Bovine Virus Diarrhoea Virus Vaccines and Vaccination

J. Brownlie
The Royal Veterinary College - Hawskshead Campus
North Mymms, Hatfield
Herts AL9 7TA - UK

Introduction

Bovine virus diarrhoea virus (BVDV) causes widespread and potentially severe infection of cattle. In Europe, there are a small number of BVDV vaccines presently licensed that are variously available to the member countries. However, in the UK, where BVDV remains uncontrolled there is no commercially available effective vaccine. The implications that vaccination will entirely control BVDV within the National Herd may be treated with caution if the experience of the USA is considered. In the USA, more than 150 BVDV vaccines have been licensed in the various States but the prevalence of the virus is still widespread. However, at the individual herd level, a combination of good management and effective vaccination can be powerful means of control.

Our present understanding of BVDV has allowed certain critical pathways in the epidemiology of the virus to be identified. For BVDV to survive within the National Herd, reservoirs of the virus are required. With little doubt, the major reservoir is the persistently infected (PI) animal. These PI animals represent about 1% of the adult herd[7] although the figure may be significantly higher among neonatal calves. Other animal sources of BVDV can include sheep or goats infected with either BVDV or Border disease virus (BDV) and even the wild ruminants e.g. deer. The risk from these latter sources would appear to be low. Over the last few years, a further source has been BVDV-contaminated vaccines, invariable in the live or attenuated vaccines.

BVDV has two biological forms called biotypes; these exist naturally in cattle but have defined pathways. They are differentiated in cell culture by their ability to cause lysis (cytopathogenic virus BVDVc) and not cause lysis (non-cytopathogenic virus BVDVnc). The establishment of persistent infection occurs as a result of an *in utero* infection with the BVDVnc biotype early in pregnancy (before 110 days post-insemination). The virus is able to cross the placenta and grow in the tissues of the early foetus. At the development of competence of the immune system, the virus would appear to be accepted in the same manner as "self tissues" and not rejected. Such an acceptance is generally considered to be foetal tolerance whereby the early foetal immune system does not recognize the virus as foreign and makes no immune response e.g. antibody. The animal becomes persistently infected and remains so for life. These are the very animals that represent the main reservoirs for the continuance of the virus within the National Herd. A break in this part of the BVDV lifecycle would be a major part of diminishing the incidence of infection. At an individual herd level, prevention of foetal infection has further benefits; BVDV is a severe foetal pathogen and considerable losses occur from early embryonic death, abortions, mummified foetuses, congenital damage to the central nervous system and finally the birth of weak, unthrifty calves many of which are PI calves.

The second biotype BVDVc is associated with mucosal disease.[3] It is not considered to be a foetal pathogen of any consequence.[4]

The one unifying approach to prevention must be to protect the early foetus from BVDVnc infection. The three major approaches are outlined below.

Control of BVDV Infection in Cattle

Maintenance of herd immunity through the continual exposure to BVDV infection.

In the absence of effective vaccines, an approach to the priming and maintenance of BVDV immunity in cattle has been to retain a PI animal as a sentinel source of infectious virus. It is common practice for PI cattle to be mixed with heifer calves that are eventually destined to join the heifer pool as replacements for the adult herd. At about 18-24 months, they will be inseminated. However, the deleterious effect of BVDV infection on bovine reproduction can occur as early as insemination and, therefore, immune protection needs to be effective by this time. Obviously, it is essential that all calves are not only infected by the PI animal but have cleared all their infectious virus before they are inseminated.

There are drawbacks to this scheme of management. One is that there is no certainty that all calves will become infected, clear the infectious virus and mount an effective immune response before insemination. Within any group of animals undergoing an acute

La Vaccination en Buiatrie, SFB, Paris, France, 1995

BVDV virus infection, there can be an erratic transmission of virus between individuals. There is also evidence that BVDV can remain in the tissues for periods far longer than apparent from the brief viraemia of up to about 14 days post infection. However, the evidence for establishing latent infection following an acute infection has not been presented. The implication of these comments is that the virus could still be present and even circulating among animals weeks, if not months, after the initial introduction of the PI animal. The possibility that infectious virus is still extant at the time of insemination must be avoided.

