Control of bovine virus diarrhoea virus

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Summary: Bovine virus diarrhoea (BVD) virus is ubiquitous in cattle populations throughout the world. Strategies for controlling BVD virus infections are continually evolving. Current control procedures are based on identification and elimination of persistently infected cattle, which are a primary source of virus for non-infected cattle, and immunisation with killed or modified live virus vaccines. Additional concerns for control are the possible contamination of semen, embryos and biologicals with virus. In the near future, genetically engineered nucleic acid probes and subunit vaccines containing selected elements of the BVD virus may be available for incorporation into control procedures.

KEYWORDS: Bovine virus diarrhoea virus - Cattle diseases - Control - Embryo transfer - Persistent infection - Pestivirus - Semen - Vaccines.

INTRODUCTION

Bovine virus diarrhoea (BVD) virus is a small, enveloped virus which primarily infects cattle (11, 23; see the introductory paper in this issue). The BVD virus is widely distributed, with most cattle-producing areas of the world reporting a high incidence of infection. Classified as a member of the Pestivirus genus, BVD virus is closely related antigenically to other pestiviruses, namely Border disease virus of sheep and hog cholera virus (classical swine fever virus). There are two strains or biotypes of BVD virus which are differentiated in cell culture by a cytopathic effect (19, 29). The cytopathic biotype of virus induces cytoplasmic vacuolation and cell death within about one day after cell cultures are infected. The other biotype of BVD virus, termed non-cytopathic, is insidious in cell culture and infects cells without exhibiting an apparent effect.

Most BVD virus infections of cattle are subclinical and result in little to no loss in meat or milk production. However, infection with either biotype of virus may cause a variety of clinical disease processes in cattle (1, 46). These clinical diseases adversely affect the rate of weight gain, milk production and reproductive efficiency; deaths are often increased and monetary loss may be substantial in an infected herd. Because BVD virus is ubiquitous, the small percentage of infections that cause measurable losses quickly add up to substantial amounts when large populations of cattle are considered. Hence, it is desirable to control BVD virus infection in cattle.

PERSISTENT INFECTION

A primary source of infectious BVD virus for susceptible cattle is a persistently infected herdmate (see the paper on Epidemiology in this issue). There are numerous
reports of disease outbreaks being linked to the presence of a persistently infected animal in a herd (2, 14, 42, 48, 56). Such infection is induced by the non-cytopathic biotype of virus and is the result of a fetal infection initiated during the first four months of gestation (31, 35). Thus, a calf is born persistently infected and cannot acquire infection after birth. Persistently infected calves may appear normal and may survive to maturity. The infection lasts for life and persistently infected cattle continuously shed infectious BVD virus in their secretions and excretions (13, 55). Any control programme for BVD virus must include identification and culling of persistently infected cattle.

Fortunately, persistent infection is relatively rare (6, 24, 38, 43, 51). Unfortunately, detection is not possible by visual examination of cattle. Laboratory testing of blood samples, either blood cells or serum, or testing material from nasal swabs is required for diagnosis (6, 24, 38, 43, 51, 52). The procedures used to detect persistent infection are not difficult, but they are time-consuming and expensive. Because widespread testing is not yet practical, most persistently infected cattle are not identified until after a disease outbreak occurs. When BVD virus-induced disease is diagnosed, the herd should be tested for persistently infected cattle. To confirm persistent infection, virus must be isolated from an animal in at least two successive tests spaced at least three weeks apart. Positive cases should be removed from the herd to prevent further spread of virus. Because virus may be passed from parent to offspring (34, 40, 55), all offspring and the dam and sire of a persistently infected animal should be tested.

The most practical solution to the problem of persistent infection is to prevent its occurrence. This is best done by vaccination prior to breeding, ensuring a high titre of neutralising antibodies during early pregnancy. Vaccination does not prevent birth of an affected calf when the dam is persistently infected. However, vaccination should reduce the number of healthy cattle that are susceptible to acute infection during early gestation. This is important because most persistently infected calves are born to healthy dams that suffered an acute infection in early gestation. When vaccination is not possible, the breeding herd should be isolated to reduce exposure to BVD virus. It is also important to test newly acquired cattle for persistent infection before they are introduced into a herd which contains pregnant animals.

