EU Thematic network
on control of
bovine viral diarrhoea virus (BVDV)

BVDV Control

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Position paper

Executive summary

An European Union (EU) Commission funded Thematic Network on control of Bovine Viral Diarrhoea Virus (BVDV) has finalised its report after three year's work. The overall objective of the network has been to provide advice to the EU Community on future management of BVDV infections, based on the experiences of a broad group of European scientists including experts in veterinary medicine and epidemiology, sociology and economics, as well as control programme managers, governmental workers and stakeholders. A significant part of the work has dealt with issues pertaining to the process that lead up to initiation of control. Furthermore, current knowledge on the virus, its prevalence, diagnostic abilities and immunoprophylactic approaches has been analysed to identify areas of future research considered necessary to support available control approaches. The network has also set out to formulate a general model for BVDV control and describe how this model applies to the prospect of making progress once control has been initiated.

A main conclusion of the network is that the technical tools and the knowledge needed for eradicating BVDV are at hand. Several EU Member States have already embarked on large scale schemes, where some are close to finalisation. Three central elements of such schemes are; the implementation of **biosecurity** aimed at preventing re-/introduction of the infection in free herds, **elimination of persistently infected (PI) animals** from infected herds, and continuous **surveillance** to monitor progress of the interventions and to rapidly detect new infections. The network has chosen to term this type of approaches "**systematic**", in contrast to control efforts with diffuse goals and without surveillance in place to evaluate progress.
In this systematic context, biosecurity involves all measures that support prevention of between-herd transmission of BVDV, including the more abstract but important risk-reducing effects of a common regulatory framework (voluntary or compulsory), of measures aimed at increasing the general awareness of BVDV risks among stakeholders and of swift access to accurate and updated information on herd or animal BVDV status for decision making in conjunction with livestock trade and other herd contacts. Although basic biosecurity measures can be implemented on any farm, there are substantial benefits in terms of cost-efficiency by implementing control at a larger scale (regional/national). This will have a greater effect on reducing the overall risk of between-herd spread, which is a strong determinant for the cost-benefit of BVDV control.
The network thus concludes that a systematic approach is needed if the goal is a long-term reduction in the incidence and prevalence of BVDV infections in Europe. Systematic control and eradication programmes have been shown to have the potential of being highly cost-effective. Strongly contributing to this is the ability to use low cost-high throughput herd level screening tools, but also the dramatic decrease in incidence of new infections seen after implementation of biosecurity, as defined above. This ability to show good progress is also of great importance in order to maintain support from the primary stakeholders.
The role of **vaccines** in systematic control is as an **additional biosecurity measure**. In areas where the risk of introducing BVDV infection is known or perceived to be high, one option is to implement systematic vaccination of cattle against BVDV in initial stages of control/eradication programmes, after removal of PI animals. The need for including a vaccination regime will differ between countries/regions and it will also change over time, as the prevalence of infected herds decreases. Since adding a vaccination regime also implies an additional cost, it should be evaluated against the expected benefits on a regular basis.
There is a series of issues with the use of vaccines that need to be considered before including vaccination in a systematic control/eradication scheme. These issues include the need to ensure compliance and the fact that vaccination interferes with interpretation of serological test results but there are also safety and efficacy issues with the vaccines themselves.

Although there are solutions for how they can be mitigated, it is vital that this aspect it given thorough consideration and that stakeholders are well informed of any risks and shortcomings of vaccines before large-scale vaccination is implemented.

As a consequence of the ongoing national BVDV control programmes in Europe, differences in prevalence of BVDV infections are becoming increasingly pronounced. Politically, these differences are reflected in the acknowledgement of BVD as a notifiable disease in eight European countries; Austria, Belgium, Denmark, Finland, Germany, Norway, Sweden and Switzerland. This together with the recent decision by the OIE to list BVD as a priority disease in terms of animal trade is a strong signal to the Community to consider development of an EU wide strategy to control BVD. Such a strategy must account for the economic, social and political differences that influence disease control in general. The economic incentives to initiate BVDV control may be present in many regions - at the farm as well as at higher levels. Nevertheless the experience is that a strong motivating factor for initiation and positive progress of control programmes is if the intitative is taken by organisations that directly or indirectly represent the primary stakeholders. Thus, if BVD is acknowledged as a priority by policy makers at the EU level, incentives should be created for farmers' cooperative bodies or similar organisations to take an active role in initiating control programmes. The use of public funding to support such initiatives, e.g. for baseline surveys and/or information campaigns, could be justified in terms of the wider societal benefits, for example to animal welfare.

Beyond Europe, the consequences of the OIE listing of BVD in terms of economic and social pressure for control are yet to be seen. US cattle producers recently responded to the problems associated with BVDV infections by drafting a policy document with the ultimate aim to eradicate BVD from America, and in New Zealand, the scientific community has moved BVD higher up on the industry's list of priorities. Altogether, there are strong indications that the disease has become an international priority. With the achievements by Member States so far, and with the concept put forward by this Thematic Network, the EU is in a good position to meet increased standards. But to retain this position, the Union needs to be proactive, both in the political and scientific field.

Continuous improvement of diagnostic tests, and monitoring of their performance, is central for sustainable BVDV control. Similarly, where vaccines are used, there will be a constant need for development and adaptation to evolving strains that circulate in the cattle population. It is clear that as long as BVDV control efforts are not harmonised across Europe, there will always be a threat of spreading of BVDV across the continent, including the less prevalent BVDV-2 and any new emerging types. Non-systematic use of any live cattle vaccine can increase this risk. However, efficient systematic control measures with or without the use of vaccines will provide the necessary protection. A future challenge is to find a joint platform where differences in needs and preconditions between Member States can be accommodated, while still promoting concerted action on BVDV control.

With the experiences and tools available today, a pan-European approach to controlling BVDV is feasible. More specifically, it offers a unique opportunity to increase the general biosecurity standards in cattle operations across the union. The principles of systematic BVDV control will, if applied more widely, contribute to the overall stability against introduction and spread of other zoonotic and epizootic agents. Such an effect could be achieved by coordinating further initiatives on the control of BVD with actions directed towards other infectious cattle diseases, where the focus is biosecurity. Such coordination would, in addition to providing a potential for long term improvement in bovine health and welfare, strongly support the future competetiveness of Europe's cattle industry.

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Genome, diagnosis & diagnostic tools

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1.1 Executive summary

The bovine viral diarrhoea virus (BVDV) genome is well characterised, and large numbers of nucleic acid sequences are available from academic databases. But for many of the virus isolates sequenced, available sequences are non-overlapping, or cover different genomic regions. Therefore it may be difficult or impossible to compare specific selections of virus isolates genetically. A dedicated database for BVDV sequences could provide reference data as well as standardised protocols for genetic classification of novel virus isolates.
The performance of the currently available diagnostic tests for BVDV is good, but in several important areas there is considerable room for improvement. This is particularly important for BVDV-induced cases of abortion, and for identification of persistent infection in foetuses and neonatal calves. Currently, there is no organised assessment of the performance of laboratory diagnostic investigations for BVDV. Consistent with the recent classification by *Office International des Epizooties* of BVD as a notifiable disease, the performance of laboratory diagnostic assays for BVDV need to be supervised, preferably by an EU community reference laboratory for BVDV.
In many European countries, organised programmes for control of BVD have been implemented. Laboratory diagnostic assays have been selected both for surveillance and zoo-sanitary purposes, and in most cases the performance is satisfactory. It is important to be aware of possible shortcomings of individual laboratory assays, and the suitability for the combined diagnostic use they have been chosen for, to avoid diagnostic errors and suboptimal use of the data they generate.

1.2 Recommendations

a. To improve the standard of genetic typing of new BVDV isolates, a BVDV sequence database should be established. This should include protocols for expert scrutiny of submitted sequences, and also give guidelines on standardised genotyping protocols and interpretation of results.

b. An EU reference laboratory for BVDV should be established. Sets of biological standards for evaluating the tests should be prepared and made available to the companies and to diagnostic laboratories. Regular ring tests should be performed. .

c. The available diagnostic tests for BVDV should be evaluated for the ability to diagnose the infection prenatally, in abortion samples and in neonatal calves. The ability of serological tests to distinguish between naturally infected and vaccinated should be explored further.

d. Guidelines for the performance of diagnostic tests for BVDV should be issued. An expert panel able to give advice on combination of diagnostic tests to be run in control programmes should be nominated.

1.3 Objectives

The following objectives were specified for the work package for genome, diagnosis & diagnostic tools (WP1):

- To evaluate current BVDV genome information, need, use and procedures for a European BVDV genome database
- To evaluate and standardise methods for strain typing and differentiation
- To evaluate and identify needs for further development of tools for early identification
- of the infection - especially with respect to in utero infections
- To evaluate methods for standardisation and validation of present and future diagnostic tools
- To evaluate methods for integrated use of diagnostic tools in screening schemes

1.4 Evaluation of current BVDV genome information, need, use and procedures for an European BVDV genome database

1.4.1 Structure and diversity of the BVDV genome

The bovine viral diarrhoea virus (BVDV) genome consists of a single stranded RNA molecule of positive polarity (Purchio et al., 1984; Meyers et al., 1989). In the last 15 years, progress in biotechnology, specifically the availability of reverse transcription polymerase chain reaction (RT-PCR) and automatic sequencing of PCR products, has made sequence comparison readily available for most virological laboratories.
Since the first complete BVDV genome was sequenced in the late 1980ies, an ever-increasing number of pestivirus isolates have been sequenced. Early genetic characterisation studies aimed at sequencing whole viral genomes, which mostly have been found to be around 12.3 kilobases (kb) long. This consists of a single open reading frame (ORF) around 11.7 kb long, flanked by untranslated regions (UTR) around 380 nucleotides (nts) at the 5'-end, and 230 nts at the 3'-end (Meyers et al., 1989). Genomes of cytopathogenic BVDVs have been found to be up to several kb longer, due to insertion of host cell genes or duplication of viral genes after recombination events (Meyers and Thiel, 1996). Even if cytopathogenic BVDVs are interesting from a virological and pathogenetic point of view, such viruses are rare in the bovine population, and represent an evolutionary dead end for the virus. Comparison of genomes of the more common noncytopathogenic BVDVs, and also with those of several border disease (BD) and classical swine fever virus (CSFV) isolates has provided valuable information on the nucleic acid sequence variability within these genomes (Becher et al., 1999; 2003; Letellier et al., 1999; Vilcek et al., 1994; 2004). Thus genomic regions with a high degree of sequence conservation have been identified, allowing the development of molecular diagnostic tests able to detect and discriminate between a wide

range of pestiviruses (Wirz et al., 1993; Sullivan and Akkina, 1995; Sandvik et al., 1997b). Similarly, genomic regions with more or less variable sequence have been identified, which provide better resolution for genetic typing of BVDVs (Becher et al., 1999). Currently at least 25 more or less complete genomes and over 800 partial sequences of ruminant pestiviruses have been published, or are available from computer databases.

Analysis of the available sequences has shown that two different species of BVDV (BVDV-1 and BVDV-2) can be isolated from cattle (Pellerin et al., 1994; Ridpath et al., 1994). In addition, several more diverse ruminant pestiviruses warranting classification as separate species have been isolated from small ruminants and wildlife (Arnal et al., 2004; Avalos-Ramirez et al., 2001; Becher et al., 1999; 2003; Schirrmeier et al., 2004), and although they most likely would be infectious to, they have so far not been isolated from domestic cattle. Genetic typing of bovine BVDV isolates has shown that at least 12 genetic subtypes of BVDV-1 can be distinguished, and at least three for BVDV-2 (Becher et al., 1997; Vilcek et al., 2004). With continued typing of more bovine isolates, the numbers of genetic subtypes of both BVDV-1 and -2 are likely to increase.

1.4.2 Geographical distribution of BVDV subtypes

The geographical distribution of BVDV subtypes in domestic cattle seems to be limited and variable. The greatest diversity of BVDV-1 has so far been found in central continental Europe, where subtypes designated 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1j and 1k have been found. In most central European countries, between three and six of these subtypes have been detected (Vilcek et al., 2004). In other countries, one subtype has been found to dominate, e.g. in Ireland (Graham et al., 2001), United Kingdom (Vilcek et al., 1999), Norway (now virtually eradicated) and Australia (Mahony et al., 2005). BVDV-2 seems to be limited to fewer countries. Initially it was discovered in North America (Pellerin et al., 1994), but later it has also been isolated from cattle in e.g. Germany (Tajima et al., 2000), Belgium (Couvreur et al., 2002) and Japan (Nagai et al., 2001). No link between breeds of cattle and specific genetic subtypes has been seen. In many BVDV positive herds, genetically identical viruses have been found in several animals, suggesting the existence of herd-specific virus strains (Hamers et al., 1998). Thus, depending on the initial status for a given geographical region, genetic surveillance of local BVDVs may show if novel viruses have been introduced to a farm, region or country. To some extent, genetic typing of local BVDV isolates may also be used to support epidemiological tracing of a given virus strain, during new cases of infection or outbreaks of disease.
Genetic typing of BVDV isolates allows pestivirologists to monitor the diversity of local isolates, and gives useful information whether viruses not previously seen in a region are being introduced. This is particularly useful in areas where organised control efforts of BVD are carried out.

1.4.3 Genome regions used for genetic typing

The genomic regions most commonly used for genotyping of BVDVs, and pestiviruses in general, are within the 5'-UTR (Baule et al., 1997), or, in the coding part of the genome, either the aminoterminal protease (N^{pro})(Becher et al., 1999) or the major envelope glycoprotein (E2) genes (Nagai et al., 2004). Other regions studied include e.g. the 3'-UTR and the NS2-3 gene. Partial 5'-UTR sequences are technically easy to amplify by RT-PCR and sequence, since it comprises two highly conserved regions approximately 250 nts apart. It is therefore a very convenient target for rapid genotyping of unknown virus isolates. A minor disadvantage of using the 5'-UTR is the relative lack of genetic diversity within this genome region, which limits the genetic resolution that can be obtained for closely related viruses. The N^{pro} gene is around 0.5 kb long and provides better resolution for classification

of closely related virus isolates. Since the gene product appears to lack any function influenced by evolutionary selective pressure, it is convenient for genotyping purposes. However, the more variable nucleic acid sequence downstream of the N^{pro} gene makes it technically more difficult to obtain PCR products suitable for direct sequencing than from the 5'-UTR, at least with a single universal reverse primer. This will particularly affect genetically diverse viruses, which usually amplify well with 5'-UTR primers. The E2 gene is nearly 1.2 kb long and contains the most variable regions of the whole genome, both at the nucleic acid and the amino acid level. Its sequence may reflect how the virus isolate in question has adapted to selective immunological pressure. Due to the diversity of the E2 gene, PCR primers used for amplification and sequencing are less likely to match all virus isolates, also making it technically more challenging to sequence than the 5'-UTR.

For each genomic region studied, the sets of sequence data provided by different authors very often do not overlap. Among the sequences available in databases, this is most common for partial E2 and 5'-UTR sequences. For the 5'-UTR there are no logical start- or endpoints such as translation initiation and termination codons, causing slight deviations in the beginning and end of submitted sequences. N^{pro} gene sequences submitted to databases more often seem to cover the whole gene. Due to the variability of the E2 gene, partial sequences are often sufficient to provide a good genetic resolution, and sets of sequences 190, 350, 420 or 790 nts long are available from sequence databases. Some of these overlap, but others are from different parts of the 1.2 kb long gene. There are scientifically valid reasons for studying different genomic regions, but if sequence data is obtained from different or non-overlapping genomic regions, a major drawback is that it may be impossible to compare the sequences of different sets of viruses.

1.4.4 Availability of sequence data

Currently, nucleotide sequence data is available over the Internet from databases at e.g. EMBL, NCBI or DDBJ. However, unsupervised submission of sequences to these databases has lead to entries listed either as Pestivirus type 1 or BVDV, and some ovine isolates are incorrectly listed as BD virus (BDV). This taxonomic confusion adds to the one caused by non-overlapping sequences. Some of the sequence database entries have been updated to ensure listings are correct, but most often they are not – and such updates rarely include the submitted sequence itself. Although the International Committee on Taxonomy of Viruses (ICTV) updates the taxonomy also for pestiviruses, no suggestions of which genetic region should be used for genotyping has been presented. This would include recommendations both for which part of the genome to analyse, and the length and location of partial sequences (see Objective 2, section 1.5 for comments on methods for virus strain typing).

A supervised sequence database only including sequences that fit with basic criteria would be a useful research tool making genetic characterisation of BVDV isolates easier. Examples of such databases available over the Internet are the sequence database run by the EU Community reference laboratory for CSFV (http://viro08.tiho-hannover.de/eg/eurl_virus_db.htm), and one set up by "EUROPA" (European Resource On the Pathogens of Aquaculture) for sequence data of pathogens affecting aquacultured species (http://www.fishpathogens.net/). A demonstration version of a BVDV sequence database adapted from the current CSFV database has been set up by Network partner Dr Irene Greiser-Wilke at the University of Veterinary Medicine in Hanover. Both databases organise available sequence data together with additional information on each virus (or pathogen) isolate. The sequence data they are based on is (mostly) available in other sequence databases, but has been checked and standardised to match other selected sequences. One useful feature of the "fishpathogens.net" database is the option to generate FASTA files with a selection of truncated sequences derived from longer sequences submitted to GenBank. The

CSFV sequence database provides very useful guidelines on genotyping of selected isolates. A database combining these functions would be a very useful research tool enabling accurate genetic classification of new BVDV isolates.

1.4.5 Requirements of a dedicated BVDV sequence database

Based on our experience, the minimum specifications for a BVDV genome sequence database should be:
- computer platform independent internet access
- fully searchable by virus species and genetic subtype
- links to parental GenBank (or other sources) accession numbers
- links to the submitting laboratory with availability of the virus isolate
- possibility of batch downloading of selected viral sequences into a single alignment file
- exclusion of partial or incomplete sequences
- user support for submission of sequences, to ensure conformity and sufficient quality
- expert scrutiny of submitted sequences before inclusion in database

When it comes to genetic regions to include and typing protocols, see Objective 2 in section 1.5 below.

