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). They reviewed the current knowledge on the disease, considered the existing disease control tools, identified current gaps in the availability and quality of the control tools and finally determined the research necessary to develop new or improved tools. Full details are available on the web site at http://www.discontools.eu/ and can be downloaded by selecting Disease Database, then the specific disease and highlighting the variables of interest. This is completed by selecting "create a report" which can then be downloaded as either a PDF or Excel spread sheet.

Disease profile

2. BRSV is an RNA virus classified as Pneumovirus in the family of *Paramyxoviridae*. It exists as a single serotype, with four antigenic subtypes and six genotypes based on the G protein-coding gene, which cluster temporally and spatially. 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. However, in severe outbreaks of BRSV 15-20% mortality can be encountered. The virus can be detected in cattle with mild to severe respiratory signs and has been isolated from lymph nodes of calves 71 days after experimental infection. However, viral excretion from persistently infected animals has not been documented. 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 herds and between herds. BRSV gains entry to susceptible cattle through the respiratory tract where it replicates and causes disease.

Risk

4. BRSV is not known to be infectious to humans although calves can be experimentally infected with HRSV. Worldwide the ubiquitous and endemic character of infection in dairy and especially beef cattle causes major losses to the industry. Large volumes of antibiotics are used in the veal production sector to try and control respiratory disease and 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 man.

Diagnostics

5. BRSV does not survive very long in the environment. The fragility of the virus makes it difficult to isolate in the laboratory and consequently BRSV infection is difficult to diagnose by virus isolation. A diagnosis of BRSV requires laboratory confirmation. Antigen detection enzyme immunoassays have been developed and are useful in detecting BRSV antigen and establishing an ante mortem or post-mortem diagnosis, but sensitivity is low. Other procedures for the detection of BRSV virus antigen are fluorescent antibody and immunoperoxidase staining. In addition conventional or real time PCR-based tests, which have high sensitivity and specificity, are used in routine diagnostics as well as for research purposes.

6. Paired serum samples can be used to establish a diagnosis of BRSV infection. However, cattle with high antibody titres at the time of infection might not get an increase in antibody titres and calves that become infected with BRSV in the presence of passively derived antibody may not seroconvert. Serum antibody titres may even decrease in such calves between sampling. The duration of BRSV maternal antibodies in calves is usually between 3 to 6 months.

7. Antibody detection kits for BRSV antibodies such as antibody detection ELISAs for detection of both IgG and IgM in serum are available and an EIA assay for antigen detection in nasal swabs along with RT-PCR kits are also commercially available. Currently, there are no DIVA tests available but an SH protein-based ELISA might be a good option, since BRSV infection induces SH protein-specific antibodies and BRSV lacking the SH protein appears to be a safe and effective a live vaccine candidate. Furthermore, the SH protein is not likely to be incorporated into a subunit or virus-vectored vaccine.

Vaccines

8. Two monovalent and many multicomponent vaccines containing modified-live or inactivated BRSV are currently on the market for intramuscular or intranasal administration in cattle. 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 vaccine induces rapid protective immunity, which is useful when disease occurs in very young calves (3 to 6 weeks old). However, live virus is excreted and, although reversion to virulence is tested prior to licencing for all live vaccines licensed in the EU, there remains a theoretical possibility that on transmission between calves, 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, and/or significant field strain variation. Young calves (<6 months) are difficult to immunise effectively as maternally-derived antibodies may compromise vaccine efficacy

9. Modified live virus vaccines can induce virus neutralizing antibody levels, 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, which 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 firstly by 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, when the immune response is not optimal , for example, if calves are vaccinated when they are transitioning from intrauterine to post-natal life or when they are stressed by factors such as transport and mixing; and also by the observation that certain vaccines can exacerbate BRSV disease. Since vaccine-augmented disease has been associated with inactivated virus, it has been proposed that a live, attenuated virus administered intranasally would make safer and more effective vaccines.

Pharmaceuticals

11. As with other viruses, antibiotics have no effect on the BRSV infection. However, antibiotic treatment is indicated in attempts to control the secondary bacterial infections. As there is a need to reduce antibiotic usage, antibiotic treatment should be linked to development of diagnostic tools to show presence of bacteria in the lungs. An antiviral may have a place in future as well as other agents that have a disease mitigating effect at low cost, in combination with antibiotics or anti-inflammatories. A greater understanding of the role of the host response in the pathogenesis of BRSV could lead to the development of immuno-modulators and specific anti-inflammatories.

Knowledge

12. BRSV is also 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.

13. As with many other virus 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 in calves on disease severity and those aspects of the virus which 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

14. BRSV is still a major cause of respiratory disease in calves and causes 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 although 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.