**SEmen AND EMBRYOS**

BVD virus may be sexually transmitted. During an acute BVD virus infection, bulls shed virus into their semen for a few days (41, 57). Acute infections are frequently inapparent and not likely to be detected unless coincident with a blood test for virus. Because an inapparent acute infection might occur at any time, raw and frozen semen should be tested for virus on a routine basis. To reduce the risk of acute infection at semen collection centres, it is necessary to maintain high levels of neutralising antibodies in bulls. A very serious problem for semen collection centres is the apparently healthy, persistently infected bull. These bulls regularly shed virus into their semen (3, 13, 47). Thus, a persistently infected bull in a semen collection centre might spread BVD virus to a number of herds, over a large geographical area, for an extended period. It is extremely important to test bulls before sexual maturity and bulls at semen collection centres should be certified as free of persistent infection.
At this time, it is not clear if BVD virus can infect or be transmitted by a bovine embryo at the developmental stages used for embryo transfer (4, 45, 53). The risk of transferring an infected embryo is probably small. There is a much greater risk of transmitting virus through contaminated fetal calf serum (see below) used as a supplement in media for embryo collection and storage. A "clean" embryo may also become infected after transfer and could result from an acute or persistent virus infection of the recipient. The procedures necessary to control transmission of BVD virus through embryo transfer are straightforward. The use of fetal calf serum in the transfer process should be avoided; embryos should be collected from and transferred to cows that are not persistently infected; embryos should be washed repeatedly before being transferred; and embryo donors and recipients should have high titres of neutralising antibody before the transfer occurs.

**BIOLOGICAL PRODUCTS AND FOMITES**

The non-cytopathic biotype of BVD virus is a frequent contaminant of bovine cell cultures and commercial fetal calf serum used to supplement cell culture media (54). Hence, if bovine cell cultures are not affected when first derived, they frequently become infected with virus from fetal calf serum within a short period. The insidious nature of non-cytopathic virus in cell culture allows an undetected persistent infection to become established. This presents a serious problem for veterinary diagnostic laboratories which must maintain cell cultures free of BVD virus in order to test tissues and blood samples for virus and antibodies. Equally serious is the potential for contamination of veterinary biologicals manufactured using fetal calf serum and/or cells susceptible to infection with BVD virus. The risk of transmitting virus is greatly reduced, if not eliminated, with inactivated or nonreplicating biologicals. Use of such biologicals is especially important in pregnant cattle to prevent inadvertent fetal infection.

Since BVD virus is fairly resistant to changes in temperature and pH (23), the virus is likely to survive for a period outside of the host. This means the virus may be spread by fomites such as clothing and equipment used in caring for cattle. Because BVD virus is readily isolated from blood, hypodermic needles and surgical instruments are other potential carriers of virus. Fortunately, the virus is sensitive to detergents and disinfectants (23). Good sanitary practices should greatly reduce the risk of spread by fomites.

**VACCINES AND VACCINATION**

Modified live virus, temperature sensitive mutant virus and killed virus vaccines have been developed for control of BVD virus infections (10, 17, 27, 32, 35, 36). All of the vaccines have been shown to be efficacious under certain conditions. The vaccines vary in cost, number of doses needed for immunisation, number of viruses and biotypes of viruses included in the vaccine, adjuvants used in the vaccine, methods used for viral inactivation, cell types used to grow virus and whether fetal calf serum is used. Obviously, the vaccines also vary in their advantages and disadvantages.

There is concern about the immunosuppressive properties retained by modified live viruses (50) and the potential for this type of vaccine to induce post-vaccinal disease.
Another important concern that applies to all vaccines is antigenic variation among BVD viruses (49). Healthy cattle infected with a single strain produce neutralising antibodies that strongly cross-react with other BVD viruses of either biotype (18, 20). However, there is experimental evidence indicating that all BVD viruses are not alike antigenically. Subtle antigenic differences among isolates have been detected in cross-neutralisation tests using antibodies raised in healthy cattle (16, 21, 25, 26). The antigenic variability is quite apparent when BVD viruses are analysed using panels of monoclonal antibodies with neutralising activity or antiserum raised in persistently infected cattle (5, 7, 12, 30). An example of the significance of this antigenic variability to vaccination programmes might be found in several reports where cows immunised with killed virus vaccines before breeding gave birth to calves infected with virus (22, 39, 49). This represents a failure of protection in “immune” cattle and may be extremely important as a means to assess the efficacy of current and future vaccines.

