# Infectious Bovine Respiratory Disease - Emerging Issues and Progress Towards Control

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Despite many years of intensive research effort, infectious bovine respiratory disease continues to be a major cause of economic loss and adverse effects on animal welfare. There have been some notable success stories, such as the development of highly effective vaccines for control of infectious bovine rhinotracheitis.[1,2] However, problems remain in prevention of enzootic calf pneumonia and shipping fever (pneumonic pasteurellosis). There are also some changing patterns of respiratory disease. Examples include an increased incidence of *Mycoplasma bovis*-associated respiratory disease associated with increased cattle movement within Europe and an increased occurrence of pneumonic and pleuritic forms of *Haemophilus somnus* infection. Although a range of vaccines against bacterial and viral respiratory pathogens is available, there is still major dependence on antibiotics for control of infectious bovine pneumonia. While there have been recent significant additions in therapeutic agents available, consumer concerns relating to the use of antibiotics in food producing animals are likely to intensify pressure for improved methods of immunoprophylaxis. These will be assisted by opportunities provided by molecular biology and immunology in increasing knowledge of immune responses, improving diagnostic methods and in the development of vaccines and immunomodulators.

Viruses, mycoplasmas and bacteria can all be involved in the enzootic calf pneumonia complex.[3] Currently bovine respiratory syncytial virus (BRSV) is considered to be the most important virus involved. Bovine viral diarrhoea virus[4] and parainfluenza-3 virus[5] are also believed to be significant contributors to outbreaks. Adenoviruses, coronaviruses, toroviruses and bovine herpesviruses have also been associated with outbreaks, but less commonly. BRSV and parainfluenza - 3 virus (PI3 virus) are capable of causing primary pneumonia which in the case of BRSV can be fatal if complicated by development of severe oedema and interstital emphysema.[5-7] Evidence has also accumulated over recent years that both these viruses can cause immunosuppression by a variety of methods including interference with alveolar macrophage and lymphoctye functions.[8-10] This is likely to lower pulmonary defences to mycoplasmal and bacterial infections. Recent studies in USA and Europe have shown that two major antigenic subgroups of BRSV exist and that this antigenic variation resides mainly in the G glycoprotein.[11,12] The role of bovine viral diarrhoea (BVD) virus in respiratory disease is believed to be mainly that of an immunosupressive facilitator of other pathogens.[4]

Of the mycoplasmas, *M. dispar*, *Ureaplasma* sp and *M. bovis* are most frequently involved. *Mycoplasma bovis* is the most pathogenic of these and can often act synergistically with *Pasteurella haemolytica A1* to produce very severe exudative pneumonia.[13] The latter organism and to a lesser extent *P. multocida*, *Actinomyces pyogenes* and *H. somnus* commonly contribute to enzootic calf pneumonia outbreaks and in this disease complex would appear to act mainly as secondary invaders. Primary infections with viruses and mycoplasmas can sometimes be subclinical indicating the likelihood of strains of varying virulence, and/or the importance of adverse managemental and environmental factors in precipitating disease.

There are several problems in the prevention of enzootic calf pneumonia outbreaks. In addition to the range of pathogens which can be involved, there are many managemental and environmental stress factors which can predispose to outbreaks including poor ventilation, draughts and bad air hygeine. The principal contributor to the latter is high stocking density exacerbated by conditions of high relative humidity.[14] In farms with severe pneumonia problems, very young age groups are increasingly affected.

In the control of enzootic calf pneumonia, provision of good management and housing is essential. Ensuring a good start in life by adequate colostrum feeding and control of neonatal diarrhoea, rearing calves in groups of similar age in well ventilated buildings, avoid-

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ing stressful procedures as far as possible at high risk periods for pneumonia and minimizing transportation and marketing stresses are important components of a control programme.[15] Unfortunately, such objectives are frequently not achieved and sometimes even under condition of apparently good management and housing problems may still be experienced, especially in larger units. Therefore on many farms additional immunoprophylaxis against key respiratory pathogens is required.