Another disadvantage to this arrangement is the professional concern that an animal which is persistently infected is retained. It is now well established that such an animal can develop mucosal disease at any time; a fatal condition of considerable distress and pain.

For the in-contact seronegative calves, a further problem is the profound effect of BVDV on the immune response of naive animals even if only for a short period following acute infection. Co-infection with other microorganisms during this time of immune suppression can enhance the pathogenesis of respiratory or enteric disease.

A small but inevitable consequence of this arrangement is that the PI animal is always the *escapee par excellance.* As soon as the regular cowman takes off for the weekend, this Houdini leaves the pen and heads for the heifer replacements - all, of course, in early pregnancy and seronegative.

The establishment of a BVDV-free herd.

It is somewhat axiomatic that the creation of a BVDV-free herd would avoid all problems associated with the virus. The feasibility of establishing such herds (or even an area!) has been facilitated by our recent understandings on the pathogenesis of BVDV and the improved detection assays now available to diagnostic laboratories. At the center of such schemes is the essential requirement to remove all PI animals from the herd and to prevent the generation of further PI individuals. Their removal would reduce the load of virus within the environment and thereby lower, possibly eliminate, the risk of infection of cattle in early pregnancy. Thus, the major cycle of BVDV pathogenesis would be broken. The reservations, as mentioned in the Introduction, about other sources of BVDV would still exist, e.g. sheep, wild ruminants and iatrogenic transmission (BVDV-contaminated needles and vaccines). Furthermore, there may still be more lessons to be learned from the prolonged shedding of virus from some animals following acute infection. Furthermore, in several apparently "closed" cattle groups or herds, there is also the unexplained maintenance of BVDV in the absence of a PI animal.

There are two particular concerns about the BVDV-free management approach. Firstly, that all virus-infected animals must be correctly identified in the initial investigations on the herd and, secondly, that the herd can be maintained thereafter free of virus. It is salutary to consider that the major outbreaks of BVDV-associated disease have usually been in closed herds. Truly closed herds are often BVDV virus and antibody free; they have all the advantages that accrue from the absence of virus but equally they are the most susceptible to infection.

Diagnosing PI animals depends on demonstrating virus, usually in blood, on two occasions three or more weeks apart but this is not always possible. New-born PI calves, after ingestion of colostrum containing maternally-derived BVDV antibodies, appear to have sera free of infectious virus. This can remain the case for up to about 4 months or until the maternal antibodies have declined sufficiently for the virus to reappear. Although these calves appear not to be persistently viraemic during this period, an examination of their tissues confirms that they are infected.

Another category of animal that can confuse diagnosis is the unborn feotus. Infection *in utero* can occur as early as 30 days gestation and up to about 110 days (Brownlie, Clarke, unpublished observations) and the foetus develop a persistent infection. The corollary to this is that 250 days later, a PI animal is born on the farm and becomes a new major reservoir of virus. This can be a real hazard when introducing newly-purchased in-calf heifers into a herd; their calves could be PI even though the dams are not, the latter having been screened as free from persisting virus before entry to the farm.

A curious but continual lapse in the apparent stringency of keeping herds closed is the vagrant bull brought in every year or two to "sweep up" behind the returning heifers. For some reason, cattle breeders forget that BVDV will infect bulls and that the virus is readily excreted into semen.[11] The bull has been the main suspect for introducing virus into several of the major outbreaks of disease.

The main conclusion of this section is that eradication is worthy of consideration where there is a genuine chance of maintaining a closed status for the herd or an area (an island would be ideal!)

The role of BVDV vaccination in the control of infection

Effective vaccination provides protective immunity without the risks inherent in infection; these risks have already been outlined above for BVDV. When considering the use of a vaccine, it is essential to consider its safety, its efficacy and the protocol for its use.

Safety

The risk of contaminating cattle vaccines with

the non-cytopathogenic biotype of BVDV is a constant concern of all commercial companies, particularly when foetal calf serum is a constituent in the manufacturing process. The risk is greater with live or modified-live vaccines where there is no inactivation step subsequent to virus growth in cell culture. There may also be the problem of distinguishing live vaccine virus from a live contaminating virus which at present is difficult, if not impossible. Inactivated vaccines are, however, inherently safer providing that contamination does not occur subsequent to inactivation.