1.5 Evaluation and standardisation of methods for virus strain typing and differentiation

Although characterisation of BVDVs usually begins with isolation of a virus from clinical material, detection by RT-PCR with subsequent nucleic acid sequencing does not require a virus isolate. The classical approach with isolation of an infectious BVDV in cell cultures can easily be complicated by adventitious pestiviruses in the cell cultures or the medium, since foetal calf serum used to supplement the medium often is contaminated with BVDV (Bolin et al., 1991). Thus, recommended standard methods for antigenic and genetic characterisation of BVDV should also include basic protocols on how to avoid, and to monitor cell cultures for viral contamination. Two fundamentally different methods for typing of a given BVDV strain can be used; antigenic and genetic typing (Paton et al., 1995).

1.5.1 Antigenic typing

Antigenic typing provides limited resolution, but can easily be used to distinguish BVDV-1 from BVDV-2 (Deregt et al., 1998). This can be done by cross neutralisation using specific antisera, or easier by immunostaining with a selection of monoclonal antibodies (MABs) specific for either virus species (Flores et al., 2000). Such a MAB panel should be made available from reference laboratories. However, no further division into antigenic subtypes is possible by antigenic typing, even with MABs. One disadvantage of antigenic typing protocols is that they may be technically demanding, in that it requires a well-managed cell culture laboratory, with experience in handling pestiviruses.

1.5.2 Genetic typing

Alignment and phylogenetic analysis of sequence data (for most practical purposes nucleic acid sequences) is a much more powerful method for typing of new isolates, allowing subdivision of both BVDV species into numerous genetic subtypes. Today, this may also be technically easier than MAB typing, since many veterinary diagnostic labs are better equipped for molecular diagnostic investigations, mostly PCR-based, than for pestivirus cell culture work. Also, several commercial labs offer sequencing of PCR products, which makes

it easy to obtain sequence data for novel pestivirus isolates. However, the currently low threshold for obtaining BVDV sequence data is often not matched by sufficient skills at analysing the data. Setting up of a BVDV sequence database, as discussed under Objective 1, (section 1.4) may address the need for this – not only when it comes to selection of genome regions to obtain sequence data from, but also for providing guidelines on how to analyse them.

1.5.3 Protocols for genetic typing

Information on suitable methods for genotyping of BVDV sequences is available in the scientific literature. However, many different approaches are described, often without mention of why they were used, what may be limitations to their use, or what conclusions can be or should not be drawn from their use. A set of standard approaches has been suggested for CSFV (Paton et al., 2000). Thus, without experience in this field, and inclusion of all relevant reference strain sequences, confusing typing results with mixed up nomenclature of specific genetic subtypes may result. Various computer programmes for editing, aligning and phylogenetic analysis of nucleic acid sequences are available, either commercially or as public domain programs from the Internet. An overview of these can be found at <http://evolution.genetics.washington.edu/phylip/software.html>. Typical for these are a very diverse user interface – commercial software packages are often designed to be more user friendly than academic counterparts, which on the other hand allows the user better control over settings that affect the outcome of the analysis. A guideline on how to use programmes in the academic "Phylip" programme package has been published on the EU CSFV reference laboratory web site, at <http://viro08.tiho-hannover.de/eg/analysis/analysis.htm>. This guideline describes genetic typing of CSFV sequences, but can equally well be adapted for matching sets of BVDV sequences.

1.5.4 Recommended genetic regions for typing of BVDV

As mentioned under Objective 1, recommendations on which parts of the genome to use as a default for genetic typing are very important. Since sequencing techniques are more likely to improve in quality as well as to be cheaper in the future, we will generally recommend that as long sequences as possible should be obtained and submitted. Then all options for genetic typing of a given set of sequences will be possible; including truncation to match older sets of sequences. We will recommend partial 5'-UTR sequences as the principal region to analyse, more specifically the 245-250 nt long region between the highly conserved ATGCCCTTAGTAGGACTA and GTACATGGCACATGGAGTTGA motifs, the latter directly upstream of the translation initiation codon. This sequence is as mentioned before easy to obtain from virtually any pestivirus, and provides adequate although not optimal statistical support for phylogenetic classification. If better genetic resolution is considered necessary, we do recommend sequencing of the entire N^{pro} gene sequence. For most BVDVs this gene is 504 nts long, and has the benefit over the specified 5'-UTR sequence that there are few deletions or insertions – which is fairly common for the 5'-UTR, and also parts of the E2 gene. A standard advantage of analysing coding regions it the opportunity to "proof read" raw sequence data for termination codons, which are likely to be found due to skipping of the reading frame if the quality of the primary sequence is unreliable. Such a built in control is not possible for the mentioned 5'-UTR sequence, in which actual deletions and insertions are fairly common, as well as artificial ones generated by poor quality sequencing.
Alternatively, if E2 gene sequences are studied, a logical way to avoid the current confusion resulting from analysis of four different E2 gene regions is to sequence the whole E2 gene. This may seem technically challenging, but should only be necessary for individual virus isolates that have failed to group consistently with previously defined genetic subtypes, on basis of partial 5'-UTR and N^{pro} gene sequences.

Before recommending a default set of aligned sequences for being used as templates for genetic typing, available data has to be screened and evaluated. Then, sequences of at least two not too related isolates for each known genetic subtype will have to be chosen to minimise the risk of incorrect allocation of novel isolates. Such basic sets of sequences should encompass 25-30 BVDV isolates. For generation of rooted phylogenetic trees, a standard outgroup sequence (e.g. the "Giraffe" pestivirus; GenBank accession no. NC 003678) would help to ensure more similar presentation of the trees. An alignment file with such sequences for both the 5'-UTR and the N^{pro} gene could be made available (downloadable) from an Internet accessible database of additional sequences, as described under Objective 1.

1.6 Evaluation and identification of needs for further development of tools for early identification of the infection - especially with respect to in utero infections

1.6.1 Diagnostic aims

In cattle, infection with BVDV can occur in many different forms – the two most important being acute and transient in immunocompetent animals; and persistent with immunotolerance if foetuses are infected in early stages of development (Duffell and Harkness, 1985). In all cases, a diagnosis is dependent on laboratory analysis of suitable clinical samples (Sandvik, 1999). Besides diagnosing infection in live animals, it is also important to recognise BVDV as a cause of abortions, where available materials for sampling often can be generally unsuitable for laboratory investigations. BVDV is also a well-known contaminant of biological products intended for in-vivo use, e.g. vaccines, semen and embryos (Voges et al., 1998; Bruschke et al., 2001). Finally, products for in-vitro use such as commercial foetal calf serum and ruminant cell cultures are often contaminated with BVDV and/or anti-BVDV antibodies, which can interfere with diagnostic investigations or growth of various ruminant viruses.

Many different diagnostic assays have been developed to address the demands for laboratory detection of the virus, or immunity to it. These can roughly be divided in reference laboratory assays both for virology and serology, secondly routine diagnostic tests designed for testing of large series of samples, as well as specialist assays for testing of biological products and clinical samples for which standard laboratory tests are unsuitable. In BVD control programmes, the routine diagnostic tests are by far the most important, but they need supplementing with reference assays and specialist assays for quality control and back up purposes. A major diagnostic target in BVD control programmes is the identification of clinically normal immunotolerant and persistently infected individuals (PIs) (Lindberg and Alenius, 1999). This requires detection of BVDV or viral components in clinical samples, most often blood. Since the prevalence of PIs is low even in thoroughly infected populations (usually between 0.5 – 2.0 %), some kind of screening to identify herds with likely active infection greatly rationalises this task, and minimises the impact of false negative virus detection test results on the progress of control programmes. For further discussion of integrated use of different diagnostic tests, please see Objective 5 in section 1.8 below.

1.6.2 Diagnostic challenges

Failure to detect PIs, i.e. false negative test results with samples from a PI animal is perhaps the greatest threat to the success of BVD control programmes. Blood sampling neonatal PI calves that recently have ingested colostrum is a classical example of a potential user-induced

false negative diagnosis for BVDV. In cell culture based diagnostic assays where BVDV needs to replicate before it can be detected, neutralising antibodies will inhibit the receptor-mediated internalisation of the virus, and give a negative immunostaining result (Palfi et al., 1993). To some extent this blocking effect of maternal antibodies also affects detection of BVDV antigens by ELISA (Zimmer et al., 2004). There are indications of a variable effect of this inhibition for ELISAs targeting different viral antigens, but the available knowledge of this is not complete. Further investigations into the performance of antigen ELISAs for this category of samples are necessary. Alternative assays such as detection of viral antigens by immunohistochemistry, which successfully has been used in the United States (Broderson, 2004), or viral nucleic acid by PCR should also be considered.

Similar to the diagnostic dilemma with neonatal PI calves, the virus titre in adult cattle may vary, occasionally down to levels that makes detection by antigen ELISA or virus isolation unreliable. In cattle suffering from chronic or "late onset" mucosal disease, lower detectable levels of BVDV antigen have been seen than in clinically healthy PI individuals, and means of increasing the chances of correctly diagnosing such animals as PIs are welcome.

"Early detection of the infection" also includes identification of pregnant animals carrying PI foetuses ("PI carriers"). Semi quantitative use of indirect antibody ELISAs can recognise PI carriers during their last trimester (Lindberg et al., 2001). It remains to be seen if PI carriers can be detected by other serological assays that are in use as routine diagnostic tests. Alternatively, in foetal fluids obtained from PI carriers by paracentesis, BVDV has been detected by both virus isolation and RT-PCR (Lindberg et al., 2002; Stokstad et al., 2003), but more research is needed to see if the sampling technique is suitable under field conditions.

Laboratory investigations of clinical material from abortion cases often fail to give conclusive results due to the decomposed status of such material. For this reason, cases of abortion have been investigated by indirect immunofluorescence for anti-BVDV antibodies (Lucas et al., 1986), but this approach is only useful for foetuses infected in the second half of the gestation period. BVDV laboratory assays independent of cell cultures circumvent the cytotoxic effect often seen with such samples. Detection of viral antigen by ELISA is not affected by cytotoxicity, but antigens can also have been degraded, or are not present at the levels that normally can be found in samples from older animals. RT-PCR is theoretically a more suitable assay, but since viral RNA also can have been degraded, -PCR primers and probes for host cell genes should be included in such assays as RNA integrity controls. Some synthetic RNA mimic targets have been developed for use in BVDV RT-PCRs (Heath et al., 2003), but they have yet to be incorporated in routine diagnostic assays. Some studies indicate that foetal fluids may be more suitable for testing by RT-PCR (Hyndman et al., 1998), but further studies should be done to verify this.

Under some circumstances, BVDV appears to have circulated over prolonged periods only by the acute route, i.e. without the involvement of PIs. This means of virus transmission may be more common in large herds, but the efficiency of virus spread by acutely infected animals has not been established with certainty. Indeed, there is experimental evidence that acutely infected calves do not infect others with which they are in contact (Niskanen et al., 2000). It is difficult to advise whether specific diagnostic efforts should be recommended for diagnosis of acute infections, since the management approaches to clear the infection are different from the culling of PIs approach that so far has been most successful for clearing herds of BVD. If diagnosis of acute infection is required, paired serology is the most likely method to provide an answer.

In cattle acutely infected (AI) with BVDV, the period of viraemia is usually very short, and also the detectable virus titre (or antigen or RNA level) is lower than in PI cattle (Sandvik et al., 1997a). The probability of mistakenly detecting AI animals for PIs is a real one, but since this will not lead to underdiagnosis of PIs, this is not a threat to the success of control or eradication programmes. This misclassification of AI animals is probably most likely to occur with RT-PCRs, because of the highest analytical sensitivity. More recently developed real-time quantitative RT-PCRs are better at indicating if individually sampled animals are PI or AI, but this approach may not be optimal if pooled blood samples are tested. Diagnostic staff should be familiar with the relative ability to detect AI and PI animals with the assays they are using.

Detection of BVDV by real-time RT-PCR assays are promising as future routine diagnostic tools, especially when run by automated robotic systems able to pool blood samples. Although the analytical sensitivity of RT-PCR is not a problem, the epidemiological sensitivity may be compromised if the primers and probes are too specific and do not detect all genetic subgroups of BVDV. Previous specificity problems arising from redetection of previously amplified RNA has long been known as a serious problem for all PCR based diagnostic tests, but this problem may be overcome by strict separation of different work areas, and reading of closed RT-PCR tubes.

The performance of commercially available diagnostic tests (mostly ELISAs) ranges from good to excellent, but the available documentation is often scarce. Estimates of the effect of interventions against BVD usually require values of the analytical sensitivity and specificity for a given diagnostic test. To facilitate predictions of the effect of diagnostic interventions aiming at identification and removal of PIs, such performance figures should be made available by the manufacturer of diagnostic kits. Furthermore, more detailed descriptions of the components of a kit (ELISA) is desirable, e.g. is it necessary to know if the viral antigen used in antibody ELISAs cover the full antigenic spectrum of BVDV or a single viral antigen. If an ELISA is based on monoclonal antibodies (MABs), the specificity/-ies should be indicated.

After new EU directives on monitoring of the health status of stud bulls recently were issued, the question on how seroconversion to BVDV should be defined has been raised on several occasions. This is by classical virological methods defined as a fourfold rise in the titre of neutralising antibodies. With the current wide use of antibody ELISAs for BVD serology there is no useful rule of thumb what "seroconversion" should be defined as. This has to be determined by the manufacturer of antibody ELISAs. To serve as guidelines, reference laboratories for BVDV should be able to provide reference sera that have been characterised by virus neutralisation assays and selected as suitable paired sera for use by commercial suppliers of diagnostic kits.

Guidelines for testing of biological products for use in vivo should be given. BVDV is a common contaminant of commercially available bovine foetal serum used e.g. as cell culture supplement, and may from this source be introduced into vaccines and embryos. Semen from BVDV-infected bulls may be infectious, and as for vaccines, it is important to choose proper diagnostic tests to monitor these biological products for infectious BVDV or BVDV RNA, depending on the hygienic requirements for these products (Givens et al., 2003).

A common problem in many infectious diseases control programmes is the inability to distinguish between antibodies (or immunity) derived from vaccination and natural infection. For BVD, both modified live and inactivated vaccines are available. Immunity from modified live vaccines is difficult to distinguish from natural infection, whereas immunity from inactivated vaccines often is short-lived and tends to induce antibodies against viral structural

rather than non-structural proteins. To some extent, antibodies derived from use of inactivated vaccines or natural infection can be distinguished with certain serological assays. However, it is difficult to give guidelines as to what extent this potential differential diagnostic approach can be used - every given vaccine/serological test combination has to be checked individually.

For several infectious diseases of animals, pen side tests are available for detection of antibodies to or microbial antigens. Such tests may be of use when it comes to determine the status of infection of individual animals, but because of the demand for systematic and organised diagnostic efforts, with keeping of records of all test results, they are not likely to be of great use in organised BVD control programmes.

1.7 Evaluation of methods for standardisation and validation of present and future diagnostic tools

A wide range of diagnostic test methodologies has been developed for BVDV over the past 20-30 years. These tests may be categorised as either direct or indirect. Direct tests are those designed to detect the presence of the virus itself, its proteins/antigens or its genome. Examples of such tests include virus isolation in cell cultures, antigen detecting ELISAs, immunofluorescent and imunohistochemical staining of fresh and fixed tissues respectively and more recently nucleic acid-based detection systems, including the reverse transcription polymerase chain reaction (RT-PCR) and nucleic acid sequence based amplification (NASBA). Indirect techniques used in BVDV-related diagnostics are based on detection of virus-specific antibodies. Commonly used methods include the virus neutralization test and a wide range of ELISAs, both developed in-house or purchased from commercial suppliers. These ELISAs are based on the principles of either activity amplification (so-called indirect ELISAs) or activity modulation (competitive and blocking ELISAs). Details of these different tests, their strengths and weaknesses, and their coherent use in relation to BVDV diagnosis and control have been thoroughly reviewed elsewhere (Lindberg and Alenius 1999, Sandvik 1999, Broderson 2004, Saliki and Dubovi 2004).

1.7.1 Need for test evaluation data

These tests may be used, either alone or in combination, for a variety of different purposes, including primary diagnosis of BVDV-related disease, as tools in control and eradication schemes, for statutory purposes (e.g. in relation to semen production) and for quality control (e.g. screening of foetal calf serum and other biologicals). A number of the tests may be used at both the individual animal and at the herd level, and on a number of different analytes (e.g. antibody ELISAs may be used to test individual serum or milk, pooled serum or bulk tank milk). Given the wide variety of uses to which even a single test may be put, it is critical that each test is thoroughly validated for each such application and that the validation data is made available to the end users, to inform their decisions on the use of a given kit for a given purpose, and the interpretation of test results in this setting. It is the responsibility of the end user of a given commercially available test to ensure that the validation data is applicable to the testing regime and the population it is used for.

1.7.2 Measuring diagnostic performance

The performance of a given test can be measured by absolute and relative methods, i.e. parameters specific to the test itself, or how it performs compared to a reference method. The analytical sensitivity of a test is refers to the limit of detection. For example, the analytical sensitivity of a given RT-PCR test will be defined in terms of the minimum copy number or

infectious dose that it can detect. The analytical specificity refers to the ability of the test to exclude cross-reactions which may generate false positive signal. The epidemiological (or diagnostic) sensitivity (Se) and specificity (Sp) of the test are defined as the percentage of true positives that are scored positive and the percentage of true negatives that are scored negative respectively. These Se and Sp values in turn, in conjunction with the prevalence in the population under test determine the positive and negative predictive values of the test, and ultimately its usefulness in that situation. It is recognised that some or all of these analytical and epidemiological factors for a given test may vary between applications. For example, the analytical and epidemiological sensitivities and specificities of a given RT-PCR test may vary across a range of uses such as testing of individual sera tissues and milk, foetal material, pooled sera and bulk tank milk. Data should therefore be available in relation to both the analytical and epidemiological performance of a given assay, and this data should relate to its use in each defined circumstance and for each required purpose. Validation of a particular test is the process of determining its fitness for a particular purpose, with the test's performance being described by the two independent measures of precision and accuracy (Greiner and Gardner 2000). Precision refers to the closeness of agreement of repeated measurements of a given sample under specified conditions. Accuracy refers to the closeness of agreement between the interpreted result (e.g. positive or negative) of each of these measurements and the true status of that sample.