Modified live and inactivated virus vaccines against a number of respiratory viruses involved in enzootic calf pneumonia including BRSV, PI3 virus and BVD/MD virus are available in Europe and North America. There have been relatively few well designed large scale field trials reported in the scientific literature upon which the efficacy and cost/effectiveness of these products in young calves (<3-4 months) can be accurately assessed. A major problem in assessing the efficacy of BRSV vaccines is the lack of experimental calf models in which severe pneumonia can *consistently* be induced. Scientific information on BRSV vaccination relates mainly to the use of modified live virus vaccines administered by the intramuscular route. Results from European field trials have been variable[16] and concerns have been expressed as to efficacy in young calves with high levels of maternal antibody.[17,18] Most field trials in North America have been carried out in beef calves and the majority have suggested such vaccines to be safe and efficacious.[16] However in some trials it was considered that the reduction in treatment rate might not justify the cost of the vaccination programme.[19] A killed BRSV vaccine which has been very recently marketed in the UK consists of gluteraldehyde fixed cells persistently infected with BRSV, with QuilA adjuvant. Experimental and field trials carried out with the experimental prototype vaccine showed it to be effective in the presence of maternal antibody.[20,21] Morbidity and mortality rates in outbreaks of BRSV associated respiratory disease were significantly reduced in vaccinated calves, although respiratory disease and deaths were not totally prevented.[21] Further evaluation of this product under more widespread conditions of field use is awaited. No vaccines are currently commercially available against *M. bovis, M. dispar* or *Ureaplasma spp.*

For more effective immunoprophylaxis of enzootic calf pneumonia, it will be necessary to produce a broad spectrum of protection against a range of primary viral and mycoplasmal pathogens and to be able to induce this rapidly and effectively in young calves. Based on current knowledge, induction of protection against BRSV, PI3 virus, BVD/MD virus and *M. bovis* would appear to be most important. In terms of administration and cost it would be best if most or all of the relevant antigens could be delivered in a multicomponent vaccine. Although this appears a formidable task, an experimental systemic inactivated quadrivalent vaccine containing BRSV, PI3 virus, *M. bovis* and *M. dispar* has been produced and was effective in reducing deaths due to pneumonia and non fatal respiratory diseases in field trials.[21]

Priming for respiratory tract mucosal immunity and avoidance of possible vaccinal inhibition by maternal antibodies may be achieved by intranasal vaccination. Intranasal vaccines for some bovine respiratory viruses such as BHV1 and PI3 virus are already commercially available. Experimental studies in calves have shown that protection against BRSV infection is strongly correlated with the ability to mount a strong mucosal memory immune response and that the best method of priming the respiratory tract for a rapid and strong mucosal memory antibody response is immunisation with live virus.[22] Although intranasal BRSV vaccines are not available in Europe or North America, studies in Japan have established an attenuated strain of BRSV which has been incorporated into an intranasal vaccine with promising results.[23]

**Vaccination has its best chance of success in closed herds with calves born on site. Possible variations in pathogen profiles between batches of bought- in calves raises concern as to likely efficacy in purchased calves. Nevertheless the major pathogens in calf pneumonia have remained relatively constant for the past two decades and vaccines which are effective in young calves against a limited number of core pathogens, could make a significant contribution to pneumonia control both in home bred and in purchased animals.**

Shipping fever (pneumonic pasteurellosis) remains a major problem for the North American feedlot industry. A range of factors including management and transportation stresses, compromise of pulmonary defences by other infectious agents and immune status, all impact on the disease process. The major cause of economic loss and death is usually severe fibrinous pneumonia caused most commonly by *Pasteurella haemolytica A1* (PhA1)[24] and severe pneumonic pasteurellosis has been induced by PhA1 alone.[25] In Europe, pneumonic pasteurellosis is also a significant problem and in the UK is seen most frequently and severely in recently weaned and newly housed single suckled calves.[26] Field vaccination strategies based on the use of viral vaccines and/or older Pasteurella bacterins have not been successful in preventing pneumonic pasteurellosis[27] and major effects have been devoted to developing more effective vaccines against PhA1.