BVDV vaccines require stringent inspection for safety because of the potential of a contaminating virus to cross the placenta and establish in the foetus to cause severe congenital damage and, thereafter, PI animals. There is obvious irony in a BVDV vaccine that becomes itself the vehicle for virus transmission and the cause of disease. Such incidents have occurred with BVDV vaccines and other ruminant vaccines.

Moreover, it is essential that no deleterious effect to foetal development is caused by any adjuvanting component incorporated in the vaccine; this is more likely to be a problem with highly-adjuvanted inactivated products.

Efficacy

The efficacy of vaccines is always the most demanding to establish. Often a critical point in the development of a vaccine is establishing an experimental disease that is a valid model of the disease seen in the field. As far as BVDV is concerned, models have been developed for both respiratory disease in calves and the *in utero* infection of pregnant cattle.[5,8]

Although vaccines purporting to protect the unborn calf are available, in countries other than the UK, there is limited documented evidence available revealing their efficacy following BVDV experimental challenge. It is for this reason that a critical review of the efficacy and safety of BVDV vaccines available in the USA was suggested.[1] This lack of information makes a direct comparison between new vaccines and those commercially available difficult.

Two experimental studies on inactivated vaccines have revealed their potential benefit but they failed to give complete protection. In Denmark, Meyling *et al.*[10] used three injections of an inactivated detergent-split vaccine plus Quil-A adjuvant to vaccinate 8 cattle in early pregnancy. They were then challenged intranasally/orally with a mixture of 4 strains (including the vaccine strain) of BVDV between 37 and 97 days of pregnancy. Fetuses from only 2 of 8 heifers were protected whereas the remaining 6 vaccinated and 4 unvaccinated control animals gave rise to BVDV-infected offspring. At about the same time, Harkness *et al.*[7] prepared an inactivated vaccine of 4 field isolates and vaccinated cattle before insemination. They were challenged intranasally, at about 80 days gestation, with 9 field strains. 7 of 11 fetuses (64%) were protected compared to 0/10 fetuses from non-vaccinated controls.

Sheep have also been used for the initial testing of fetoprotective efficacy for one BVDV vaccine. In Sweden, Carlosson *et al.* [6] achieved encouraging results with an experimental immunostimulating complex (ISCOM) subunit vaccine incorporating a Danish isolate of BVDV. After natural service, 15 ewes received two doses of vaccine three weeks apart. Three weeks after the second vaccine, at 47-64 days gestation, the vaccinated and 14 non-vaccinated ewes were challenged intramuscularly and subcutaneously with a heterologous Swedish BVDV isolate. The 15 ewes in the vaccinated group delivered 26 live lambs none of which showed evidence of *in utero* infection whereas only 6 live lambs were born to the non-vaccinated group.

At present, there is no BVDV vaccine on the UK market. An inactivated BVDV vaccine (Bovidec - C-Vet Veterinary Products) has been developed and has recently finished a series of experimental trials. In those experiments, cattle were vaccinated before and during the period of insemination and we were able to show a 100% protection against *in utero* challenge with a heterologous isolate of non-cytopathogenic BVDV. Control unvaccinated animals, similarly challenged, had evidence of over 90% foetal infection with some abortions and production of PI calves.[5] The value of colostral antibodies that have specific BVDV neutralizing titres can be seen from two studies where low-titre colostrum (or possibly poor absorption of antibodies) was insufficient to passively protect young calves from experimental challenge whereas titres above 16-64 were show to be protective.[2,9]

The demand for field efficacy to demonstrate foetal protection any new BVDV vaccine should be considered with considerable caution. There are real difficulties in setting up such a study and the number of susceptible animals in early pregnancy that are required to reveal protection against natural challenge with the virus is large.

Protocol for vaccination

The timing of vaccination can be crucial and usually targets those times of maximum viral ex-

posure and least protection i.e. neonatal vaccination for calfhood diseases or vaccination of dams in late pregnancy to induce high colostral antibody to give immediate passive protection to new-born calves.

For BVDV, there are two clearly identifiable periods when protection will be most important; the neonatal calf and the animal in early pregnancy.