1.7.3 Standardisation of tests

To allow comparison of the same tests when used in different laboratories (reproducibility), the comparison of different test methodologies and the development of new assays, reference assays and reagents should be defined. Virus isolation and the virus neutralization tests are recommended as the reference diagnostic assays for direct and indirect methods respectively. It is recognised that in some circumstances there cannot be a single reference assay, and in such situations it may be necessary to include the results of more than one assay. Defined reference methods should include standard operating procedures, and should specify, where necessary, the use of reference virus strains and reagents, which should be available from designated reference laboratories.

The objectives, methods and limitations of different approaches for test validation have recently been described (Greiner and Gardner 2000), and the OIE have also published principles for the validation of diagnostic assays for infectious diseases (Anon 2004 a, b). Based on these guidelines, standardised protocols should be drawn up for the validation of different BVDV diagnostic kits and methodologies so that the performance of test methods can be more readily compared. The OIE guidelines form a useful basis for this (Anon 2004a, b). To supervise the diagnostic performance in European countries with several BVDV diagnostic laboratories, national reference laboratories should be established for bovine pestiviral diagnosis, under the auspices of the European OIE reference laboratory (Veterinary Laboratories Agency – Weybridge, UK). A questionnaire distributed to partners in the current Thematic Network project rated ring tests for BVDV diagnostic assays very high. An initial BVDV serology ring test encompassing laboratories nominated by the BVD thematic network partners has been carried out (for a summary of results, see Table 2). This test included test sera with antibodies against BVDV-1 and BVDV-2, as well as low antibody titre vaccinal sera. Twenty-two laboratories in 17 countries returned test results obtained with seven commercial antibody ELISAs as well as 5 in-house developed ELISAs. The results showed that the general diagnostic standard is high, but that some serological assays could be calibrated for improved accuracy in detection of low-titre antibodies. Further ring tests, also including tests for BVDV and BVDV antigen should be arranged, preferably on a regular basis by a designated EU Community reference laboratory for BVDV. In addition, such a reference laboratory should assist national reference laboratories with calibration of routine test kits by providing defined reference sera/reagents and virus strains. A forum should be

established to allow the exchange of validation data for commercial test kits that is generated by testing laboratories. Such a forum could also be used to discuss specific diagnostic problems as and when they arise.

When it comes to standardisation of diagnostic test performance within Europe, this will require shipment of both reference BVDV strains to national reference laboratories, and ring test samples containing BVDV to general diagnostic laboratories. Although infectious to ruminants and pigs, such samples pose no threat to human health. Consignments including laboratory reference samples are currently categorised as "dangerous goods" by courier companies, requiring unnecessary complicated and costly shipment. Since there are no restrictions on trade with PI animals within Europe, this requirement is out of place. The appropriate regulatory bodies should note this requirement, and issue realistic biosecurity shipment guidelines for BVDV containing samples.

1.8 Evaluation of methods for integrated use of diagnostic tools in screening schemes

The term "screening schemes" is not very precise and may be used for basic prevalence surveillance, as well as detailed diagnostic investigations on the individual animal level to identify animals PI with BVDV. Obviously basic serological prevalence investigations do not need combinations of diagnostic tests, whereas for the latter objective there is a potential benefit from combining different diagnostic tests to rationalise the identification of animals PI with BVDV – which the term "screening scheme" will be used for here.
In its most basic form, screening schemes for BVD may comprise antibody testing of representative serum (or milk) samples to provide basic information of the prevalence of BVDV. In BVD control programmes run in unvaccinated cattle populations, serological surveillance is a valuable basic method to find regional differences in prevalence, and to monitor the effect of ongoing control measures on the incidence and prevalence of BVDV. The other main diagnostic activity in BVD control programmes is to identify PI animals for removal, which are responsible for maintenance of the infection and typically comprise 0.5-2 % of the population. In herds with PI animals, most other animals kept nearby for longer periods of time will be antibody positive and naturally immune - often more than 80 % of the non-PI cattle. An overview of use of diagnostic tests in BVD control programmes is given in Lindberg and Alenius (1999).

1.8.1 Benefits of combined use of diagnostic assays

Optimal use of diagnostic resources in BVD control programmes relies on surveillance data, from a strategic point of view to focus efforts where the potential output is greatest, e.g. to minimize spread of BVDV from high to low prevalence zones by means of live animal trade. From a tactical point of view, the diagnostic performance of laboratory tests (positive predictive value) can be enhanced significantly by limiting the number of animals that need to be tested for BVDV to identify the PI individuals. This is due to the less than perfect performance of all diagnostic tests, even with a sensitivity of 96-98% sufficient PI animals can remain undetected to cause otherwise well-designed control programmes to fail. Such an enhancement of the positive predictive value can be achieved by serological prescreening; by excluding mainly seronegative herds from individual animal testing for BVDV. Similarly, in herds with ongoing infection, where most BVDV-immunocompetent animals are immune, antibody positive adult animals can similarly be excluded from individual BVDV testing. Specificity figures of BVDV tests also ranging between 96-98% (which actually should be regarded as very good for a commercial test) mean that many BVDV-free animals may be culled unnecessary if a PI diagnosis is made without serological prescreening of samples. The

impact of culling of falsely diagnosed PI animals on the success of an eradication programme is negligible, but such a misclassification may cause unnecessary follow-up testing of animals that would have been at risk of getting infected by a potential virus shedding animal.

Some aspects of the performance of a given test (predictive value) will depend not only on the epidemiological situation in the group of animals tested, but also on the availability of samples. For example, the lack of available bulk tank milk from beef cattle makes serological prevalence surveillance more difficult than for dairy cattle. This may be regarded more as a practical sampling problem rather than an analytical problem, but once tested for BVDV, samples are more often tested as individual samples, where the impact of false positive and negative diagnoses is greater than for herds prescreened by bulk milk serology. Thus, the predictive value of a given diagnostic test for BVDV may be different when used for beef than dairy cattle.

Vaccinal antibodies induced by inactivated vaccines seem to peak at much lower levels than after infection (Graham et al., 2003), and if monitored by bulk milk antibody ELISAs, they could potentially be categorised as low antibody levels, as also seen in dairy herds with a low percentage of naturally infected cows. However, in herds with cows both naturally infected and vaccinated with inactivated vaccines, it may be difficult to deduce status of infection by assaying antibody levels by the currently available ELISAs.
The approach of serological prescreening for selection of animals to be tested for BVDV can also be used in cattle populations where modified live vaccines are used, provided only BVDV negative animals are vaccinated, and good records of the BVD status of individual animals are kept.

1.8.2 BVD diagnostic assays in use by network partner laboratories

In Table 1, the BVDV diagnostic assays in use by laboratories in network partner countries is summarised. As can be seen, ELISAs for both antibodies to and for BVDV are used in the majority of the countries. For serology, ELISAs are used by 90 and 100 % of the laboratories for bulk milk and individual sera, respectively. 2-3 countries report use of pooled blood from young stock or pooled heifer's milk. Such samples have been used as "intermediate" serology aiming at distinguishing between recent or historic infection of a herd, or to detect recent reinfection of cleared herds. Theoretically, false test results may be obtained if blood from one PI and 3-4 antibody positive animals is mixed (by formation of antibody-antigen complexes). This has been seen during surveillance by bulk milk serology for dairy herds with active infection with BVDV (Sandvik et al., 2001; Obritzhauser et al., 2002), but it remains to be seen if this also is a problem for pooled blood samples. Compared to testing of such blood or milk samples individually, there is an obvious cost advantage, which alternatively can be traded for more frequent testing, which e.g. would allow detection of reinfection of a cleared herd much sooner. This strategy for serology screening might be considered by labs / control programme organisers not already testing such samples.

BVDV antigen testing of bulk milk or pooled blood samples was reported by a few countries. The potential for interference by antigen-antibody complexes is far more serious for this approach, at least with the majority of commercial antigen ELISAs. This approach should be reconsidered with the particular ELISA used, including testing of experimental samples.

BVDV antigen ELISAs on samples from individual animal was reported to be used by 75% of the interviewees. Considering the ease of use and short testing time, this figure may be lower than expected, but on the other hand the labs which were not using antigen ELISAs all used cell cultures for detection of BVDV instead. The latter test method is more resource demanding, but may perform as well or even better than antigen ELISAs when used by

experienced diagnosticians. Very few labs reported use of virus isolation in cell cultures with pooled individual milk or blood samples, a combination of sample material and diagnostic test that cannot be recommended. In BVDV positive herds, most of the animals contributing to a pooled sample will be antibody positive, thus infectious BVDV is likely to be neutralised and not detected by cell culture assays.
BVDV detection by RT-PCR using samples from individual animals was reported used by 67% of the laboratories. This is a potentially very sensitive detection method (analytical sensitivity), but may also pick up BVDV RNA in samples from acutely infected animals. If used for identification of PI animals, either an antigen ELISA or a virus isolation assay would be suitable to verify the PI status of RT-PCR positive samples. The high analytical sensitivity of the RT-PCR makes it particularly useful for testing pooled milk or blood samples for BVDV, which around 25% of the laboratories did. One drawback of testing bulk milk over pooled blood samples is that not all animals are contributing to the tank milk, and may remain undetected.
Among other assays in use were the virus (serum) neutralisation test (VNT/SNT) or indirect fluorescent antibody test (IFAT) for serology, and immunoperoxidase/immunofluorescence assay (IPX/IF) for viral antigen. These are often considered as more resource demanding than the previously mentioned ones for large scale testing, but are very good as reference methods, and may even perform well as standard tests if set up in a rational format.

1.8.3 Recommendations for optimal use of BVD diagnostic tests

With significant national as well as regional differences in the structure of cattle production, and the large number of BVDV diagnostic assays available today, it is very difficult to give specific guidelines on which combinations of diagnostic tests are good, excellent, or suboptimal. A BVD control programme aiming at eradication cannot succeed without adequate performance of the diagnostic tests, but it can fail from other factors than the diagnostics. Thus it is difficult to conclude that the diagnostic tests do not work as they should have without having assessed control programme management decisions based on the test results. Nevertheless, experience from existing control programmes have highlighted some areas where given combinations of diagnostic assays may not perform optimally, or where commonly adopted strategies for practical reasons can be difficult to fulfil.

In large scale BVDV screening schemes, it is only realistic to use diagnostic assays that can be scaled up to cope with the number of samples that need to be tested. This may require the use of diagnostic assays that has a lower diagnostic performance than desired. To compensate for this, different back up tests should be selected to monitor the performance of the main diagnostic assays. This can be done by retesting a predefined number of routine samples originally tested e.g. for BVDV antigen by ELISA for BVDV RNA by RT-PCR, or virus isolation in cell cultures. The combination viral antigen/viral RNA has the advantage over the antigen/infectious virus combination that the second test is independent of whether maternal antibodies should be present in the sample, whilst a cell culture assay for BVDV may be equally affected by maternal antibodies as an antigen ELISA. An alternative approach to monitor for undiagnosed PI individuals is by follow-up serology of young stock as described below. This approach works best for BVDV tests with a high sensitivity (96-99 %); if the diagnostic performance of the BVDV assay is less (below 95 %), too many infectious animals may be missed for the control programme to succeed. Compared to back-up testing using a different assay for BVDV, the serological follow-up monitoring has the advantage of assaying for horizontal infection with BVDV in the herd over an extended period of time, and thus indirectly verify that all PI animals were detected since acute infections have ceased to occur in the herd.

When deciding which diagnostic screening approaches to use in control programmes, some combinations of assays and sample materials are better suited than others for a particular task. The first task is to identify herds with active BVDV infection, and for this, serological assays have dominated. In Sweden and Norway, semiquantitative use of an indirect antibody ELISA has proven to work well for unvaccinated dairy herds (Niskanen, 1993). In Denmark, where the herd prevalence was higher than in the Nordic countries, the use of spot-test serology on representative young animals proved to give a better indication of ongoing or current infection (Houe, 1992). If bulk milk tests positively by RT-PCR, BVDV is obviously circulating among the milking cows, but a negative test result is not proof of a BVDV free status.

A second step in organised screening schemes is identification of individual PI animals on BVDV-positive farms. Testing of pooled blood samples is a rational means of excluding groups of animals from being BVDV carriers. Obviously, pooled blood samples will inevitably contain antibodies to BVDV, compromising the use of virus isolation or antigen ELISAs, but not RT-PCR (Rossmanith et al., 2001). Individual blood samples contributing to BVDV RNA positive pools can subsequently be tested by any of the three mentioned methods to identify infected animals. When retesting samples that contributed to a RT-PCR positive pool, RT-PCR is probably the test most likely to identify an acutely infected animal as positive. If repeat samples are obtained from viraemic animals to verify a status as PI, RT-PCR may also detect viral RNA in acutely infected animals many weeks after infection. A real-time quantitative RT-PCR can be calibrated to distinguish between acutely and PI animals, but it would be much simpler to retest candidate PI animals by antigen ELISA or virus isolation, since the results from the latter two assays also make use the antibody response of acutely infected animals to block detection of viral antigen or replication.

After the initial screening for and removal of PI animals has been completed, a third step in test and cull control programmes is to test all calves born the following year for BVDV. Colostral antibodies to BVDV are known to interfere with detection of infectious BVDV or viral antigens by ELISA in PI calves up to approximately 3 months of age (Palfi et al., 1993), thus, specific approaches for testing this age group are needed. Virus isolation and most antigen ELISAs are likely to give false negative test results with blood samples, but RT-PCR is not, and E^{rns} antigen detecting ELISAs or e.g. skin biopsies may provide reliable BVDV test results in this group of calves. An interesting approach to early detection of PI foetuses is semiquantitative serology during the final stage of gestation; significantly higher BVDV-antibody levels have been found in cows carrying PI than uninfected foetuses (Lindberg et al., 2001).

A fourth and very important step in clearing BVDV positive herds for PI animals is follow-up testing of young stock for antibodies to BVDV. The less than perfect performance of all known BVDV diagnostic tests means that some PI animals will be missed when large numbers of herds are screened for BVDV, and identification of young (8-10 months old, after waning of colostral antibodies) seropositive animals is a good indication of missed PI animals.

It is vital for the success of screening schemes that all diagnostic assays have been evaluated thoroughly for their intended purpose, and that diagnostic personnel are aware of the limitations of the laboratory tests being used (Sandvik, 2004). Integrated use of diagnostic tests also includes diagnostic testing commissioned to external diagnostic laboratories, which should be accredited to perform the required tests, and participate in proficiency testing schemes to ensure adequate performance is maintained.

Integrated use of diagnostic tools in well-designed BVD control programmes may not only result in data necessary for identification of PI animals. If serological prescreening is carried out prior to BVDV testing of animals without or with low levels of antibodies, useful data on immunity to BVDV of individual animals will accrue. After removal of PI individuals, often 80-90 % of the remaining animals are antibody positive and immune. Since immunity after

natural infection lasts many years, and often the whole life of cows kept for commercial purposes, this knowledge is very useful for control programmes that use vaccination to supplement other biosecurity measures to prevent reinfection of the herd. If inactivated vaccines are used, it is significantly easier to follow up with more frequent revaccination of these than of the whole herd, since the immunity derived from use of inactivated vaccines may be insufficient to prevent transplacental infection with BVDV in animals at risk of infection (Laven et al., 2005).

1.9 Summary of research needs

1.9.1 Current BVDV genome information

1. Continued surveillance for novel BVDV variants (subtypes/escape mutants) is necessary. This is important to discover novel virus subtypes, or mutated known isolates that are not picked up by the diagnostic methods in use. Equally important is collection, analysis and circulation of information on such viruses to veterinary virologists and other scientists involved in BVD control programmes. This will also result in a better insight into genetic variability among both BVDV species. This activity should be organised by a reference laboratory for BVDV.
2. Basic studies into the genome replication mechanisms of BVDV, e.g. on the potential of antiviral drugs should be encouraged, since this theoretically can open up new approaches for control of BVD.

1.9.2 Strain typing and differentiation

1. The antigenic variability of different BVDV-1 and -2 viruses should be characterised further, with the aim to provide a better understanding of the cross protection from immunity to one virus strain against others. Studies on how antigenic diversity correlates to the genetic variability are also needed.
2. When escape mutant strains are discovered, they should be typed antigenically
3. Virus isolates from clinically unusual cases of BVD should be characterised.
4. Different protocols for genetic typing of BVDVs should be compared scientifically, with the aim to give recommendations for a standardised typing protocol.

1.9.3 Further development of diagnostic tests

Although many of the laboratory diagnostic tests available today perform very well, there is a constant need for improving the performance, and to specify the limitations of diagnostic tests.
1. For some ELISA tests intended used for routine diagnostics, there is considerable room for improvement of the diagnostic performance. Improvement of commercial assays will have to be done by the manufacturer, but often this requires collaborative studies with universities or research institutions.
2. The ability to diagnose some specific categories of BVDV infected animals should be improved. These include:
a) detection of PI calves with anti-BVDV colostral antibodies
b) detection of pregnant animals carrying PI foetuses
c) distinguishing between animals acutely and persistently infected with BVDV
d) reliable detection of BVDV in aborted foetuses
3. For serology, assays able to distinguish vaccinated and naturally infected animals need further development. Some antibody ELISAs also need to be calibrated better for more reliable detection of low levels of antibodies in seroconverting animals.
4. The performance of some RT-PCR methods may need improvement:

a) for reliable use on specific "difficult" sample materials, e.g. semen
b) to ensure detection of escape mutants and genetically diverse subtypes
c) ring tests for other pestiviruses have shown an unacceptable variation in the results
5. To improve the diagnostic capacity for the whole spectrum of BVDV subtypes known today, more monoclonal antibodies against selected viral proteins should be produced.

1.9.4 Standardisation of diagnostic tests

1. Reference virus strains and specific antisera relevant for BVD diagnosis within Europe should be produced and made available to national laboratoriess. This would best be managed by an EU Community reference laboratory for BVDV, which also should give guidelines on standardisation of diagnostic protocols.
2. Regular ring tests to monitor the performance of both BVDV serology, detection of BVDV by virus isolation, antigen ELISA and by RT-PCR should be established.