During the past two decades, modified live vaccines and subsequently subunit vaccines against PhA1

have been available in North America. Both have provided enhanced protection in comparison with older commercial bacterins.[24] There are practical problems associated with the use of live vaccines under field conditions.[28,29] It appears likely that continuing development of PhA1 vaccines will be centered around subunit vaccines. Those currently available include products containing leukotoxin and soluble cell surface antigens and surface antigen extracts. These have been shown to induce significant although not total protection against experimental challenge with PhA1.[30,31] A limited number of field trials of such vaccines, most of which have utilised culture supernatant vaccines, have been described in the scientific literature. In these, reports of efficacy in preventing bovine respiratory disease have been variable.[29,32-34]

Immune mechanisms of resistance to PhA1 are complex and still not fully resolved. Although leukotoxin (LKT) is an important virulence factor of the organism and neutralizing antibody to LKT appears of major importance in resistance to pasteurellosis, an immune response to LKT alone does not appear sufficient to protect calves against disease and other soluble antigens are apparently equally important.[35,36] However, enrichment of a culture supernatant PhA1 vaccine containing LKT and other soluble antigens with recombinant LKT markedly enhanced the protective capability of the latter against induced PhA1 disease.[35] Other studies involving the use of bacterins with oil adjuvants have indicated that resistance to experimental PhA1 challenge can be induced without production of LKT neutralizing antibody.[37] Continuing research is seeking to further define potentially important immunogenic cell surface components of PhA1, particularly various outer membrane proteins including those which are iron regulated. Differences have been detected in outer membrane protein profiles and in antibody recognition of outer membrane proteins between PhA1 cells recovered directly from the lungs of calves and those in bacterial cells grown *in vitro*.[38] Studies on immunity to PhA1 are continuing so that the most appropriate combination of antigens for maximal induction of protective immunity can be determined.

Another important problem in feedlot cattle is the *Haemophilus somnus* disease complex. In Western Canada various manifestations of *H. somnus* infection collectively account for the single largest cause of mortality in calves placed in large feedlots during autumn.[39] Respiratory forms of *H. somnus* infection including pneumonia and fibrinous pleuritis have been reported with increasing frequency in North America and in some European countries.[40-42]

Satisfactory control and prevention of Hemophilosis in young cattle appears difficult to achieve and difficulties can be compounded by the unpredictability of outbreaks, diagnostic problems and rapidly fatal disease in some animals. Attempts to control *H. somnus* respiratory disease in the field using commercial whole cell killed bacterins have been only moderately successful although under experimental conditions better results have been obtained.[39,43-45] Experimental studies on vaccination and immunity to *H. somnus* infection have demonstrated significant protection against induced disease using an outer membrane anionic antigen fraction.[45] Also, individual outer membrane protein antigens have been identified which appear to be promising candidates for inclusion in subunit vaccines and in the development of improved diagnostic assays.[46,47] Continuing studies on epidemiology, pathogenesis and immunity appear necessary for improved procedures for control of Haemophilosis to be developed.[39,48]

In addition to the problems in the development of PhA1 and *Haemophilus somnus* vaccines, there can be difficulties in providing optimal conditions for their use. In feedlot cattle the first opportunity for vaccination is often when the animals arrive, limiting the time available for induction of protective immunity. Particularly in North America where transport distances are great and where viruses such as BHV-1 and BVDV are involved in the shipping fever complex, animals are often severely stressed and some degree of immunosuppression is likely. Preconditioning programmes which include vaccination against respiratory pathogens prior to sale have not gained widespread acceptance due to logistics and expense and many of the advantages claimed have not been substantiated by controlled research data.[49] Care in purchase of animals, minimizing transportation stress and good feedlot management in relation to penning and feeding practices is very important in seeking to reduce the impact of feedlot respiratory disease.[50]

Various prophylactic mass medication regimes using antibiotics have been used for control of respiratory disease in feedlot cattle. In a review of one hundred and seven field trials of prophylactic mass medication in feedlots, concern was expressed at the lack of well designed randomized controlled field trials.[51] In the same review, meta-analysis of randomized controlled field trials indicated that prophylactic parenteral mass medication with long acting oxytetracycline or tilmicosin on arrival at the feedlot would significantly reduce morbidity and mortality rates due to bovine respiratory disease.[39,51] However there were unreliable data on the effects of mass medication on performance, insufficient data on the most effective treatment regimes and no valid data on the efficacy of feed and water mass medication for prophylaxis of bovine respiratory disease. The study highlighted the need for additional well designed randomized controlled field trials of adequate size. **Con-**

**cerns from the food processing industry in relation to injection site trauma and scarring of muscle tissue, necessitate careful intramuscular infection techniques or consideration of possible alternative routes of antibiotic administration.**[52]

In North America there is evidence that an increasing number of PhA1 and *P. multocida* isolates are exhibiting plasmid-mediated multiple drug resistance to various commonly used antibiotics including penicillin, ampicillin, tetracyclines and sulphonamides.[53,54] In Europe there appears to be variation in the prevalence of resistance in different areas.[55,56] Diagnostic bacteriological examinations in outbreaks of respiratory disease facilitate detection of resistant strains and are helpful in formulation of effective therapeutic regimes.

