of various investigations into the antibody response and efficacy of lactogenic immunity following different vaccination protocols is given in Table 4. Reduced immunogenicity in pigs of cell culture attenuated TGEV has been described\(^{104}\). Oral vaccination with a live, attenuated TGE vaccine, whilst producing neutralizing antibody, did not stimulate good lactogenic immunity in suckling pigs\(^{105}\). Intramuscular vaccination of sows with live, attenuated TGEV leads to the enhancement of specific IgG levels in colostrum and milk\(^{97,111}\). Higher titres of TGEV-specific IgG have been achieved using intramammary injection, with an associated increase in the protection provided to suckling pigs\(^{97}\). These results are supported by the observations of other workers\(^{112-115}\). Feline infectious peritonitis virus (FIPV) is a member of the same antigenic class as TGEV and consequently the two viruses are serologically related. Good levels of cross-protection, associated with high titres of TGEV-specific neutralizing antibody have been reported in sows vaccinated orally with FIPV\(^{116}\). In contrast, the results of a more recent study have shown that whilst TGEV neutralizing antibodies of the IgG subclass are stimulated in milk and colostrum, the enhancement for suckling pigs was low\(^{117}\).

It may be possible to boost the level of IgA in mammary secretions. Preliminary investigations have revealed that specific secretory IgA levels in milk can be enhanced by the parenteral injection, at parturition, of TGEV or rotavirus into naturally infected pigs\(^{105,109,119}\). Intramuscular vaccination of sows with live, attenuated TGEV leads to the enhancement of specific IgG levels in colostrum and milk\(^{97,111}\). Higher titres of TGEV-specific IgG have been achieved using intramammary injection, with an associated increase in the protection provided to suckling pigs\(^{97}\). These results are supported by the observations of other workers\(^{112-115}\). Feline infectious peritonitis virus (FIPV) is a member of the same antigenic class as TGEV and consequently the two viruses are serologically related. Good levels of cross-protection, associated with high titres of TGEV-specific neutralizing antibody have been reported in sows vaccinated orally with FIPV\(^{116}\). In contrast, the results of a more recent study have shown that whilst TGEV neutralizing antibodies of the IgG subclass are stimulated in milk and colostrum, the enhancement for suckling pigs was low\(^{117}\).

Future considerations

IgG can be induced readily in the mammary secretions of cattle, by intramuscular or subcutaneous injection of adjuvanted immunogen. In pigs however, whilst live, virulent virus is capable of inducing high levels in IgA in milk, it is apparent that the ideal candidate vaccine virus must be sufficiently attenuated to produce only mild or no disease in neonatal pigs, whilst retaining sufficient virulence to infect the intestinal tract of adult swine. More work is essential in the possible use of inactivated vaccines for the boosting of existing IgA levels in mammary secretions. These may require prior natural infection of the sow, the incidence of which will vary between herds, with an associated affect upon the efficacy of such a vaccine. Further investigation into the variety of strains and serotypes of rotaviruses is of obvious importance, as is the response to vaccination of cattle and swine by rotaviruses or coronaviruses. Current data suggests that cross-protection between rotavirus serotypes is limited, although there is little information concerning the specificities of the antibodies induced by vaccination of previously infected animals. Such animals naturally exposed to a variety of serotypes may produce a heterogeneous antibody response, capable of reacting with a broad spectrum of rotavirus serotypes.

It is apparent that the enhancement of lactogenic immunity through the vaccination of the dam provides a suitable mechanism by which neonatal pigs and calves can be protected against rotavirus and coronavirus infections. The production of truly effective vaccines, however, awaits further work in some of the areas outlined above.

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