1.9.5 Integrated use of diagnostic tests in screening schemes

1. The over-all diagnostic performance of routine tests selected for combined use in control programmes need to be determined as accurately as possible.
2. Data on the combined diagnostic performance of RT-PCR on pools with subsequent antigen or BVDV detection in individual blood samples should be published.

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Table 1: List of diagnostic tests in use by network partner laboratories (anonymised, A-M), as per questionnaire circulated in 2003. 1 = test performed, 0 = not performed. Assays used by more than 50% of network countries are highlighted with a shaded background.

Diagnostic test \ Country	A	B	C	D	E	F	G	H	I	J	K	L	M	% in use
ELISA AB BTM	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**1**	**1**			**91**
ELISA AB pooled heifers	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**0**			**18**
ELISA AB pooled young stock	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**1**	**0**	**0**	**0**			**27**
ELISA AB individual animal	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		**100**
ELISA ag BTM	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**		**8**
ELISA ag pooled heifers	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**		**0**
ELISA ag pooled young stock	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**		**17**
ELISA ag individual animal	**1**	**0**	**1**	**0**	**1**	**1**	**0**	**1**	**1**	**1**	**1**	**1**		**75**
BVDV in cell cultures BTM	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**		**1**	**8**
BVDV in cell cultures pooled heifers	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**		**1**	**8**
BVDV in cell cult. pooled y. stock	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**		**1**	**17**
BVDV in cell cult. individual animal	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**1**	**0**	**1**		**1**	**83**
RT_PCR BTM	**1**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**			**27**
RT_PCR pooled heifers	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**			**0**
RT_PCR pooled young stock	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**1**		**25**
RT_PCR individual animal	**0**	**1**	**1**	**1**	**0**	**1**	**0**	**0**	**1**	**1**	**1**	**1**		**67**
Other samples tested	**Semen**	**0**	**0**	**0**		**0**	**0**	**0**	**0**	**0**	**0**			
Other assays				**SNT**			**IFAT**				**SNT**		**IPXIF**	

Table 2. Summary of results of a BVDV serology ring test - ELISA test results. Participating laboratories and assays are anonymised.

Serum identity :	**A**	**B**	**C**	**D**	**E**	**F**	**ELISA TYPE**
Serum status : Country	**Negative**	**BVDV-1 positive**	**BVDV-1 hyperimmune**	**BVDV-2 positive**	**Vaccinal AB - below detection limit**	**Vaccinal AB - low positive**	**Comm = commercial IH = in-house I = indirect, B = blocking**
1	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 1 - I*
2a	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 2 - B*
2b	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 3 - I*
3	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*POS.*	*In-house - B*
4	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*In-house - I*
5	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*POS. / Doubtful*	*Comm 1 - I*
6	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*Doubtful*	*Comm 3 - I*
7	*POS.*	*POS.*	*POS.*	*POS.*	*Doubtful*	*Doubtful / NEG.*	*Comm 4 - I*
8	*NEG.*	*POS. mod*	*POS. strong*	*POS. mod*	*NEG.*	*POS. weak*	*Comm 1 - I*
9	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*In-house - B*
10	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 1 - I*
11	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 5 - B*
12a	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 1 - I*
12b	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 1 - I*
13	*NEG.*	*Doubtful*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 6 - B*
14a	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*In-house - I*
14b	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 1 - I*
15	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG ./ POS.*	*Comm 1 - I*
16a	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 1 - I*
16b	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 7 - B*
17	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*Comm 1 - I*
18	*POS.*	*POS.*	*POS.*	*POS.*	*NEG.*	*Doubtful*	*In-house - I*
Ref. lab.	*NEG.*	*POS.*	*POS.*	*POS.*	*NEG.*	*NEG.*	*In-house - I*

Epidemiology and risks

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2.1 Executive summary

Due to the many different clinical manifestations, BVDV has often been seen as part of the production disease complex. However, we strongly recommend that BVDV is always considered and treated as a specific infectious disease. The risk that BVDV can "hide" under other conditions should always be considered, and this has implications for societal priority settings, such as a reduction in antibiotic usage and for improvement of animal welfare. Awareness regarding this fact has to be increased.

Today, there is convincing evidence that bovine viral diarrhoea virus (BVDV) can be controlled and even eradicated, also from high prevalence/density areas, if there is a systematic approach to do so. However, there are substantial differences between countries and regions that have to be acknowledged, both with respect to risk factors and to conditions in favour of successful control. In particular, the attitude towards uptake of biosecurity among stakeholders, researchers and decision makers seem to be a strong positive determinant, as is a low degree of fragmentation within cattle industries (often associated with the presence of cooperative structures) and a trusting relationship between industry and authority decision makers. A thorough analysis of the geographical diversity in this respect is essential for improving the planning of future control and eradication efforts, and should be incorporated into socio-economic and feasibility studies.
BVDV is one of many infectious diseases where the main driver is livestock movements/contacts and where attitudes/traditions among stakeholders have to be targeted to reach disease control objectives. Expert opinion within the network suggest that if livestock movements/animals contacts were under control, close to 95% of new BVDV infections would be eliminated. An additional benefit from controlling, re-routing and/or reducing animal movements is an increase in the ability of a livestock system to cope with introduction of epizootic disease. Thus, BVDV control have features that make it a strong candidate for research on improved biosecurity and disease control at a European level. In fact, the European experience with BVDV control is of more general interest and could serve as a template for guidelines on how to manage endemic diseases with an industry driven epidemiology.
The amount of data available from countries that have eradicated BVDV, together with its general European relevance, provides an excellent opportunity for the development of generic within- and between-herd transmission models, suitable for assessing the impact of control measures under different conditions. This is yet another way in which BVDV could serve as a model for infectious diseases, in particular those that share similar risk factors. Such research should preferably be fostered in a suitable research environment, such as a Centre for

Epidemiological Research on Infectious diseases, where precollected data could be stored, merged and made accessible for researchers.

2.2 Recommendations

a. BVDV should always be considered and treated as a specific infectious disease. The risk that BVDV can "hide" under other conditions should always be considered, and this has implications for societal priority settings, such as a reduction in antibiotic usage and for improvement of animal welfare. Awareness regarding this fact has to be increased.

b. Whenever BVDV control is an issue, the European community should state that systematic control is the way forward if sustainable results and long-term effects are desired. At current, there are no principal or biological obstacles to allowing approaches with or without use of vaccination to co-exist in Europe or even within countries, but implementation should be systematic.

c. A comprehensive herd level survey to assess BVDV status across Europe should be performed. Monitoring systems should be set up so that incidence of BVDV infection can be estimated in regions of Europe currently without systematic control, so that more accurate estimates of the potential of control measures in reducing risk of introduction can be obtained.

d. Future design and implementation of BVDV control strategies should build upon local expert knowledge of the region- and country-specific risk factors for BVDV introduction and reasons for BVDV persistence in infected herds. We need better understanding of the variation in biosecurity attitudes among stakeholders within Europe, as well as the effect of different means for amending them, because these are strong determinants for the prospects for successful implementation. In fact, BVDV control share biosecurity focus areas with many other infectious diseases among livestock, including CSF, IBR and even FMD. Therefore, we recommend that more research is targeted towards this area and that BVDV control is used as a model for developing biosecurity and disease control at the European level.

e. The European community should support research where precollected data are joined across countries, to increase the power of the analyses and to make the results more applicable to the community as a whole. A Centre for Epidemiological Research on Infectious diseases should be established, where such data are stored, merged and made accessible for researchers.

f. Epidemiological models of within-herd transmission are valuable tools to study the opportunity of BVDV control programmes in the very different epidemiological contexts that exist for BVDV in Europe, and their use should be encouraged. Models for dairy herds are available, but should be further used to study possible effects of control schemes at the herd level. Results from dairy models cannot be extrapolated to beef herds and the one existing model should be refined for this production system. Stochastic models are preferred. Models should take account of the contact structure in a herd, and represent possible horizontal transmission by transiently infected animals. To improve existing models, experimental or field information need to be

produced to justify assumptions for mathematical modelling on the force of infection and to estimate transmission parameters.

g. Models describing between-herds transmission dynamics of BVDV infection should be developed, where the impact of different control strategies can be quantified. Countries with systematic control programmes should be encouraged to share data for this purpose with the scientific community. Also here, BVDV could serve as a model for infectious diseases sharing the same risk factors.

h. The European Union should support the development of OIE sanctioned guidelines on how to manage diseases like BVD (and also IBR/IPV), i.e. diseases where there is sufficient information to state that a significant reduction of the prevalence can be achieved and maintained in a cost-efficient manner. The EU should also promote, for reasons of coherence, that a chapter for BVDV in the Terrestrial Code is developed. For the purpose of such a chapter, there are detailed recommendations on relevant demands in section 2.7.4.

i. There is a need to clarify if and how live and/or killed vaccines against BVDV and other agents are to be allowed at EU approved bull stations. In our opinion, although bulls vaccinated against BVDV can be allowed to enter, further vaccination is not necessary and should not be allowed at EU approved bull stations. The text in the current directive on intra-Community trade in and imports of semen of bovines (Council Directive 2003/43/EC) does not take a position on this item.

j. The risk of spreading BVDV through iatrogenic means (contaminated injectables, including vaccines) should be thoroughly considered when choosing strategy for an extension of BVDV control to a larger scale (region/nation).

k. There should be more focus on the risk of spreading BVDV through contaminated biologicals, in particular products associated with bovine fetal serum. The EU should promote bovine fetal sera used for e.g. vaccine and embryo production to be sourced from herds, regions and countries that are free from BVDV.

l. Molecular epidemiology should be further investigated with respect to its usefulness in tracing sources of new infections, in parallel with traditional methods. Routines for tracing new infections should be considered early on in the planning of future control schemes.

m. There is a need for continuing research into the various ways by which BVDV can survive and be transmitted between animals and herds, including potential reactivation of latent virus.

n. The significance of differences in virulence on occurrence of clinical manifestations and production losses, as well as the prevalence and effect of co-infections are important areas for future research.

o. Researchers designing prevalence surveys should use measures that have a true epidemiologic meaning in terms of presence/absence of infection, and consider the risk of animal/herd misclassification inherent in test strategies based on serology.

2.3 Objectives

The overall objective of work package 2 of the BVDV control network has been to compile and evaluate the current knowledge on BVDV epidemiology and risk factors of relevance to BVDV control, with special reference to the European situation.

More specifically, the objectives were as follows:

- To evaluate risk factors for BVDV and their relative importance in different regions
- To evaluate methods for identification of risk factors in the late phase of control
- To evaluate the risk of re-infection in freed areas
- To evaluate health and production effects of BVDV under different production settings
- To evaluate methods for infection dynamics modelling and identification of information necessary for improving the epidemiological models
- To establish a system for collecting information on BVDV data sources in Europe
- To evaluate the research potential in joining BVDV information within Europe

This work was made possible by the ability to access both published and unpublished data/information as well as expert opinion available within the network.

2.4 Background

Infections with bovine viral diarrhoea virus (BVDV) are endemic in cattle populations in most parts of the world. The high prevalence in combination with the negative effects on reproduction and general health condition in affected herds result in significant economic losses to the cattle industry globally (Houe, 2003).
Consequently, attempts to control or even eradicate the infection by different means have been explored.
The key to BVDV control is to prevent foetal infections in early gestation; i.e. interfere with the process by which persistently infected (PI) individuals are generated (Coria and McClurkin, 1978, Done et al., 1980, McClurkin et al., 1984). The two main strategies have been directed towards a) vaccination and b) zoo-sanitary control (Bitsch and Rønsholt, 1995, Bolin, 1995). The latter refers to when exposure to the agent is avoided by biosecurity measures.
In this context, it has been common practice to talk about vaccination versus zoo-sanitary control, because these have been the main two directions of development. However, in the following we will divide strategies into non-systematic and systematic, respectively. The former refers to any measures implemented on a herd-to-herd decision basis (i.e. where there is no coordinated effort and no benefits from simultaneous actions in multiple herds); typically these have involved immunization strategies using live or killed vaccines as well as test-and-slaughter of PI animals but without any systematic follow-up or monitoring of the outcome. Systematic control implies a goal-oriented reduction in the incidence and prevalence of BVDV infections, typically implemented on a sectoral/regional/national level, where the progress is being monitored so that the effectiveness of the measures in place can be evaluated (Lindberg and Alenius, 1999). Up to date, such schemes have been based on non-vaccination approaches, but programmes are underway that will also involve an optional vaccination step (Moennig et al., 2004). The former will be described in this paper whereas

the latter is discussed in more detail in the report from Work Package 3 of the Thematic network (Moennig and Brownlie, 2006).

Systematic control implies that three items are in place; 1) a biosecurity framework, 2) procedures for virus elimination in infected herds and 3) surveillance. The foundation is biosecurity, which involves *all measures aimed at reducing between-herd transmission*, but with strong emphasis on preventing contacts with/movements of PI animals and dams carrying such foetuses. The second measure (applicable to infected herds only) is virus elimination by systematic removal of PI animals. The third measure is surveillance. Surveillance is fundamental for evaluating the effectiveness of the measures implemented. Also, so far there are no biosecurity frameworks that are 100% secure, which is why there will be a need to quickly detect if there are breakdowns.
In this context, vaccination is regarded as an optional biosecurity item and thus, investments in vaccines are additional to the costs associated with any other necessary biosecurity measures, virus elimination and surveillance. Vaccination alone, without the three other items in place, is not considered systematic control.
It should be noted that non-systematic control approaches have been used for decades without any noticeable effect on prevalence of BVDV infections. In contrast, systematic control schemes have resulted in BVDV being close to eradicated in those European countries that have implemented them, within a time frame of 10-15 years.

2.4.1 BVDV control in Europe

The Thematic network has gathered information on how BVDV control activities are carried out within participating countries. From the enquiries performed within the network it can be seen that in most parts of Europe, BVDV control is at current non-systematic and by vaccination. Of the countries that use vaccines, the UK, Ireland and The Netherlands only have killed vaccines licensed. The Scandinavian countries, Austria and Slovenia provide an exception to the general picture as they have no vaccines licensed. The Scandinavian countries and Austria have large regional or national systematic eradication schemes in place where vaccines are not employed. The first systematic programs aimed at eradicating BVDV without the use of vaccines were launched in 1993-1994 in Denmark, Finland, Norway and Sweden. Despite different preconditions in terms of legal support, and with initial prevalences of herds with PI animals varying from <1% in Finland to 50% in Denmark it has taken all countries approximately 10 years to reach their final phases (Hult and Lindberg, 2004, Nyberg et al., 2004, Rikula et al., 2004, Voss, 2004). In Austria, the outline of the scheme has followed the Scandinavian model, and after seven years as a regional project (involving the Lower Austria region) the scheme was extended to the entire country in 2004. Today, approximately 30% of all herds in Austria are certified as being free from BVDV (Rossmanith et al., 2004).

Systematic control efforts have also been implemented to a varying extent in other parts of Europe, such as on the Shetland Islands where BVDV has been eradicated (Synge et al., 1999), and in Brittany in France (Joly et al., 2004), in The Netherlands (Moen et al., 2004) and in Germany (Moennig et al., 2004). Time-limited, project type control efforts have also been implemented in the Rome area, and in the Lecco and Como regions of Italy (Ferrari et al., 1999, Luzzago et al., 2004). Although vaccines are available in all these countries, all programs except for the one in Germany, are based on non-vaccination approaches.

2.4.2 Experiences from ongoing systematic control schemes

The ways in which current systematic schemes are constructed and organised differ quite a lot (Sandvik, 2004). This is partly due to differences in the initial prevalence of the countries that have implemented them, but perhaps more to the structure of the cattle industries, economic preconditions and varying willingness of authorities to provide legal support for the schemes (Lindberg, 2004). There are, however, some general technical characteristics of the programs. They all have an initial step where non-infected and infected herds are identified, using different combinations of serological herd tests such as bulk milk tests and spot tests (sample of animals in a certain age group). Non-infected herds are monitored by repeated sampling, applying one of the above-mentioned methods and infected herds are cleared from the infection through a systematic removal of PI animals. Also, for all schemes there is a regulatory framework for disrupting the major routes of BVDV transmission between herds. The principles of non-vaccination eradication schemes, as well as the basis for priority setting regarding transmission risks are described in detail elsewhere (Lindberg and Alenius, 1999, Lindberg and Houe, 2004). Also, Appendix 1 provides in-detail information about the schemes in Austria, Denmark, Finland, the Netherlands, Norway and Sweden, submitted by the partners in the Thematic network.

2.4.2.1 Progress of systematic large scale approaches to control BVDV

2.4.2.1.1 Non-vaccination approaches

The progress of the Scandinavian schemes in terms of reductions in prevalence and incidence are shown in figure 1a and b.

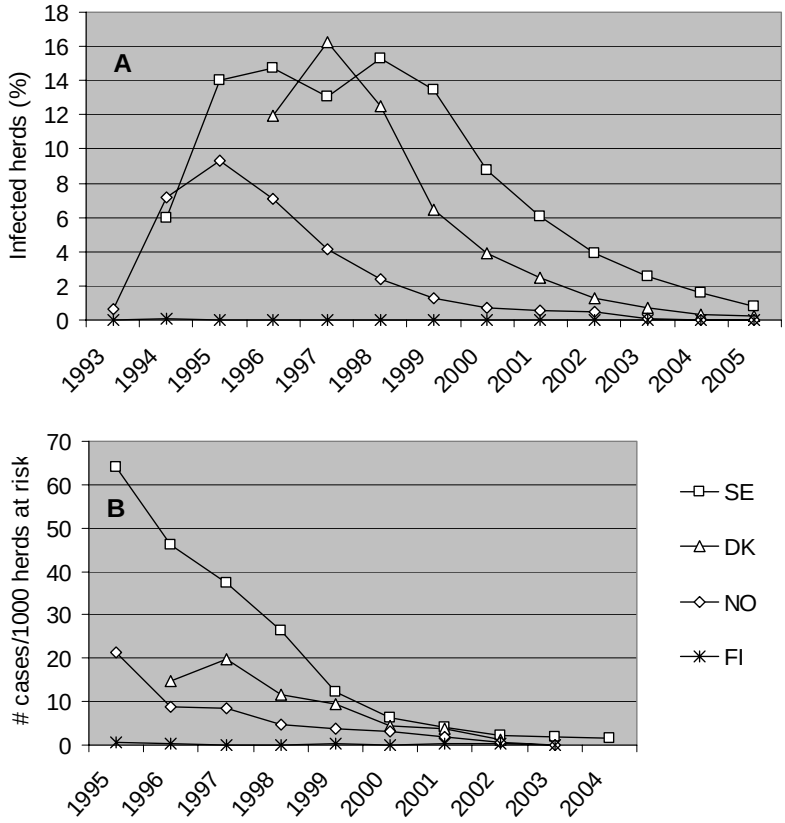

Figure 1a and b. Prevalence of infected herds in the systematic eradication schemes in Denmark, Norway, Sweden and Finland, 1993-2005 (A). B shows the incidence of new herd infections in the same schemes, 1995-2004. Case definitions for prevalence and incidence calculations are given in Appendix 1.