In France a national veterinary network is involved in monitoring of antimicrobial resistance in bacterial isolates from diseased cattle and provision of data for analysis of mechanisms of antibiotic resistance.[56]

In recent years a number of new anti-bacterial compounds have been introduced with are particularly suited to the therapy of bovine respiratory disease. They include the flouroquinolones enrofloxacin and danofloxacin, florfenicol, the semi synthetic macrolide tilmicosin, baquiloprim in combination with sulphadimidine and the cephalosporin antibiotics ceftiofur and cefquinome. These newer compounds have very good tissue penetration and activity against major bacterial pathogens of the bovine respiratory tract. Tilmicosin, the fluoroquinolones and florphenicol are also active against bovine respiratory tract mycoplasmas.

Modulation of severe pulmonary inflammation is an important adjunct to anti-microbial therapy. Both steroidal and non-steroidal agents are available as powerful anti-inflammatory tools. The latter do not have the immunosupressive effects of the former. Non steroidal agents such as flunixin meglumine or tolfenamic acid have significantly enhanced clinical recovery in experimental bovine models of viral pneumonia and pneumonic pasteurellosis[57,58] and in natural outbreaks of undifferentiated respiratory disease.[59] In recent years, considerable progress has been made in understanding physiological and pharmacological aspects of pulmonary function in healthy and diseased animals.[60] There is considerable current interest in the role of pro-inflammatory cytokines such as tumor necrosis factor and various interleukins which are involved in induction and control of pulmonary inflammatory reactions and which may on occasions interfere with pulmonary function and contribute to lung injury. Further work is required in this area for the bovine animal. Increasing information on mechanisms of inflammation within the bovine lung in various respiratory diseases is likely to provide further opportunity for therapeutic intervention to modify or eliminate effects of mediators which may have adverse effects on pulmonary function. Increased knowledge of physiopathological mechanisms in major bovine respiratory diseases will also be helpful in correcting mechanical disorders associated with smooth muscle and mucociliary dysfunctions.[60]

Particularly with the advent of the Single European Market, there are increasing movements of cattle between European countries. Such movements increase the risk of spread of respiratory pathogens. Recent reports of recognition or of increasing prevalence of *Mycoplasma bovis* associated respiratory disease in several EU countries have been linked to increased importations of cattle.[61-63] Contagious bovine pleuropneumonia (CBPP) is currently present in Italy and in the Iberian peninsula and there is continuing uncertainty about the CBPP status of parts of Eastern Europe. While there are detailed rules governing intracommunity movement of cattle from member states in which CBPP exists, the frequently insidious nature of the disease in Europe and some limitations in standard diagnostic procedures for CBPP create concern about the possibility of movement of asymptomatic carrier animals within Europe and the spread of the disease into new areas.[64,65] Thus there is a need for continuing vigilance and for the rapid definitive diagnosis of disease should it occur, along with a requirement for development of improved diagnostic tests particularly to detect asymptomatic carrier animals. Current research is seeking to improve the speed, sensitivity and specificity of diagnostic methods for CBPP.

Within the EC, countries or regions with the highest animal health status will obtain maximal advantage from the free internal market. Therefore eradication of certain major pathogens and diseases from individual countries and from the Community as a whole will be highly advantageous. For some infectious diseases, vaccination can be a powerful tool to lower the prevalence of infection as a first step to eventual eradication.[66] Recently, attenuated and inactivated glycoprotein E negative marker vaccines for bovine herpesvirus-1 (BHV1) have been developed, together with a companion gE-Elisa which allows serological differentiation between BHV-1 vaccinated cattle and naturally infected animals. In experimental trials these vaccines were found to be safe and efficacious and to markedly curtail virus shedding after challenge.[67] If larger scale field trials demonstrate that these vaccines can significantly reduce circulation of BHV1 then they may prove to be an important tool in facilitating eradication of BHV1 from herds and eventually from countries with a moderate to high prevalence of virus. In North America the development of new BHV-1 subunit glycoprotein vaccines and glycoprotein III deletion vaccines together

with appropriate diagnostic tests will afford similar opportunities.[68]