There are many strategies for vaccination and much scepticism about the efficacy of vaccines and vaccination strategies. This is a time of uncertainty for BVD virus vaccines, but it is likely that vaccination has some benefits and general recommendations can be made. Because only a single dose is required for immunisation, modified live virus vaccines are useful in large herds which are grazed over large areas or when the facilities available for handling cattle are poor. Live virus vaccines should be used only in healthy cattle that are not pregnant, and not in animals that are in contact with pregnant cattle. Killed virus vaccines are advantageous when live virus is undesirable, as in dairy herds where pregnant cattle are always present and in semen collection centres. Revaccination with killed virus vaccines should probably be done on a yearly basis; however, some situations may require more frequent vaccination, and these vaccines usually require administration of two doses given weeks apart to achieve immunisation. Vaccination of calves should be done after colostral antibodies have declined, but it may not be necessary to wait until colostral antibodies have completely disappeared (8, 15, 37). Cattle should not be vaccinated at times of stress.

THE FUTURE

Recent advances in research make the future look promising for control of BVD virus infections. These advances include sequencing the viral RNA, determining the genomic organisation of the virus and identifying many of the viral gene products (11; see the paper on Molecular Biology in this issue). This information will allow more rigorous comparisons to be made of BVD viruses. The availability of monoclonal antibodies to BVD virus allows maps to be made of antibody binding sites on viral proteins. These maps will provide aid in determining the contribution of three-dimensional structure to immune protection and help locate biologically significant sites on viral proteins. The products of this new knowledge that have already appeared, or will soon appear, include diagnostic probes (9, 44), molecularly engineered vaccines and, possibly, new therapies to treat active infections. Some of the new products and techniques will undoubtedly be improvements over those now used to diagnose and control BVD virus infections. In addition, we may learn that some of our existing
products and techniques are as good or better than can be obtained using the
techniques of molecular biology.

Whatever tools are used, we must gain additional knowledge of the antigenic
variability among BVD viruses and we must learn what constitutes a protective immune
response if we are ever to control infection fully. Considering the enormous progress
made in the last decade in our understanding of the virus and the diseases it induces,
there is good reason to hope that the next decade will bring highly effective control
programmes for these infections.

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PROPHYLAXIE DU VIRUS DE LA DIARRHÉE VIRALE BOVINE. – S.R. Bolin.

Résumé : Le virus de la diarrhée virale bovine est ubiquiste dans les cheptels
bovins du monde entier. Les stratégies mises en œuvre pour combattre les
infections par le virus BVD évoluent constamment. Les méthodes actuelles de
prophylaxie reposent sur l'identification et l'élimination des bovins infectés de
manièr persistante, qui sont la source première du virus pour les bovins non
infectés, et sur l'immunisation au moyen de vaccins à base de virus inactivé
ou de virus vivant modifié. La contamination éventuelle de la semence, des
embryons et des produits biologiques par le virus est également préoccupante
pour la prophylaxie. Dans un avenir proche, les techniques du génie génétique
pourront mettre à la disposition des méthodes de prophylaxie des sondes d'acides
nucléiques et des vaccins sous-unitaires contenant des éléments sélectionnés du
virus BVD.

MOTS-CLÉS : Infection persistante - Maladies des bovins - Pestivirus -
Prophylaxie - Semence - Transfert d'embryons - Vaccins - Virus de la diarrhée
virale bovine.

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PROFILAXIS DEL VIRUS DE LA DIARREA VIRAL BOVINA. – S.R. Bolin.

Resumen: El virus de la diarrea viral bovina es ubicuo en el ganado bovino
del mundo entero. Las estrategias para combatir las infecciones debidas al virus
BVD evolucionan constantemente. Los métodos actuales de profilaxis se basan
en la identificación y eliminación de bovinos infectados de manera persistente,
que son la primera fuente de infección de los bovinos no infectados, así como
en la inmunización por medio de vacunas a base de virus inactivado o de virus
vivo modificado. La contaminación eventual por el virus del semen, de los
embriones o de los productos biológicos también preocupa a la profilaxis. En
un futuro cercano, las técnicas de ingeniería genética podrán aportar a los
métodos de profilaxis sondas de ácidos nucleicos y vacunas subunitarias con
elementos seleccionados del virus BVD.

PALABRAS CLAVE: Enfermedades de los bovinos - Infección persistente -
Pestivirus - Profilaxis - Semen - Transferencia de embriones - Vacunas - Virus
de la diarrea viral bovina.
REFERENCES