It has been suggested that factors like herd size, herd density and initial prevalence should influence the choice of control strategy (Greiser-Wilke et al., 2003). However, in contrast to what could be expected, the progress of current non-vaccination schemes has been faster in areas where the initial prevalence and the herd density was/is high, e.g. in Denmark and South-East Sweden, than in low-prevalence areas like Finland and Northern Sweden (Lindberg, 2004). So, although the above-mentioned factors may be associated with BVDV infection in areas without control, they are not necessarily major obstacles to eradication. Instead, awareness about BVDV in general, and motivation to adopt good biosecurity practices in particular, seem to be of greater importance. The prospects for reaching a high level of motivation tend to be higher in high density areas than in low density areas, because risk awareness among stakeholders is higher. Synchronicity is also a powerful tool. Simultaneous measures within an area can have a major impact on the incidence of new infections, irrespective of the initial prevalence and herd density (Bitsch and Rønsholt, 1995, Lindberg, 1996)
In other words, it is the way in which control activities are organized and implemented that will determine the progress. An example is the comparison between Denmark and Norway, where the initial prevalence of dairy herds with recent or ongoing infection in the countries was 40 and 9% respectively, but where both countries will have finalized the eradication after approximately 11 years of activity (Nyberg et al., 2004, Voss, 2004).

2.4.2.1.1 Vaccination approaches

Vaccination has been, and is, fairly commonly used in Europe, on a herd-to-herd decision basis(Moennig and Brownlie, 2006). However, it should be noted that to date, there is limited experience with using vaccines in a systematic large scale scheme context. Germany is in the process of launching a national scheme based on such a design, but results about the effect on prevalence and incidence are still to be reported.

2.4.3 Recommendations

There is a solid mass of information supporting that BVDV can be controlled and even eradicated if there is a systematic approach to do so. Most evidence is from areas where no vaccines are used, but the general systematic approach can easily be combined with vaccination as an additional biosecurity measure. There are no principal or biological obstacles to allowing these approaches to co-exist in Europe or even within countries as long as they are implemented in a systematic manner. We strongly suggest that whenever BVDV control is an issue, the European community should state that systematic control is the way forward if sustainable results and long-term effects are desired.

2.5 Risk factors for BVDV infection and their relative importance in different regions

In this section we discuss not only risk factors, but also means to mitigate them, in the systematic control context.
The term “risk factors” is used for factors or circumstances that are associated with increased probability of having BVDV infection. They can be present at any level of hierarchy, from individual to herds, region or even country. For BVDV control it is relevant to consider risk factors from the herd level and higher.

Means to mitigate between-herd spread of BVDV can be summarized in terms of necessary and desirable biosecurity measures. The additional benefit on biosecurity gained by upscaling control measures are discussed further at the end of this chapter.

2.5.1 Risk factors for the presence of BVDV under endemic conditions

By nature, risk factor studies found in the literature vary considerably in design and also in relation to which infection measure is used. Therefore, one should be careful in trying to generalize the size of measures of risk factors. Still, some are repeatedly identified and should be the ones of most general interest.
Documented risk factors under endemic conditions and in a European setting include (without priority): herd size, mean distance to neighboring herds, number of infected neighbors, having heifers on common pasture, over-the-fence contacts on pasture, purchasing animals without BVD documentation, not using dairy advisors, being in a high prevalence area and the length of time period the herds has been enrolled in systematic control (Table 1). In addition there have been some indications of the following circumstances being potential risk factors: sheep on pasture with cattle, breaking through pasture fences, veterinarians re-using needles, wild animals on pasture, beef and milk versus only milk production, calves on forest pasture, and others (Houe et al., 1997; Houe 1999; Valle et al., 1999; Houe, 2005).
Some of the identified risk factors are likely to be proxies for other risks factors/behaviors. Thus, a higher risk among larger herds may be due to larger herds buying more animals and/or its larger contact surface in terms of number of animals/frequency of visitors. Similarly, “not using dairy advisors” and “not being enrolled in systematic control” are likely to be proxies for level of awareness of BVDV biosecurity issues and/or degree of risk behavior in this respect.

Many of the identified risk factors are likely to interact with the infection level in the area where the factor is present or the behavior/event takes place, being more important in high prevalence areas than in low prevalence areas. Examples of such risk factors are mean distance to neighboring herds, putting heifers on common pasture, over-fence contact on pasture and purchasing animals without BVD documentation. Some studies have also directly identified infection level in the area as being significant (“number of infected neighbors”/ “being in a high prevalence area”).

Most risk factor studies have been performed at the herd level and very few studies have compared different regions. There is one meta-analysis of several prevalence surveys that indicates that cattle population density is an important risk factor for the infection level in an area under endemic conditions (Houe et al., 2003).

2.5.2 Regional differences in importance of BVDV risk factors

As is evident from the success of systematic control schemes, the principal sources of BVDV infection and the reasons for its persistence in infected herds are well known. However, the relative importance and impact of different risk factors is likely to vary between herds and regions and depend on livestock management and any specific BVDV-control measures in place. A study was performed within the Thematic Network to highlight regional risk factors in this respect. The study and its results are presented in section 2.5.2.1 – 3. In addition, data on transboundary movements of cattle (from Eurostat) were provided by Switzerland. These are presented in section 2.5.2.4.

Table 1: European studies on risk factors for presence of BVDV at the herd level (cross-sectional/case-control type studies).

Country/ region	Risk factor	Outcome variable	Measure of association	Number of animals/ herds	Size of measure of association	Reference
Norway	Heifers on common pasture	Herds with AB pos young stock .	OR	292 herds	5.1 (CI 1.97-13.19)	Valle et al., 1999
Norway	Over-the fence pasture contacts	Do	OR	279 herds	2.5 (CI 1.31-4.71)	Do
Norway	Purchase without BVDV documentation	Do	OR	160 herds (Subset of herds that had purchased animals)	5.4 (CI 2.01-14.5)	Do
Norway	Not using dairy advisors	Do	OR	314 herds	4.1 (1.86-8.96)	Do
Norway	Other animal traffic (exchange of calves, common summer housing)	Do	OR	314 herds	28.6 (CI 3.23- 252.22)	Do
UK	Herd size	High antibody level in bulk milk	OR (per additional cow)	1070 herds	1.0025 (1-1.005)	Paton et al., 1998
Denmark	Herd size	Presence of PI animals vs. none	OR (per 10 cows)	> 8000 herds	1.09 (CI 1.06-1.11)	Ersbøll & Stryhn, 2000
Denmark	Mean distance to neighbours	Presence of PI animals vs. none	OR (per 500m)	> 8000 herds	0.87 (CI 0.81-0.93)	Do
Denmark	Number of infected neighbours	Presence of PI animals vs. none	OR (for >= 3 inf. Neighbours vs. none)	> 8000 herds	1.54 (CI 1.17-2.02)	Do
Sweden	High prevalence of BVDV in the area	Presence of PI animals vs. none	OR	800 herds using ET	1.73 (CI 1.21-2.47)	Lindberg, 2003
Sweden	No. of years not enrolled in systematic control (during the study period)	Presence of PI animals vs. none	OR (per year)	800 herds using ET	1.39 (CI 1.25-1.56)	Do
Sweden	Herd size	Presence of PI animals vs. none	OR (per additional cow)	800 herds using ET	1.008 (CI 1.005-1.011)	Do

2.5.2.1 Materials and methods

2.5.2.1.1 Questionnaire design

A one-page questionnaire with mutually exclusive questions was designed by the network epidemiology work group based on scientific knowledge of BVDV transmission routes, dynamics of infection and eradication from infected herds (see Annex 2).
The following routes of introduction were considered: (i) buying persistently and transiently infected cattle and healthy cows bearing an infected foetus, (ii) contact with infected cattle from other herds at pasture, markets and shows or during transportation, (iii) contact with infected wildlife, (iv) man or man-related introduction of BVDV, through contaminated clothes, drugs, semen and embryos and (v) other means. Similarly, reasons for BVDV being maintained in infected herds were that (i) either the farmer was not aware he/she had a BVDV problem in the herd or because (ii) in spite of acknowledging having a BVDV-problem he/she did not have or seek veterinary advice. It was also considered that BVDV could be mintained in herds using BVDV-vaccines, and that the reason for maintenance in such herds would be that the farmer believed he/she did not have to take any other measures to control the infection.
Additionally, a number of questions regarding difficulties leading to a prolonged clearance period during implementation of systematic control were included for the Scandiniavian countries.

2.5.2.1.2 Questionnaire presentation and distribution within the network

Members of the network were asked to complete at least one questionnaire with data relevant to dairy and/or beef herds in their country from specific BVDV-studies and/or expert opinions.
For large countries and more generally, for countries with diverse cattle production systems, data could be collected from each region or type of dairy and beef production system if considered necessary. Moreover, representatives of the Scandinavian countries were asked to complete separate questionnaires to describe their situation before and after BVDV control was initiated.

2.5.2.1.2 Data analysis

For countries where estimates from several regions were given, country weighed average values were obtained taking into account the regional cattle census. Data from specific countries and regions were incorporated in a table and frequency distributions were calculated with data from each specific question in the questionnaire.

2.5.2.2 Results

2.5.2.2.1 Response rate

All countries participating in the network returned at least one completed questionnaire and answers to questions were based on qualified guesses/expert opinion in all cases except the questionnaires from Portugal (region Entre-Douro e Minho) and from Anatoliki Makedonia, Thrakia in Greece, whose estimates were based on quantitative studies.
The Netherlands, Northern Ireland, Republic of Ireland, England & Wales, Scotland, Norway, Luxembourg, Switzerland and Slovenia returned one questionnaire summarising the present/recent national situation for dairy and beef herds. Germany, Portugal, Austria and France completed one questionnaire each, providing regional data for dairy herds in Lower Saxony, Entre-Duoro e Minho, Lower Austria and Brittany, respectively. Lower Austria has an ongoing eradication scheme and information from this country was from after the scheme was implemented. Similarly, Brittany has systematic control in place but the information

referred to 1999-01 prior to the start of the control schemes. Italy returned two questionnaires describing the present regional situation for dairy herds in Lazio and the Northeast (Veneto-Friuli, Venezia, Giulia and Trentino Alto Adige). Greece completed eleven questionnaires for dairy cattle in six regions (Anatoli Makedonia & Thraki, Kentriki Makedonia, Thessalia, Ipeiros, Sterea Ellada and Attiki) holding 70% of the cattle in the country. Spain returned twelve questionnaires from 10 Autonomous Communities (Galicia, Asturias, País Vasco, Cataluña, Castilla-León, Castilla-La Mancha, Extremadura, Andalucía, Valencia and Murcia) with 85% of the country's cattle. Belgium provided two questionnaires for all herds in the south and north of the country. Denmark and Finland completed two nation-wide questionnaires reflecting the situation of beef and dairy herds before and after implementing the national BVDV control schemes. Sweden returned two questionnaires from each of 11 regions covering the whole country and corresponding to the areas served by all regional livestock cooperatives, with data relating to the situation before and after implementing the national control scheme.
Data collected with the questionnaire is summarised below. Values for Greece, Spain and Sweden represent regional average weighed values and data from Belgium is the arithmetic mean of the values for North and South Belgium.

2.5.2.2.2 Risk factors associated with introduction of BVDV into uninfected herds under endemic conditions

The relative importance of different risk factors for introduction of BVDV into uninfected herds, under endemic conditions, is shown in figure 2. The outcome for each of the risk factors considered is also discussed in more detail below.

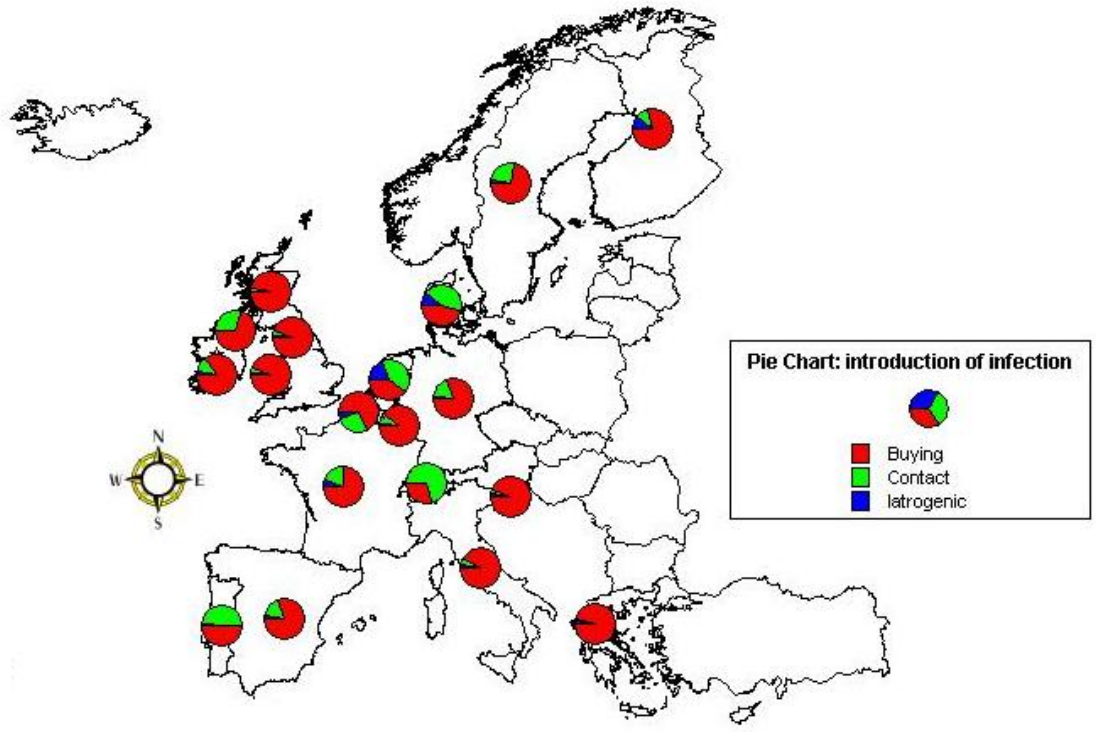

Figure 2. Expert opinion regarding the relative importance of different risk factors for introduction of BVDV into uninfected herds in European countries under endemic conditions.

2.5.2.2.2.1 Buying infected cattle

In countries where BVDV is or was endemic (before systematic control schemes were in place), buying persistently infected cattle, including cows pregnant with infected foetuses,

was perceived as being the single most important risk factor in all countries except for Switzerland, Holland and Denmark.

The overall relative contribution of this risk factor was 74%. However, there were differences between countries and regions. It was ≥90% for Italy, Luxembourg, Great Britain, Greece and Slovenia, but only 40-50% in Denmark, Netherlands, Switzerland and Portugal. In Brittany, where the estimated relative importance of buying infected cattle was 85%, almost one third of the risk associated with farmers buying-in veal or young bulls for fattening in separate units on dairy farms.

2.5.2.2.2.2 Contact with infected cattle from other herds

Direct and indirect contact with persistently infected cattle from other herds at pasture, markets and during transport was considered overall to account for 22% of cases of introduction of BVDV infection into previously uninfected herds under endemic conditions. It was perceived as the most important risk factor in Switzerland, accounting for 70% of cases. In the Netherlands, it was considered to be of similar importance as buying infected cattle. There, as well as in Belgium, N. Ireland, Portugal, Sweden and Denmark it was believed to account for 22-49% of new cases. However, it appears to be a risk factor of relatively less importance in Greece, Italy, Great Britain and Slovenia where it is considered to account for <1-5% of cases.

2.5.2.2.2.3 Contact with PI wildlife

The risk of introducing BVDV to previously uninfected herds through contact with infected wildlife was considered to be very low, accounting for between 0-2% of all cases.

2.5.2.2.2.4 Iatrogenic and passive man-related transmission

Man-related introduction of BVDV to uninfected herds through BVDV contaminated equipment, clothes, drugs, semen and embryos was considered to account for, overall, 4% of cases of introductions into previously uninfected herds. In most countries its relative importance was between 1-6%, except in Northern Ireland where it was considered to be negligible and Belgium, Denmark, Finland, and the Netherlands were it was perceived to be as high as 10-20%.

Among modes of iatrogenic and other man-transmitted infection, the route of highest importance was considered to be transmission through clothes and instruments followed by introduction via contaminated vaccines and other drugs. However, AI and ET, including such equipment, are considered to be responsible for 80-90% of all man-related cases in North Belgium and in dairy cattle in Lower Saxony, 30-50% in Finland, Netherlands and Norway and in Scania in Sweden before the eradication schemes were in place. Among other modes of iatrogenic infections, blood transfusions could account for 1% of introduction of infection into previously BVDV free herds in Asturias in Spain.

2.5.2.2.2.5 Other means of BVDV introduction to uninfected herds

No other risk factors were considered relevant in most countries except in Denmark, Norway, and some regions of Spain and Sweden where up to 10% of cases are attributed to unknown reasons and/or could not be traced back to any of the above mentioned risk factors. Castilla La Mancha in Spain considered insects as possibly responsible for some cases.