In the past decade there have been major advances in understanding the ruminant immune system including the functions and development of various lymphoctye populations and the regulation and expression of humoral and cell mediated immune responses.[69] These have been greatly facilitated by the use of molecular biology technology and monoclonal antibodies. Such advances are being very beneficial to studies of immuo bovine respiratory pathogens. As an example, vaccine virus recombinants expressing various viral proteins, and synthetic peptides are being used in studies on cell mediated and humoral immune responses to bovine respiratory viruses and in determination of major protective antigens and epitopes.[70,71] The use of molecular biological techniques and monoclonal antibodies is also contributing to improvements in diagnostic methods for bovine respiratory pathogens. The use of monoclonal antibodies has improved speed sensitivity and specificity of antigen detection and serological methods for a range of viral, mycoplasmal and bacterial pathogens.[72-74] Highly sensitive and specific polymerase chain reaction techniques have been developed for rapid detection of such pathogens as *Mycoplasma mycoides mycoides small colony*[75-77] and BRSV.[78]

Recombinant DNA and monoclonal antibody technology is providing the basis for a new generation of vaccines which has the potential to be more effective and in some cases safer than conventional live or killed vaccines. New technology provides the opportunity for construction of vaccines containing antigens or genes coding for antigens important in protection while eliminating those which may be associated with undesirable or adverse effects. Examples of such novel vaccines include synthetic peptides, ISCOMS, anti-idiotype vaccines and genetically engineered "carrier" vaccines using viral or bacterial vectors. Carrier vaccines could facilitate simultaneous expression of key protective antigens from a range of respiratory pathogens, together with co-expression of appropriate cytokines for optimal orchestration of immune responses. Novel vaccines have been produced for some respiratory pathogens of veterinary importance. For example, new generation glycoprotein subunit and deletion vaccines have been produced for BHV-1.[68] Genes coding for protective glycoproteins of BHV-1, BRSV and PI3 virus have been expressed in viral vector systems where they stimulated high levels of immunity and varying levels of protection against experimental challenge.[17,79,80] BRSV and PI3 virus ISCOMS have also been produced.[81,82] In most cases further developmental work and studies on efficacy are necessary. There are also potential risk factors connected to the use of carrier vaccines such as changes in tissue or host tropism and virulence, exchange of genetic information with other vaccine or wild-type strains and environmental spread and genetic instability[83] and these will require further investigation before such products can be made widely available. **To harness the maximum benefit from recombinant DNA technology in developing novel vaccines it will be important to acquire as much information as possible on mechanisms of pathogenesis and protective antigens of individual respiratory pathogens.**[84]

In the control of respiratory tract infections, induction of immunity at the mucosal surface is of major importance. This is likely to be best achieved by administration of vaccines topically within the respiratory tract.[22,79] In the development of future vaccines, prospects for mucosal immunisation should be kept very much in mind. The use of BHV-1 or bovine adenovirus as vectors for carrier vaccines would be particularly suitable for mucosal vaccination.[79] Although mucosal immune responses are more easily evoked by replicating than by non-replicating antigens, application of delivery systems such as ISCOMS, liposomes or biodegradable microspheres[85] could facilitate strong and sustained mucosal responses to subunit vaccines. Stimulation of gut associated lymphoid tissues by crude PhA1 leukotoxin has been shown to increase systemic and pulmonary antibody levels including anti-leukotoxin antibodies. This raises the interesting possibility of developing oral vaccines to prevent PhA1 pneumonia if antigen preparations capable of traversing the rumen into the gastro-intestinal tract could be formulated.[86]

Cytokines such as interferons and interleukins play a critical role in the regulation of immune responses. Molecular biology has facilitated the production of recombinant cytokines in quantities and at a cost which makes them potential prophylactic or therapeutic tools for bovine respiratory disease. Experimental calf studies utilizing recombinant human interferons in the prophylaxis of bovine respiratory disease provided disappointing results.[87,88] However experimental and field studies using recombinant bovine interferons were more encouraging especially when interferon treatment was administered prior to infection.[89-91] *In vivo* studies in calves indicated that recombinant bovine interferon - gamma enhanced neutrophil function and resistance to bacterial infection in calves immunosuppressed by dexamethasone.[92,93] Recombinant interleukins (1beta and 2) have been used as experimental adjuvants in studies with bovine respiratory disease vaccines where they appeared to enhance antibody titres and resistance to viral infection.[94] The use of recombinant bovine cytokines has potential in increasing vaccine efficiency and in reversing some forms of immunosuppression. However many further studies on cytokine function, interactions, toxicity and delivery systems are neces-

sary to exploit this to maximal effect.