For the neonatal calf, a BVDV vaccine would be considered as part of a multi-component vaccine protecting against the respiratory disease complex. It should have the ability to prevent viraemia and reduce, if not eliminate, nasal shedding following infection.

The value of protecting the foetus by immunizing the dam at the time of insemination has been described above and has been shown to give protection during the critical time of foetal development.

Summary

There are different ways to control BVDV infection in cattle. These have been outlined under the headings of (i) maintenance of herd immunity through the continual exposure to BVDV infection (ii) the establishment of a BVDV-free herd (iii) the role of BVDV vaccination in the control of infection. There are real ethical concerns about the maintenance of PI animals within any herd (i) and the preferred control measures are either total eradication (ii) or vaccination and careful management (iii). Total eradication gives the optimum benefits but stringent control measures are required to protect the seronegative and hence highly vulnerable population. A new vaccine has been developed (Bovidec) which has given 100% protection in experimental challenge studies of heifers in early pregnancy.

References

1. Bolins S. Control of bovine virus diarrhoea virus. *Rev. Sci, Off. Int. Epiz.,* 1990, 9 : 163-172. 2. Bolins S., Ridpath J.F. Assessment of protection from the systemic infection or disease afforded by low to intermediate titres of passively acquired neutralizing antibody against bovine viral diarrhea virus in calves. *Am. J. Vet. Res.,* 1995, 56 : 755-759. 3. Brownlie J. Clarke M.C., Howard C.J. Experimental production of fatal mucosal disease in cattle. *Vet. Rec.,* 1984, 114 : 535-536. 4. Brownlie J., Clarke M.C., Howard C.J. Experimental infection of cattle early in pregnancy with a cytopathic strain of bovine virus diarrhoea virus. *Res. Vet. Sci.,* 1989, 46 : 307-311. 5. Brownlie J. *et al.* - Protection of the bovine fetus from bovine viral diarrhoea virus by means of a new inactivated vaccine. *Vet. Rec.,* 1995, 137 : 58-62. 6. Carlsson U., Alenius S. Sundquist B. Protective effect of an ISCOM bovine virus diarrhoea virus (BVDV) vaccine against an experimental BVDV infection in vaccinated and non-vaccinated pregnant ewes. *Vaccine,* 1991, 9 : 557. 7. Harkneww J.W., Sands J.J., Richards M.S. Serological studies of mucosal disease in England and Wales. *Res. Vet. Sci.*, 1978, 24 : 98-103. 8. Howard C.J. *et al.* - Systemic vaccination with inactivated bovine virus diarrhoea virus protects against respiratory challenge. *Vet. Microbiol.,* 1994, 42 : 171. 9. Howard C.J., Clarke M.C., Brownlie J. -Protection against respiratory infection with bovine virus diarrhoea virus by passively acquired antibody. *Vet. Microbiol.,* 1989, 19 : 195-203. 10. Meyling A. *et al.* - Experimental exposure of vaccinated and non-vaccinated pregnant cattle to isolates of bovine virus diarrhoea virus (BVDV). *Pestivirus Infection of Ruminants.* Harkness J.W. Ed., Brussels CEC, 1987 : 225 p. 11. Paton D.J. *et al.* - Evaluation of the quality of virologic status of the semen from bulls acutely infected with BVDV. *Vet. Rec.,* 1989, 124 : 63.

Abstract

Inactivation of the bovine spongiform encephalopathy agent by rendering procedures

D.M. Taylor, S.L. Woodgate, M.J. Atkinson

The Veterinary Record, December 9, 1995 137: 605-610

Bovine brain infected with the bovine spongiform encephalopathy (BSE) agent was used to spike material processed in pilot scale facsimiles of 12 rendering processes which are used within the European Union, and three which are not. The raw materials for experimental rendering represented those used in practice, and consisted of appropriate proportions of BSE-infected brain tissue, bovine or porcine intestine, and bovine bone. Meat and bone meal, and tallow were produced from the rendered tissues. Suspensions of all the meat and bone meal samples were assayed in inbred mice for BSE infectivity, and two of the tallow fractions were tested similarly. Four of the 15 processes produced meat and bone meal with detectable BSE infectivity. Neither of the tallow samples had detectable infectivity.