2.5.2.2.2.6 Risk factors associated with introduction of BVDV into uninfected herds in areas with systematic control

The relative importance of risk factors for introduction of BVDV into previously free herds is not perceived to have changed in Sweden and Finland after implementation of eradication

schemes, although the numbers have decreased. In Denmark and Norway, however, buying infected animals is relatively less important today than other direct animal contacts. Passive introduction of BVDV by humans are perceived to account for 40% and 20% of the new cases, respectively, and and 10% of cases in Denmark have an unknown origin (Table 2). The distribution of risk factors in Lower Austria after the control scheme was implemented is very similar to what is reported from Sweden.

Table 2. Perceived relative importance of risk factors for introduction of BVDV into previously uninfected herds in Sweden, Denmark and Finland before and after control schemes, and Norway and Austria after the scheme was implemented.

	Sweden		**Denmark**		**Finland**		**Norway**	**Austria**
Risk factor	*before*	*after*	*before*	*after*	*before*	*after*	*after*	*after*
Buying infection	71	74	40	5	80	80	25	60
Other direct animal contacts	26	22	40	55	10	10	70	20
Wildlife	1	1	0	0	0	0	<1	<1
Man-related	3	2	10	40	10	10	20	2
Unknown			0	10				

2.5.2.2.4 Reasons for the maintenance of BVDV in infected herds

The relative importance of different reasons for maintenance of BVDV in infected herds, in areas where there is no systematic control, is shown in figure 3.

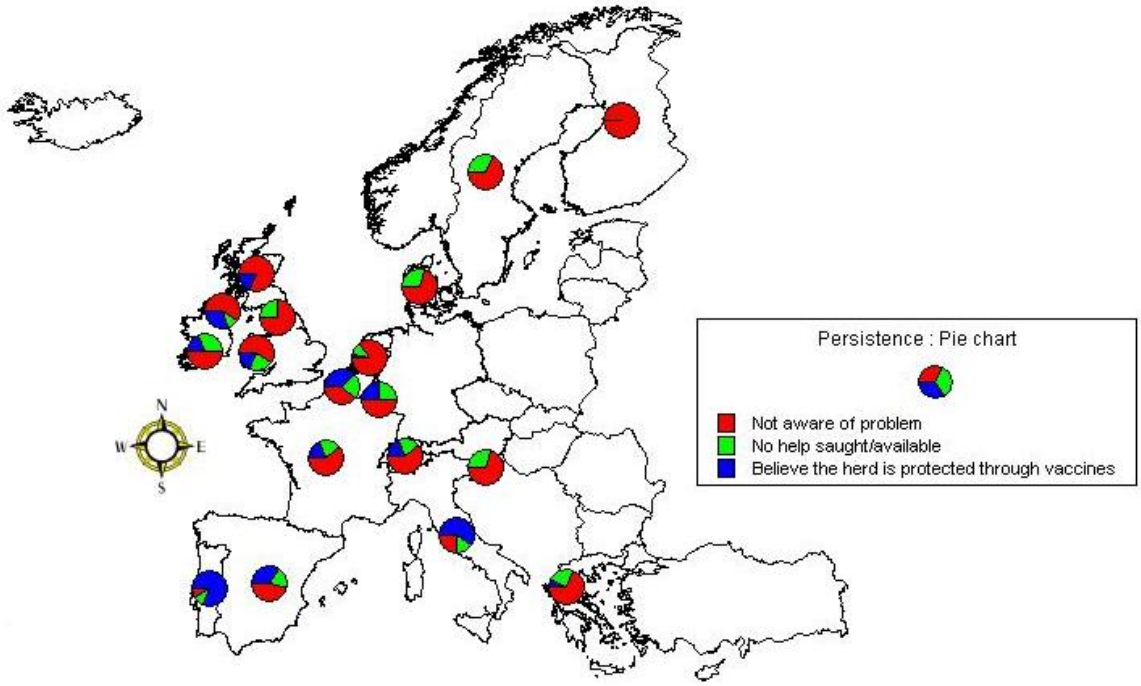

Figure 3. Expert opinion on the relative weight of different reasons as to why BVDV is maintained in infected herds in European countries, under situations when there is no systematic control.

Where no national control schemes are in place, almost 60% of the cases of BVDV persisting in infected herds is attributed to the farmer not recognising a BVDV problem. However, farmers acknowledging a BVDV problem but not seeking or finding good veterinary advice, and failure to achieve protection through vaccination (for countries where vaccines are used)

were similarly important and accounted for approximately 20% of BVDV maintenance in infected herds. However, there were important differences between countries and regions. For example failure of vaccination programmes represented 40-80% of cases in North Portugal and Lazio and Northeast Italy while it was considered to account for 0-7% of cases in Netherlands, Slovenia and Greece. In Switzerland, 50% of the cases where BVDV is being maintained are assessed to be associated with buying and raising veal calves leading to repeated introduction of the infection.

Following the implementation of BVDV control schemes in Scandinavia, problems with BVDV being maintained were mostly associated with lack of farmer co-operation. In Norway, in the very few herds were infection persisted for longer than normal, it was due to diagnostic test problems. Diagnostic test problems were otherwise only a minor reason (0-<6%) in the other Scandinavian countries (Table 3). Lack of farmer co-operation in the form of failure to arrange appointments for testing was the main reason for BVDV maintenance in Finland and in some regions in Sweden, whereas farmers not following veterinarians advice on biosecurity was the overall most important reason Sweden, of similar weight as unknown indirect transmission routes in Denmark. Biosecurity breakdowns in Sweden were most often associated to farmers being unable to understand or take-in the advice and in some cases to unknown modes of BVDV transmission. Finally, even when farmer co-operation is good, the experience was that it may be more difficult to clear infection from large herds or herds where virus transmission is slow.

Table 3: Reasons for BVDV being maintained in Scandinavian herds longer than necessary, after implementing control schemes.

Risk factor	**Relative contribution %**			
	Sweden	Denmark	Finland	Norway
Farmer does not recognise a BVDV problem	21	0	0	0
Farmer recognises a BVDV problem but does not seek advice	4	0	0	0
Other reasons	75	100	100	100
Farmer fails to arrange visits	*32*	*20*	*98*	*10*
Farmer does not follow advice	*50*	*40*	*1*	*20*
Diagnostic problems	*2*	*0*	*1*	*70*
Biosecurity failure	*9*	*0*	*0*	*0*
Technical problems	*4*	*0*	*0*	*0*
Unknown & bad luck	*2*	*40*	*0*	*0*

2.5.2.3 Discussion

In countries where BVDV is endemic and no systematic control schemes are in place, the experts responding to this questionnaire suggest that the main risk factor for BVDV introduction into previously non-infected herds is buying infected cattle and cows bearing persistently infected foetuses. Contact with infected wildlife was considered of minor importance in all countries and regions. Furthermore, the overall expert opinion on why BVDV persists in herds in endemic areas is lack of awareness among farmers regarding the infectious status of his/her herd, and consequently, failure to seek advice. Experts from countries where vaccines are available also highlighted the problem with farmers using BVDV vaccines, believing the herd is protected against BVDV infection and thus failing to implement necessary basic biosecurity routines and also failing to remove ongoing infection.

These results clearly confirm experience from countries where national BVDV control Schemes are in place, that in addition to appropriate legislation to regulate animal trade, cornerstones of successful eradication schemes include education of farmers and veterinarians about BVDV infection, biosecurity and vaccine use and providing the support to implement appropriate measures. Indeed, the observation that BVDV persists in some herds where vaccines are used might be further evidence of the difficulty of achieving adequate protection through vaccination, the risk that farmers that use vaccines do not realise the need to maintain biosecurity and possibly, the chance that vaccine virus may circulate within the herd.

The results obtained from countries with ongoing national eradication schemes indicate that buying infected cattle and contact with cattle from other herds remain the most important risk factors for introducing infection into previously BVDV free herds. However, there were considerable differences between countries. The overall distribution of risk factors before and after the scheme did not change for Sweden which was in contrast to Denmark and Norway. In the latter, it is perceived that buying infected cattle has become less important than other contacts after implementation of the schemes. If this observation is correct, it could be related to design of the schemes. Differences in terms of measures aimed at educating stakeholder about BVDV could affect farmers' attitudes towards buying and selling cattle and more generally their attitude and understanding of the control scheme. The experts from Denmark and Norway also considered iatrogenic infection and the use of BVDV contaminated drugs to be an important risk factor. This highlights that correct information at all levels is a key aspect to disease control.

2.5.3.4 Transboundary movement of cattle within Europe

In order to assess the magnitude and regional variation in the major risk factor for BVDV transmission between herds - livestock trade - the network decided to analyse data on transboundary movements of cattle from 2003 and 2004. The data were provided by Switzerland, but were originally sourced from Eurostat.
Figure 4 shows the import for all countries in 2004. In that year, 3.4 million cattle were exported/imported among member states. Using 1.5% as an estimate of PI prevalence, close to 52 000 PI animals were moved. Countries highly challenged in this context were Italy, The Netherlands and Spain, to a lesser extent France, Germany, Belgium and Greece. Of the countries that have a low prevalence as a result of systematic control, only Denmark has a developed a significant net export.

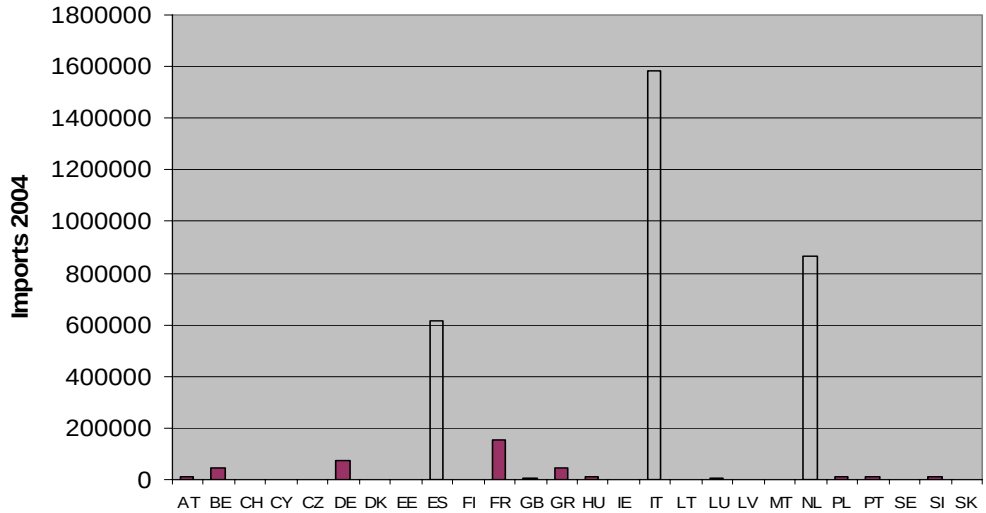

Figure 4. Imports of cattle from other EU member states during 2004. *Source: Eurostat*

These data do not provide information on the intensity of livestock trade within countries, and notably, a large proportion of these animals were for slaughter and may not have been introduced into farms. However, the data is still provides an idea on the potential of transmission and the regional variation in this respect.

2.5.3 Biosecurity in the systematic control context

Biosecurity in systematic BVDV control involves all measures that serve to prevent between-herd transmission. This very broad definition suggests that there is more to biosecurity than what is done on the farm to prevent introduction of the virus, although this is where the basic biosecurity measures have to be implemented. More specifically, we suggest that the concept of biosecurity, as it relates to systematic BVDV control, includes both the formal regulations (compulsory rules or voluntary guidelines), the level of stakeholder awareness (provides incentives to comply) as well as the ability to access to information on BVDV status (facilitiates compliance). The latter involves everything from sampling routines, laboratory procedures to means for transferring BVDV status information to those that need it for decision making.

2.5.3.1 Regulations

Regulations (voluntary or compulsory) provide the formal framework that outline what practical measures are required to break transmission between herds (including any additional use of vaccines). Measures that are obligatory in the regulations will often be equivalent to the basic biosecurity level. A list of risk factors that may have to be considered in a regulatory framework is given in table 4. The regulations also outline what tests need to be made to obtain and sustain a BVD-free status.

2.5.3.1.1 Voluntary vs compulsory

It is fully possible to reach good progress of the control on a voluntary basis (without legally supported sanctions) if stakeholders are sufficiently educated and motivated, and this may be a way forward during the initial stages. Also, for eradication on a sectoral basis (dairy/beef/breeders), it is possible that voluntary means could be sufficient to reach the goal. However, to reach country-wide eradication, the experience has been that legislative support is needed in the end. For countries where a major part of the industry is owned by cooperatives, industrial demands and quality schemes may provide an alternative way to formalise participants' obligation to comply with the regulations of a scheme.

2.5.3.1.2 Level of control

Although systematic control can be implemented on any level from herd to nation or above, there is an additional benefit of doing it at a higher level of aggregation. The risk of contracting BVDV infection is strongly influenced by the prevalence of the infection among herds that share contact patterns. If measures are taken in many herds at the same time, the risk of new infection will be reduced for all of them, also for those that have a lower level of biosecurity. Thus, the organisational level on which systematic control is implemented – herd, compartment, region or nation – has direct consequences for the risk of re-/infection and, consequently, for the benefit-cost of the measures.

2.5.3.2 Level of awareness

Stakeholder awareness is another integral part of biosecurity in systematic BVDV control programmes. Awareness works as a first line defense, because of the major influence that farmers' management decisions have on the risk of contracting BVDV, e.g. routines for

Table 4. Risk factors for introduction of BVDV into cattle herds, with priority setting and proposed means of control

Risk	Perceived need for control	Plausible ways through which BVDV is introduced by the route into a non-infected herd	Comments	Proposed control
Livestock trade	Yes, imperative	Purchase of : 1. a PI animal 2. a dam carrying a PI foetus 3. a seronegative animals in early pregnancy, infected during trade. 4. (Other animal which becomes transiently infected during trade and transmits virus to newly-pregnant non-immune animals in the destination herd.)	a) Effect on disease spread by PIs in the market will be multiplied if contacts with seronegative animals in early pregnancy can occur. b) Prevalence of dams carrying PIs likely to be higher than prevalence of PI animals. The latter has been estimated to 1-2% in an endemic situation (Houe, 1995). c) Transiently infected animals are regarded as transmitters of low efficiency (Niskanen et al., 1996).	Test for virus and antibodies in herd of origin. Stop viraemic animals and pregnant animals with high antibody titres from being traded (control of 1+2). Recommend quarantine with re-test after 4 weeks (control of 3+4). Create a certification system that enables trade between non-infected herds, based on herd samples to prove freedom from disease.
Exhibitions	Yes	1. Seronegative animal in early pregnancy becomes infected at the exhibition and returns to herd of origin 2. (An animal becomes transiently infected and succeeds in infecting newly-pregnant non-immune animals after returning home.)	a) PIs present at exhibitions will constitute a severe risk for farmers bringing seronegative animals in early pregnancy. b) Transiently infected animals are regarded as transmitters of low efficiency.	Test for virus and antibodies in herd of origin. After exhibition: Four weeks quarantine and re-test if seronegative prior to exhibition. or Arrange exhibitions for animals from certified BVD-free herds only. Freedom from disease should be reinsured by recently performed retests.
Animal contacts on pasture or over fences.	Yes	1. Seronegative animals in early pregnancy become infected on pasture. 2. (Some other animal becomes transiently infected and subsequently transmits the infection to other, newly-pregnant non-immune animals in the herd)	a) Not controlling for release of PIs on common pastures will constitute a severe risk for farmers pasturing seronegative animals in early pregnancy. b) PI carrying dams may spread disease if they abort or calve on pasture. c) From a disease control point-of-view, and in terms of herd incidence, over-fence contacts will be less important than common pasturing.	Intentional contacts: Same principle as for exhibitions. Unintentional contacts: Follow-up testing for antibodies (paired serum samples). As an alternative, the animal(s) with which contact has occurred could be tested for antibodies and virus.

Table 4. Cont'd

Risk	Perceived need for control	Plausible ways through which BVDV is introduced into a non-infected herd	Comments	Proposed control
Live vaccines	Non-systematic use of live vaccines of any type can jeopardize attempts to control BVD.	At least one susceptible animals in early pregnancy becomes infected due to usage of live vaccine contaminated with non-cytopathogenic BVDV strains during the production process, *or* disease emerges as a result of recombinations between vaccine- and field strains (Ridpath and Bolin, 1995, Desport et al., 1997).	Risk of introducing strains new to the cattle population in question.	Vaccines should be used under veterinary supervision, in a systematic control context. In parallel surveillance directed towards strains circulating in the population should be in place.
Semen and embryos	Yes	At least one susceptible animal in early pregnancy becomes infected by other dams transiently infected due to AI with semen from PI bull or transiently infected bull, *or* persistent foetal infection develops in dam receiving AI with semen from PI bull or transiently infected bull.	Risk of introducing strains new to the cattle population in question. A case has been reported with a seropositive bull constantly shedding virus in semen, in the absence of general persistent infection (Voges et al., 1998). Although this phenomenon is probably of low frequency occurrence, it should be noted that such bulls could only be detected by testing semen.	Test for antibody and virus on all bulls entering AI stations. Regular testing for antibodies on seronegative bulls during stud period. (Test of semen from antibody positive bulls). Embryo donors should come from herds free from BVDV and embryos ahould be protected from BVDV contamination during the transfer process.
Visitors, including vets, AI technicians and herdsmen in the replacement system.	Unlikely to be of major importance and impact, but preventive measures are appropriate in scheme rules	At least one susceptible animal in early pregnancy becomes infected due to contact with inadequately cleaned and/or disinfected clothes, boots, instruments and similar.	Risk for transmission will depend upon; • time interval between visit in infected/non-infected herd (prevalence of infection in the area) • type of vehicle (faeces, clothes, instruments (Gunn, 1993), contaminated injectabila) and amount of virus transmitted (Houe, 1998). • pregnancy- and immune status of in-contact animal(s) in the herd	Normal hygienic measures should be taken by professionals with ambulatory services to farmers as well as other visitors. For veterinarians: use knowledge about BVDV status of herds to plan routes or to call for change of clothes.