Progress is steadily being made in the control of infectious bovine respiratory disease. However to the veterinary practitioner, concerned with prevention, such progress must appear very slow. The major viral, bacterial and mycoplasmal pathogens have been recognized for many years and the key players have remained relatively constant. There have been considerable advances in the range of therapeutic tools available for bacterial and mycoplasmal infections and in the diagnostic methods available for detection of respiratory pathogens. An increasing and improving range or range of vaccines is evolving against key respiratory pathogens. Nevertheless in terms of control of enzootic calf pneumonia, pneumonic pasteurellosis and Hemophilosis further progress on immunoprophylaxis is required and on a practical basis there is till major dependence on antibiotics for control. However, in the background, immunological studies empowered by the availability of molecular biology and monoclonal antibody technology are yielding increasing information on protective immune responses and key antigens of infectious agents associated with these diseases. This will be very important in ensuring that the optimal antigens or genes for inducing protective immunity will be highlighted for incorporation into conventional or genetically engineered vaccines. While much is expected of the latter, very few novel "biotech" vaccines are as yet commercially available. Further progress may also be achieved through continuing development of conventional vaccines. In both cases particular attention should be paid to delivery systems which are likely to facilitate stimulation of mucosal immunity.

When new prophylactic or therapeutic agents are produced, it is important that they are evaluated by well designed and carefully controlled experimental and/or field trials. The former should include wherever possible, evaluation in experimental calf models in which disease similar to that occurring under natural conditions is induced by natural routes of infection. The latter should be carefully designed preferably with input from a statistician, have clearly defined objectives, random allocation to treatment groups and examinations which are blinded.[95] Both positive and negative results should be reported in the literature. **It is essential, however, that in the continuing quest for more effective prophylactic bologicals, the major importance of good management, housing and husbandry in control of infectious respiratory disease is not overlooked.**

Finally, as well as being a major source of economic loss, infectious bovine respiratory diseases because they are common, involve many animals, are frequently severe and at present cannot be reliably prevented, also represent a significant threat to animal welfare. The conditions under which infectious respiratory disease such as enzootic pneumonia and shipping fever occur can reflect a range of environmental and transportational stress factors which impact negatively on welfare and which are likely to have adverse effects on immune function. Further multidisciplinary field and experimental studies on the contribution of environmental stress factors to respiratory disease in housed calves are indicated and a statistical approach is necessary for these.[14] It is also necessary to develop more objective methods of stress measurement possibly based on immunological markers. **All these factors in an increasingly animal welfare conscious society, should weigh heavily in making bovine respiratory disease research a high priority for continuing Government and Industry funding.**

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# Investigation of an Alternative Animal Model of Bovine Viral Diarrhea Virus (BVDV) Infection

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A severe form of BVDV infection in immunocompetent cattle characterized as peracute disease has been reported in North America. This severe form of BVDV infection has been associated with type II BVDV, which is genotypically distinct from type I BVDV. The purpose of this study was to determine if swine may serve as a potential alternative animal model for type II BVDV infection. Sixteen 2-month old crossbred pigs were placed in an isolation facility and segregated into 4 groups of 4 pigs each. A control group (A) was sham-inoculated and 3 principal groups were inoculated intranasally with $10^3$ (B), $10^5$ (C), and $10^7_{TCID50}$ (D) of noncytopathic type II BVDV, respectively. Clinical parameters were measured daily; and serum and buffy coat samples were obtained at days 0, 3, 5, and 7 post-inoculation for virus isolation. On day 7 all pigs were euthanized and tonsil, spleen, bronchial and mesenteric lymph nodes, lung, and ileum were collected for virus isolation and histopathology. No evidence of clinical disease was noted in any of the pigs, and type II BVDV was not isolated in groups D and C, respectively. Virus was also isolated from 23 of 24 tissues obtained in group C, and all tissues in group D. No histopathologic lesions were noted. Viremia can be established in feeder pigs with type II BVDV. As a result, swine may serve as an alternative animal model for study of type II BVDV pathogenesis.

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