DISCONTOOLS

Bovine Respiratory Syncytial Virus (BRSV)

Summary

Introduction

1. This note provides a brief summary of the Disease and Product analysis prepared by a DISCONTOOLS group of experts on Bovine Respiratory Syncytial Virus (BRSV). Full details are available on the web site at http://www.discontools.eu/.

Disease profile

2. BRSV is an RNA virus classified as Orthopneumovirus in the family of *Pneumoviridae*. It exists as a single serotype, with four antigenic subtypes and at least 10 genotypes based on the G protein-coding gene. BRSV is species specific although sheep and goats may be infected experimentally. Worldwide infection with BRSV is a major contributor to the multi-pathogen bovine respiratory disease complex which results in a substantial economic loss for the cattle industry worldwide.
3. BRSV infections associated with respiratory disease occur predominantly in young beef and dairy cattle. It is the single most important respiratory viral pathogen of calves causing severe bronchiolitis, pneumonia, and upper and lower respiratory tract disease. Mortality is usually less than 5% in young calves with deaths resulting from BRSV infection alone or as a result of secondary bacterial pneumonia. BRSV can also be isolated from cattle without clinical signs of disease. The transmissibility of BRSV is high with rapid spread of the virus between immunologically naive animals within and between herds.

Risk

4. BRSV is not known to be infectious to humans although calves can be experimentally infected with human RSV. Worldwide the ubiquitous and endemic character of BRSV infection in dairy and especially beef cattle causes major losses to the industry. Large volumes of antibiotics are used in the veal production or feedlot sectors to control respiratory disease. The use of antibiotics in livestock should be reduced in order to reduce the risk of emergence of antibiotic resistant organisms that may spread to humans.

Diagnostics

5. A diagnosis of BRSV requires laboratory confirmation. BRSV antigen detection is performed by direct or indirect immunofluorescence or immunoperoxidase staining on ante mortem (e.g. Broncho alveolar lavage cells) or post-mortem samples (e.g. lung sections). Nowadays the most used direct diagnostic techniques are conventional or real time PCR-based tests, which have high sensitivity and specificity, and are used in both routine diagnostics as well as for research purposes.
6. Paired serum samples can be used to establish a diagnosis of BRSV infection. However, calves that become infected with BRSV in the presence of passively derived antibodies may not show a significant increase in specific BRSV antibodies post infection. The duration of BRSV maternal antibodies in calves is usually between 3 to 6 months.
7. Antibody detection kits for BRSV antibodies such as ELISAs for detection of IgG in serum are available. Currently, there are no DIVA tests available but an N protein-based in combination with a PreF subunit vaccine ELISA might be a good option, since BRSV infection induces N protein-specific antibodies.

Vaccines

8. Several monovalent and many multicomponent vaccines containing modified-live or inactivated BRSV are currently on the market for intramuscular or intranasal administration. The immunity conferred by BRSV infections or vaccination is probably short lived and may only last 3 or 4 months so that frequent vaccination may be necessary to control disease. Intranasal vaccination with live attenuated BRSV vaccines induces rapid protective immunity, which is useful when disease occurs

in very young calves (3 to 6 weeks old) nevertheless the duration of protection is generally shorter. Furthermore, live virus is excreted and, although reversion to virulence is tested prior to licensing for all live vaccines licensed in the EU, there remains a theoretical possibility that reversion to virulence could occur. BRSV infections are often recurrent despite the presence of neutralizing antibodies, suggesting the importance of cytotoxic T cell (CTL) and or mucosal IgA responses in protection. Calves under 6 months are difficult to immunise effectively as maternally-derived antibodies may compromise vaccine efficacy in relation to the duration of protection.

9. Modified live virus vaccines can induce virus neutralizing antibodies, although these may not be high following intranasal vaccination. In contrast, inactivated virus vaccines induce significantly lower levels of virus neutralizing antibodies and some stimulate Th-2 responses although this might vary according to the adjuvant, which even though very seldom in the field, may have a disease enhancing effect following exposure to live virus. The different types of vaccines induce different responses depending upon the route of vaccination, dose and adjuvant.
10. The development of safe and effective BRSV vaccines has been hampered by i) difficulties to develop a standardised virulent calf challenge model with clinical expression; ii) the need to induce protective immunity within the first month of life, at a time when maternal antibodies can pose a major obstacle to successful vaccination, or when the immune response is not optimal and iii) the observation, although very seldom, that certain vaccines can exacerbate BRSV disease.
11. New field trials with recent BRSV vaccines to evaluate their effect on the prevention of BRSV infection and its consequences need to be performed to have a real idea of the cost benefit of the implementation of such preventive measures.

Pharmaceuticals

12. Effective therapeutic drugs (antivirals and anti-inflammatory drugs) to treat BRSV infection at low cost are needed to decrease the morbidity and mortality as well as to limit the use of antibiotics.
13. Antibiotic treatment is indicated to treat secondary bacterial infections. Antibiotic treatment should be linked to the development and use of diagnostic tools to show the presence of secondary bacterial infection and other viral respiratory pathogens in the lungs, to decrease antibiotic usage.

Knowledge

14. BRSV is structurally and antigenically related to human (H)RSV, which is the single most important cause of bronchiolitis and pneumonia in infants. BRSV in calves is an excellent model for development of HRSV vaccines and pharmaceutical products. Comparative studies of the immunobiology of these viruses will yield important insights that should benefit both man and cattle.
15. As with many other viral infections, there remain significant areas of uncertainty in the understanding and knowledge about BRSV. These relate to genetics, pathogenesis, immunology, vaccinology, epidemiology and control. The role of genetic variation and nutrition on disease severity in cattle and factors that determine virulence are poorly understood. The survival of BRSV in the environment is not really known, even if it is probably short. Nevertheless, outbreaks can occur without animal introduction suggesting that the virus is resistant enough to enable indirect transmission. It is not known whether carriers exist nor whether there are reservoirs of infection.

Conclusions

16. BRSV is still a major cause of respiratory disease in calves and is probably responsible for considerable economic losses worldwide. More effective vaccines, especially of the DIVA type, combined with biosecurity measures based on identified routes of virus introduction in herds are needed to combat the disease successfully in a well-controlled manner in endemic areas. No compulsory eradication programs are currently being considered. Efficient new therapeutics are needed to limit excessive inflammation associated with BRSV infection to avoid the use of antibiotics, to limit bacterial super-infections and to ensure animal welfare.