Table 4. Cont'd

Risk	Perceived need for control	Plausible ways through which BVDV is introduced into a non-infected herd	Comments	Proposed control
On-farm collection of slaughter animals or brokered calves by professional transportation staff.	Preventive measures are appropriate in scheme regulations.	At least one susceptible animal in early pregnancy becomes infected due to virus transfer by • transportation staff • farmer entering transportation vehicle Risk for airborne transmission of virus from transportation vehicles parked close to stable entrances or air intakes have not been investigated.	Risk of successful transmission will depend upon; • number of infected animals in the vehicle, and type of infection (PI/transient) • time interval between visit in infected/non-infected herd • degree of handling at pick-up or delivery, i.e. degree of contact between transportation staff and cattle in the herd and/or between farmer and cattle in the vehicle • pregnancy- and immune status of in-contact animal(s) in the herd	Recommend farmers to have delivery- and pick-up points outside cattle accomodations. Recommend employers of transportation staff to give their personnel directives not to enter cattle premises. Demand cleaning and desinfection of transport vehicles. If possible, arrange with separate routes for calf collection from BVD-free herds and non-BVD free herds respectively.
Other species (sheep, goats, swine, deer, elks).	Preventive measures for sheep may be appropriate in scheme regulations.	At least one susceptible animal in early pregnancy becomes infected due to contact with a persistently infected sheep/goat/pig/deer/elk.	No evidence exists that wild ungulates, swine or goats has transmitted the infection to cattle, even though interspecies transmission is possible (Nettleton, 1990). Strains proven to be involved in transmission from sheep to cattle have been of bovine origin (Paton et al., 1995). BVD control was not compromised by sheep when implemented on the Shetland Islands (Synge et al., 1997)	Check prevalence of Border disease in the area and judge whether problem exists. If so, require sheep from herds with a previous history of Border disease, and sheep in close contact with BVDV infected cattle herds to be tested free from BDV/BVDV before introduction into non-infected herds. Exception can be made for sheep from certified BVDV-free farms.
Vectors (ticks, mosquitos, flies).	No, at least not in the temperate climate zones	At least one susceptible animal in early pregnancy becomes infected due to contact with virus-carrying vector.	Insects, such as biting flies have been shown to be capable of carry BVDV under experimental conditions (Tarry et al., 1991). Vector-borne transmission has never been described under natural conditions.	None

purchasing/introducing new animals, for pasture usage, vaccination, maintenance of fencing and so on. Awareness also affects the will to comply with regulations and endure any financial consequences during implementation of an eradication campaign.
Awareness about biosecurity is, theoretically, achieved through education and information and the efficiency of such activities are most likely a key factor for success of these schemes. It is very valuable if a harmonised message can be conveyed in order to avoid confusion. This task is highly facilitated if there is a common organisational framework and/or coordination in this sense.

Awareness is, however, not the ultimate goal. More specifically, the desired outcome of information and education is to influence the behaviour; i.e. make people implement measures that reduce the risk of between-herd transmission. However, the transition of theoretical knowledge into a desired behaviour is complex and highly individual. It is a function of an individual's attitudes and his/her subjective norms, where the attitude is influenced by personal perceptions (positive/negative) regarding the outcome, and its importance. Attitudes are important in disease control. For example, a documented risk with vaccines is that they can convey a false sense of security and thereby lead to an increase in risky behaviour (Chesney et al., 1997, Vannier et al., 1997). In the BVDV control context, this may lead to biosecurity policies being put in second place.
The subjective norm – i.e. the perceived social pressure – depends on from whom a message comes and to what extent a person like/trust or dislike/distrust that source of information. Thus, a good sense of trust between stakeholders and program initiators should be a driver for compliance, not only in BVDV control, but for control of infectious diseases in general.

2.5.3.3 Access to information on BVDV status for decision making

In order to give decision makers (including farmers or livestock traders in the process of buying animals) access to information on BVDV status, an efficient system for obtaining and disseminating information on herd- and individual BVDV status is needed. This includes a sufficiently dimensioned and well trained field organisation for sampling and competent laboratory services. It also involves a system for transfer of the diagnostic information to those that need it for decision making, i.e primarily farmers and livestock traders, but also veterinarians and other professionals with ambulatory farm services. The information needed for decision making can be anything from a "BVDV free herd" sign on the door of a cattle shed to instant online access to herd BVDV status data. More important is that it is updated and accurate.

2.5.4 Recommendations

According to experts within the Thematic network, there are substantial differences between countries and regions with respect to the relative impact of risk factors both for introduction of BVDV and for persistence of the virus in infected herds. This has to be acknowledged when BVDV control is discussed. Information from more countries/more regions within certain larger countries would allow a more precise picture and analysis of the geographical diversity in Europe and could help to improve present and planned control and eradication schemes. We recommend that future design and implementation of BVDV control strategies, including resource allocation, should build upon local expert knowledge of the region- and country-specific risk factors for BVDV introduction and reasons for BVDV persistence in infected herds.

The risk of spreading BVDV through iatrogenic means, in particular through use of BVDV contaminated drugs (and including vaccines) is well documented. The highest risk is associated with live vaccines (of any kind), but there is also a risk associated with increased general usage of injectables (e.g. by implementing large-scale vaccination using killed vaccines). We recommend that this risk is thoroughly considered when choosing strategy for an extension of BVDV control to a larger scale (region/nation).

The study performed by the network suggests that if livestock movements/animals contacts were under control, close to 95% of new infections would be eliminated. It has been suggested that BVDV infection is well correlated with the presence of other infectious diseases at the herd level, such as salmonella and IBR. Thus, by controlling movements of animals from BVD-infected herds, there could be a general reduction in the infectious pressure in the market. There are additional benefits from reducing animal movements. One very important example is the increased stability of the livestock system to cope with introduction of epizootic disease. Once again, we suggest that BVDV control could serve as a model disease for improved biosecurity and disease control at a European level.

An interesting recent report suggests that virus will persist also in acutely infected animals for longer periods than previously thought (ref). It is still not known for how long and if virus can be reactivated. This would set the potential for eradication into new light. So, although there is confidence that we know how to control and eradicate BVDV, there is still a need for continuing research into the various ways by which BVDV can survive and be transmitted between animals and herds.

The structure of the cattle industry and its advisory services as well as the attitudes and subjective norms among farmers, within academia and among industry and authority decision makers on issues concerning organised disease control (including biosecurity) will be strong determinants for the prospects for successful implementation of systematic BVDV control.
A better understanding of the variation in this respect among stakeholders within Europe would provide an important basis, not only for the choice of control strategy, but also for the way in which this strategy should be implemented. In fact, biosecurity as it pertains to BVDV control has got a wider application. BVDV could be a model for many infectious diseases where the main driver is livestock movements/contacts and where attitudes/traditions among stakeholders have to be targeted to reach disease control objectives. Therefore, we recommend that more research is targeted towards understanding the differences in attitudes of stakeholders towards biosecurity, across Europe.

2.6 Methods for identification of risk factors in the late phase of control

One of the highest priorities in controlling an infection at a larger scale is to prevent new herds from becoming infected. Although the major routes of BVDV transmission are well known (Lindberg and Houe, 2004), cases of new infections still appear in areas where the infection is subject to systematic control. It is of high importance to follow up on such cases to see if they conform to the paradigm or if there are routes not fully understood and/or controlled that could create difficulties when eradication efforts are to be finalised. Therefore, tracing of sources of incident cases should be an integrated part of any control/eradication scheme on BVDV.

From a theoretical point of view, there are three techniques for tracing infection that can be used alone or in combination:

1) interviews with cases and follow-up testing and interviews with their contacts (contact tracing),
2) epidemiological analysis of data on risk factors and confounders collected through questionnaires or in interviews, and
3) molecular techniques, where similarities/differences in the genome of infecting agents are used to identify and trace time-place associations between cases.

Despite that there are established methods for this purpose, few of the current control/eradication schemes on BVDV have such routines implemented (see Appendix 1).

2.6.1 Experiences from using contact tracing and risk factor analysis in ongoing schemes

The inherent difficulty in tracing the source of new cases of BVDV infection through interviews and questionnaire data - even in areas/system where herds are frequently monitored for BVDV - should be acknowledged. This difficulty lies in the often-experienced delay between the actual introduction of the infection, detectability in herd level test methods and the ability to confirm a persistent infection as an outcome of the exposure. Such a delay can of course be reduced if action is taken already at the presentation of a positive herd level test. However, as a significant number of these tests can be "false alarms" (signs of exposure without the infection becoming established) such investigations will run a risk both of being inaccurate and labour demanding.

The information in table 1 deals with risk factors for having BVDV infection (being a case), not for becoming a new case. In fact, there is very limited information about risk factors for new infections, possibly because one absolute precondition is prior knowledge that case herds have in fact been free from BVDV and that they are followed over time. At current, such knowledge is only obtained in an organised manner in countries/regions with systematic control. In Denmark, a follow-up was made of causes of new infections during the first 5 years of the scheme (1994-1999). The study was based on farmer interviews and the major findings conformed to prior knowledge about how BVDV is transmitted (Bitsch et al., 2000), such as by purchase of dams carrying persistently infected (PI) foetuses (28%), or by pasture contacts between susceptible animals in early pregnancy and neighbouring PI animals (38%). However, in 25% of the cases, the source of the virus could not be identified.
In Sweden, investigations based on farmer interviews are routinely performed in all newly infected herds since January 2002. The interview should be carried out as soon as possible after the new infection is detected. All types of direct and indirect contacts are investigated using a predefined checklist. All questions are asked in relation to the probable time period during which infection has been introduced. This time period is established by using available information from e.g. previous monitoring at the herd level or the individual level, conception period for mothers of animals identified as being PI and/or the time period between paired tests for animals identified as having seroconverted. The outcome of farmer interviews performed in herds that have become newly infected after certification herds show that over 50% of the cases were caused by failure to adhere to the scheme's biosecurity regulations. Thirty-five per cent of the cases were related to contacts during the grazing season (runaway contacts with unknown/infected herds not subject to follow-up and/or sharing pasture with infected herd) and 19 per cent of the cases are due to purchase of either a PI animal or a dam carrying a PI foetus. Eight per cent of the cases were suspected to be due to indirect transmission of the infection, for example by farmer collaboration, sharing transportation

vehicles and similar. However, in 38 per cent of the cases traced between January 2001 and December 2004, the source of the infection remained unknown.

It is clear that there is a constant challenge in keeping the awareness among farmers and other stakeholders at a sufficiently high level, especially towards the end of an eradication campaign. Farmers with herds that have been free for many years can have a tendency to think that the agent does not constitute a problem any more, and fail to adhere to biosecurity regulations.
It is also clear that indirect routes of between-herd transmission of BVDV play a relatively higher role in areas with systematic control as the biosecurity measures undertaken efficiently reduce the risk of transmission via the conventional routes. Such cases are particularly difficult to trace, and possibly a significant number of the new infections where the source could not be disclosed are a result of indirect transmission.

2.6.2 Experiences from using molecular epidemiology

Recently, molecular epidemiology has been introduced in the Swedish scheme as a tool to identify links between infected herds that are not disclosed by the other approach. The sequences are used for phylogenetic analysis to seek epidemiological relationship between old/existing and new cases. Today, genome sequences for all strains isolated since late 2002 are available (Ståhl et al., 2004). The findings in this project have been valuable in a number of cases where suspected direct and indirect routes of transmission have been supported by the phylogenetic analysis. Also important, it has been possible to rule out suspected sources of infection. It is anticipated that with fewer infected herds remaining and a more complete chronology among herds that are involved in transmission chains, this tool will become increasingly valuable. It will also continue to be an important tool after conclusion of the eradication, to trace the source if the infection reappears/is reintroduced.

2.6.3 Recommendations

Tracing sources of new infections are very important in the late phase of an eradication or after reintroduction. Due to the inherent problems associated with contact tracing and data collection based on interviews/questionnaires, we recommend that molecular epidemiology should be further investigated with respect to its usefulness in this context. This will be facilitated by the creation of a genome database, as suggested in the position paper from WP 1. We also recommend that routines for tracing are considered early on in the planning of future control schemes.

2.7 Risk factors for new/re-infection in areas free from BVDV

In areas where BVDV has been eradicated, the main routes for reintroduction will be by imports of livestock, semen or embryos.
Imports of semen and embryos are considered to be, in general, safe ways of importing genetic material for livestock improvement, in comparison with livestock. However, considering the global trade with these former commodities, they constitute vehicles, not only for introduction of BVDV in general, but also possibly of strains of BVDV that are new to the native cattle population. For example, a new atypical pestivirus strain isolated from a Brazilian fetal bovine serum has recently been described (Schirrmeier et al., 2004). Although it appears to behave clinically like most BVDV strains, it is antigenically very different. There

is a risk that it would go undetected in current monitoring systems based on serological tests, and could consequently spread without control if it was introduced.

2.7.1 Semen

Semen may carry BVDV if the bull is persistently infected (PI) or acutely infected (Kirkland et al., 1991) There has also been a case described where a seropositive bull, Cumulus, persistently shed virus in his semen, despite that virus detection in blood failed (Voges et al., 1998). The underlying biology of this persistent testicular infection is still unclear. However, irrespective of the cause, and disregarding the fact that it is seems to be a rare event, it highlighted a risk of accepting semen as safe based on a serum test on the bull that is virus negative / antibody positive (Niskanen et al., 2002).
When the EU directive on intra-Community trade in and imports of semen of bovines (Council Directive 2003/43/EC) was amended recently, measures to manage Cumulus-type bulls had been incorporated. Today, bulls that were antibody positive when they enter an AI station need to have semen from the first collection tested for virus. Bulls that are antibody negative at the time when they enter an AI station need to be tested at least once per year for antibodies.

2.7.2 Embryos

BVDV is one of many pathogenic agents that have to be considered in sanitary control during embryo transfer (ET) operations (Stringfellow and Seidel, 1998). Risk of transmission occurs if the donor is PI, and possibly also during a transient infection (Brock et al., 1991). However, transfer of embryos from PI donors have indeed been performed without spread of the infection, and without production of PI calves (Wentink et al., 1991, Bak et al., 1992). Still, new research indicates that there may be strain-related differences in adherence to the zona pellucida, and that some strains cannot be removed with standard washing procedures (Waldrop et al., 2004).
However, perhaps a more probable route by which ET could lead to transmission of BVDV is by the use of foetal bovine serum (FBS) in the process (see below). The risk that in-vivo derived embryos may constitute is mainly associated with any potential use of FBS in wash media. This risk is more general for in-vitro produced embryos. In in-vitro production, FBS is always added during culturing. There is also a problem to ensure that material used for oocyte collection are free from BVDV (Guerin et al., 2000). In general, risk management procedures that work for in-vivo derived embryos have been shown to be less efficient for in-vitro produced embryos (Stringfellow et al., 2004).

2.7.3 The role of foetal bovine sera

FBS is often contaminated with BVDV, a fact known since decades but still a problem (Makoschey et al., 2003). Apart from being used in ET operations, FBS are extensively used in the production of live vaccines against BVDV (as well as against other infections). During manufacturing, sera from 500-2000 unborn calves are pooled into batches (EDQM, 2001). As the prevalence of persistent infection in foetuses is 8-10% under endemic conditions, the likelihood of including one or more PI foetuses in a batch of 1000 is close to 1. This ever-present problem is managed by the manufacturers by radiation or by treatment with inactivating substances. Unfortunately, examples where the inactivation has failed are abundant (e.g. Erickson et al., 1991, Audet et al., 2000, Barkema et al., 2001, Studer et al.,

2002). This fact means that any product where fetal bovine sera are used (such as embryos and live vaccines) should be considered risk factors for reintroduction of BVDV.

2.7.4 Recommendations

BVDV is a virus with an epidemiological significance similar to BHV-1. It has got similar distribution, it is mainly spread through livestock trade, it has a significant economic impact on cattle industries - but it is controllable. Considering there is a chapter for IBR/IPV in the OIE Terrestrial Code, it would be reasonable to include a chapter also for BVDV.
We support the idea to – in parallel to developing a chapter - develop OIE sanctioned guidelines on how to manage diseases like BVD (and also IBR/IPV), i.e. diseases where there is sufficient information to state that a significant reduction of the prevalence can be achieved and maintained in a cost-efficient manner. We believe the European experience in this respect would be a valuable and natural starting point for such guidelines.

2.7.4.1 Livestock

In areas where BVDV are/will be eradicated, there will already be a system in place for controlling the risk of introducing the infection by purchasing livestock. The same system should be equally applicable to introductions from other countries. We recommend that the animal should have been tested free from BVDV in the herd of origin according to approved techniques and protocols. Antibody positive pregnant animals should not be imported, unless the animal was proven to be positive before pregnancy and has been tested free from BVDV. Animals free from BVDV should not be transported together with animals with unapproved/unknown BVDV status.

2.7.4.2 Semen

The current directive on intra-Community trade in and imports of semen of bovines (Council Directive 2003/43/EC) states that bulls that are antibody negative at the time when they enter the facilities should be tested once per year, but bulls that are antibody positive only have to have their semen tested once. This wording may promote the implementation of mass vaccination of stud bulls which would be an unfortunate evolution. There are several problems associated with this. For example, live vaccine strains may be shed in semen. Also, vaccination precludes the opportunity to monitor bulls for seroconversions and thereby, accidental introduction of BVDV may be concealed. Killed vaccines are “safe” but need (at least) annual boosters to maintain immunity. In our opinion, there is a need to clarify this aspect of BVD-MD surveillance at bull stations; Should vaccines be allowed, and if they are allowed, what vaccines should be used and how should they be used.
Otherwise, risk management with respect to semen should be based on proof of freedom from BVDV either in the herd of origin, or if this is not an alternative, the bull should have been proven antibody negative after sampling, and previously been shown to be non-PI. If neither the herd nor the bull fulfil these demands, an aliquot of each collection of the semen should be subject to a test for presence of virus.

2.7.4.3 Embryos

The Health and Safety Committee of the International Embryo Transfer Society, a guiding body for the OIE in embryo risk management matters, classifies BVDV in its category 3, for “diseases or disease agents for which preliminary evidence indicates that the risk of transmission is negligible provided the embryos are properly handled between collection and transfer, but for which additional in vitro and in vivo experimental data are required to

substantiate the preliminary findings". Notably, the term "preliminary evidence" does not apply to BVDV, as there is a considerable amount of research on this matter. Rather, there is increasing evidence that BVDV can indeed constitute a risk, despite application of the hygienic procedures recommended by the IETS (and which are generally approved for international movements of embryos). Also, these guidelines only address the problem of contaminated FBS by stating that "All media and supplements to media, including sera….must be free of pathogens…". However, they also suggest that "Serum may have to be specifically approved by the importing country.".
It should also be noted that the IETS, to date, has chosen to refrain from categorising in-vitro produced embryos with respect to evidence of risk, simply because there are still too much uncertainty about the potential risk of disease transmission associated with such products, for any agent.
Unlike semen, it is not possible to reduce risk significantly by asking for proof of freedom from BVDV in the herd of origin, or in the donor, not as long as FBS are used in wash media. So although the basis for risk management should be to demand that that embryos have been derived according to the guidelines of the IETS, additional demands should differ depending on type of product used for washing.
In addition, if synthetic products or products from countries free from BVDV are used it is sufficient with proof of freedom from BVDV either in the herd of origin, or if this is not an alternative, the donor should have been proven antibody negative after sampling, and previously been shown to be non-PI.
If it can not be certified that wash fluids are free from BVDV, the abovementioned measures are applicable in conjunction with a test for BVDV on an aliquot of fluid from the last wash.

2.8 Health and production effects of BVDV infection

BVDV exhibit a broad spectrum of clinical manifestations that subsequently can give rise to production losses. Depending on individual herd preconditions, the scenarios range from new infections in naïve herds, associated with extreme, but transient, reproductive losses, to long-term infection where a large proportion of the adult animals become immune and where losses are mainly associated with impaired calf health and suboptimal performance.

From the literature it can be seen that effects of BVDV infection on production often have been investigated in case studies or in experimental studies. This can both lead to over- and underestimation of the effect. For case studies, it can be anticipated that cases are non-representative of the general population of herds, as the more severe outbreak will attract more attention than mild outbreaks. Results from experimental studies are difficult to extrapolate to the field as they rarely can capture the complex herd level picture with differences in initial herd immunity, varying number of animals in different stages of gestation at the time of the infection and differing virulence of the infecting virus interacting with environmental factors such as infectious pressure from other agents and management.

However, production losses have also been evaluated in some observational studies, where there are prospects for getting a more representative picture. Still, although effects at the individual level will be fairly similar across populations, herd level effects are much more difficult to generalise, both because they vary between productions systems within and between countries, but also due to the different underlying study designs including other effects controlled for.

In this context, we will emphasise what has been found in observational studies performed under European conditions, and only briefly mention experimental studies if there are no observational studies available.

2.8.1 Postnatal infections

Most transient infections are reported to be subclinical. However, a low percentage of animals may develop the BVD-specific clinical and pathological signs of so-called acute BVD, including salivation, diarrhoea and erosions throughout the gastrointestinal tract (Ames, 1986, Moerman et al., 1994, Baker, 1995). Outbreaks associated with virulent type 2 BVDV strains have been seen in North America, causing very high morbidity and mortality following transient infection (Hibberd et al., 1993, David et al., 1994, Carman et al., 1998). Such outbreaks have not yet been reported to occur in Europe, except for one large outbreak in the Netherlands (Barkema et al., 2001). This outbreak was associated with use of a live vaccine against BHV-1, contaminated with BVDV.
Irrespective of whether the transient infection is immediately followed by BVD specific signs or not, there will frequently be a series of sequelae. These can be divided into reproductive disorders (as described under foetal infections) and increased occurrence of other diseases. Specifically, “other diseases” includes mastitis and retained placenta but also a broad range of diseases allocated to the group “miscellaneous”. There have been studies showing both significant and non-significant effects on cell count and in calves, a significant effect on respiratory diseases, diarrhoea and mortality has been shown (Table 5). Many losses associated with postnatal or transient BVDV infections are a direct consequence of the mentioned clinical manifestations, but in addition there are documented effects of a general reduction in milk yield.
Long-term losses associated with BVDV infection, e.g. loss of genetic material and effect on the longevity of cattle infected as calves, have not been characterised, nor quantified.

2.8.2 Fetal infections

Health- and production effects associated with fetal infections include abortions, congenital defects, birth of weak and undersized calved as well as unthriftyness and increased mortality among animals born PI.
For example, in a Danish study (Houe et al., 1993), conception rates were considerably and significantly lower in periods when BVDV was known to be circulating (38%), compared to periods where the herds were known to be immune (47%). The increase in odds for a seroconverting animals to abort has been estimated as 3.1 (Rufenacht et al., 2001) and in herds with recent infection the odds ratios were estimated as 2.6 and 11.6 for two different registration periods (Fredriksen et al., 1998).

Several experimental fetal infections have shown to cause congenital defects, stillbirths and weak born calves, but these effects seem not to have been quantified in epidemiological studies.

PI animals have been shown to be significantly smaller than non-PI animals (Table 5). The annual incidence risk of dying or being slaughtered due to unthriftyness was calculated as 0.28 and 0.31 among 34 PI animals in 10 Danish dairy herds (Houe, 1993). Prevalence surveys have shown that the prevalence of PI animals is much higher among young stock, which is also an indication of a high mortality among these animals (Houe and Meyling, 1991, Frey et al., 1996).

Table 5. Health and production effects of BVDV under different production settings in Europe, observational studies.

Country/region	Outcome variable	BVD condition (risk or exposure factor)	Measure	Number of animals/herds	Size of measure	Reference
Holland	Reduced milk yield with > 10%	Seroconversion vs no seroconversion	OR	22 seroconverted 32 no seroconv.	11.5 (CI 3.0-43.5) for more than 10% reduction in milk yield *	Moerman et al., 1994
Holland	Moderate or severe broncho-pneumonia	Receiving colostrum from AB negative dams (A) vs. AB positive dams (B)	Incidence risk	AB-neg colostrum: 44 calves AB-pos colostrum: 86 calves	A: 68.2% developed symptoms B: 40.7% developed symptoms	Moerman et al., 1994
Sweden	Heart girth	PI calves vs non-PI calves	cm at 80 days cm at 180 days	8 PI 13 non-PI	80 days: PI: 96.3 ± 4.7 cm ; non-PI: 100.5±2.3 cm 180 days: PI: 123.3 ± 8.8 cm ; non-PI: 130.2±2.0 cm	Larsson et al., 1994
Sweden	Mastitis	Recent herd infection compared to low level of AB in bulk milk	OR	91 herds (7 with recent inf. and 84 without inf.)	1.8 (CI: 1.1-2.8)	Niskanen et al., 1995
Sweden	Miscellaneous diseases	Do	OR	Do	2.8 (CI: 1.7-4.4)	Do
Sweden	Retained placenta	Do	OR	Do	2.8 (CI: 1.6-4.7)	Do
Sweden	Oestrus stimulating treatment	Long-term herd infection compared to low level of AB in bulk milk	OR	142 herds (58 with inf. and 84 without)	1.8 (CI: 1.3-2.6)	Do
Sweden	Calving interval	Long-term herd infection compared to low level of AB in bulk milk	days	142 herds (58 with inf. and 84 without)	Long-term inf.: 394 (389-398) Non-infected: 385 (381-389)	Do
Sweden	Average annual milk yield per cow	Herds with detection of virus vs. free herds	Kg ECM	319 case herds 2270 control herds	Interaction with herd size: 30 cows: -142 kg (CI:-281 − -3) less in case herds. 40 cows: -198 kg (CI: -330 − -66) 50 cows: -254 kg (-389 − -119)	Lindberg & Emanuelson, 1997
Sweden	Average bulk milk somatic cell count x 1000	Herds with detection of virus vs. free herds	cells/ml	319 case herds 2270 control herds	10,300 (1,600- 18,900) cells/ml more in case herds.	Lindberg & Emanuelson, 1997
Norway	Clinical mastitis	Herds with rise in bulk milk antibodies vs. herds with continuous low level	Incidence rate	300 exposed herds vs. 13,671 non-exposed	7.1% (CI 0.2-11.4) increase in exposed herds	Waage, 2000
Switzerland	Fetal death (mid-term abortion)	Seroconversion vs no seroconversion	OR and PAF	62 cases 952 controls	3.10 (CI 1.16-8.29) , PAF 7% (CI 2.4-14)	Rüfenacht et al., 2001
France	Late return to service (after 25 days)	Past-infected-recently-recovered vs Not recently infected	RR	150,854 AI 122,697 cows 6,149 herds	1.03 (CI 1.01-1.05)	Robert et al., 2004
France	Late return to service (after 25 days)	Past steadily infected vs Not recently infected	RR	150,854 AI 122,697 cows 6,149 herds	1.11 (CI 1.05-1.17)	Robert et al., 2004

Table 5. Cont'd

Country/region	Outcome variable	BVD condition (risk or exposure factor)	Measure	Number of animals/herds	Size of measure	Reference
France	Late return to service (after 25 days)	Recently infected VS Not recently infected	RR	150,854 AI 122,697 cows 6,149 herds	1.11 (CI = 1.02-1.22)	Robert et al., 2004
Holland	Prevalence of animals with clinical signs	Transient infection	%	136 cattle (1 herd)	7 of all animals with transient infection showed clinical signs (5%)	Moerman et al., 1994

2.8.3 Recommendations

Due to the many different clinical manifestations, BVDV has often been seen as part of production diseases (respiratory disorders, diarrhoea, reproductive disorders). However, we strongly recommend that BVDV is always considered and treated as a specific infectious disease. The risk that BVDV can "hide" under other conditions should always be considered, and awareness regarding this fact has to be increased, in particular as it has implications for priority settings, both in terms of reducing antibiotic usage and for improvement of animal welfare.
The significance of differences in virulence on occurrence of clinical manifestations and production losses, as well as the prevalence and effect of co-infections are important areas for further investigations.

2.9 Modelling BVDV infection

Simulation modelling has the advantage that the behaviour of an infection can be investigated, assumptions about different routes of spread can be tested and the potential effect of different control measures can be estimated even though there is incomplete knowledge about the system. At the same time, it is a good way of identifying critical gaps in the current knowledge (Anderson and May, 1991, Dijkhuizen and Morris, 1995). However, modelling studies on BVDV transmission models *per se* are fairly scarce. Those seen in the literature are mainly aimed at assessing the economic impact and to compare different control strategies (e.g. Pasman et al., 1994, Sørensen et al., 1995). Consequently, they do not explicitly address the infection from a transmission point of view, but of course include assumptions about it in order to estimate the total effect on reproduction and production.

2.9.1 Within-herd models

One of the objectives of this work package was to evaluate methods for modelling BVDV infection dynamics and to identifying information necessary for improving such epidemiological models. In doing this, several steps were considered:
- To identify existing models
- To review their advantages and limits
- To describe existing and potential uses of models
- To identify information necessary to improve assumptions underlying models
- To identify information required to define relevant scenarios for simulation studies

2.9.1.1 Basic modelling approach

Nine models representing within-herd transmission were identified and selected for review: six were published in peer-reviewed journals and three further models were obtained from on-going research projects in the network partners research groups and described in unpublished text (Table 4). These nine models mainly focused on dairy herds and only one represented the structure and demography of a beef cow-calf herd. Most of the models were stochastic. Stochastic models appear to be preferable in our situation because herd size in Europe does not allow the population to be considered as infinite, which is an important assumption in deterministic models. Moreover, stochastic models provide the investigator with estimates of the expected variability of outcomes. For instance, stochastic models showed that after a single virus introduction in a susceptible herd, an early extinction of the epidemic can be observed whereas herd infection can last for more than ten years when new PI animals are

born from post-natal infection of susceptible dams (Viet et al., 2004). These variable behaviours have been observed in the field. Uncertainty about the outcome is therefore a useful information for decision makers: e.g. probability of virus persistence or probability of occurrence of worst case situations in epidemic size are required on top of average results to compare possible control programmes.

Table 4. Type of model and main differences in herd population structure and dynamics in nine studies employing simulation modelling to describe within-herd transmission of bovine viral diarrhoea virus (BVDV).

Models (in chronological order)	Type of herd	Effect of chance	Time process (time step)	Herd structure [b]	Early exit of male calves	Demographic process modified by BVDV infection
Pasman 1994	Dairy	Deterministic	Discrete 3 mo	1/2/3	No	Birth
Sørensen 1995	Dairy	Stochastic	Discrete 1wk	CA/YH/BR/CO	Yes	Birth Culling Death
Innocent 1997	Dairy	Stochastic	Discrete 1 mo	CA/H/CO	Yes	Birth Death
Cherry 1998	NA [a]	Deterministic	Continuous	1 group for all animals	No	Birth Death
Groenendaal 2000	Dairy	Stochastic	Discrete 3 mo	1/2/3	Yes	Birth Culling Death
Gunn 2003	Dairy	Stochastic	Discrete 3 mo	1/2/3	No	Birth Culling
Gunn 2004	Beef	Stochastic	Discrete 1 yr	1/2/3	NA	Birth Culling
Viet 2004	Dairy	Stochastic	Continuous	CA/YH/BR/CO	Yes	Birth Culling Death
Ezanno 2006	Dairy	Stochastic	Discrete 2 wk	CA/YH/BR/LC/DC	Yes	Birth Culling Death

[a] *NA: not applicable*
[b] *1/2/3: groups defined by age: 1-year, 2-year and 3- or more year old animals, respectively*
[b] *CA, YH, BR, H, CO, LC, DC: groups defined by category: calves, young heifers, bred heifers, all heifers, all cows, lactating cows, dry cows, respectively*

Most models were discrete time models. A possible drawback if the time-step is short may be a long duration of simulation experiments. Inversely, if the time-step is long, it is not possible to take account of short-lasting events (e.g. duration of shedding by transiently infected animals is much shorter than the time-step in 5 out of 7 models). Selecting a time-step has to result from a balance between computing time for simulation studies and precision of the process to be represented.

2.9.1.2 Population dynamics

When representing the population dynamics, all but one model accounted for the grouping of animals by age or physiological stage which is common management in most herds in Europe. Surprisingly, only three of the models assumed that this herd structure had an influence on BVDV horizontal transmission (Table 5). Neglecting the contact structure could be justified for a highly contagious pathogen (e.g. with important indirect or airborne transmission) but it is not the case for BVDV. Consequently, one simulation study proved that accounting for the contact structure highly influenced the model outcomes (Viet et al., 2004).

Three of the dairy herd models did not account for early exit of male calves. In many European countries, male calves in dairy farming systems are sold at a very young age (unless fattened in the herd of origin). Neglecting these exits tends to overestimate virus persistence in the herds, as on average, about half of the PI animals are in fact a source of virus in the herd only for a few days or weeks.

Table 5. Approaches for modelling horizontal and vertical transmission of bovine viral diarrhoea virus (BVDV) within a herd, in nine studies employing simulation modelling to describe within-herd transmission of the virus.

Models (in chronological order)	**Horizontal transmission**				**Vertical transmission**	
	Shedding animals [a]	Function for the force of infection	Speed of infection by PI [b]	Contact structure	Distinct pregnancy stages with different outcomes	Probability of birth of a PI calf [d]
Pasman 1994	PI	Constant	75	3 age groups No transmission between groups	NG [c]	NG
Sørensen 1995	PI	Constant	94	Homogeneous	5	0.21
Innocent 1997	PI = TI	Reed-Frost	9	Homogeneous	2	0.28
Cherry 1998	PI > TI	Density-dependent	94	Homogeneous	2	0.11
Groenendaal 2000	PI	Reed-Frost	83	Homogeneous	3	0.24
Gunn 2003	PI	Reed-Frost	NG	Homogeneous	NG	NG
Gunn 2004	PI	Reed-Frost	(94 in 1 yr)	Homogeneous	1	0.24
Viet 2004	PI > TI	Frequency-dependent	36	4 category groups Transmission between groups	3	0.27
Ezanno 2006	PI > TI	Frequency-dependent	36	5 category groups Transmission between groups	3	0.29

[a] *PI: persistently infected animals; TI: transiently infected animals, PI=TI: equal transmission coefficients, PI>TI: higher transmission coefficient for PI than TI animals*
[b] *Number of animals transiently infected within 3 months in a closed group of 100 susceptible animals with 1 PI*
[c] *NG: Not given*
[d] *Overall probability if a pregnant cow is infected, assuming a random uniform distribution of the stage of pregnancy at infection*

As expected, all models included an effect of the BVDV on birth rate (with a wide range of probabilities of calf survival – because of foetal death, abortion or stillbirth – varying from 57% to 96%). All models but one also assumed a higher mortality or culling rate of persistently infected animals, as has been proven for BVDV.

2.9.1.3 Transmission parameters

Options and assumptions to model the BVDV infection process and transmission differed widely between models (Table 5). Regarding horizontal transmission, only four models accounted for shedding by transiently infected (TI) animals. Although the low transmission by TI animals often results in extinction of the infection in a population unless it leads to the production of a persistent infection in at least one foetus, the possibility of further spread of BVDV infection after introduction of such an animal in a susceptible herd has indeed been reported from the field. Simulation experiments confirmed that probability of early extinction is high, but that possible virus persistence cannot be totally neglected (Viet et al., 2004, Ezanno et al., 2006)

Mathematical modelling of the force of infection assumed either that all the animals of a group were likely to be in direct contact within a time-step – in Reed-Frost models – (which seems acceptable for long time-steps), or that any animal had a constant number of contacts per unit of time (in frequency- and density-dependent models). Data from field studies on behaviour of cattle in group would be useful to consolidate these assumptions. The probability of being infected was calculated in 4 different ways, underlying on contrasted assumptions. Two models assumed that once at least one PI animal is present in a herd, the probability of a susceptible animal to be infected is constant (whatever the herd size and number of PI animals). The other approaches assumed that this probability depended on the total number of shedding animals, on the density of shedding animals per surface area, or on the proportion of shedding animals in the herd. Besides different mathematical functions, the parameters used in the transmission equation led to highly variable speed of infection. No data were provided to justify the choice of a mathematical function for the force of infection, or to estimate the corresponding parameters. Better justification is recommended.
For vertical transmission, the probability to give birth to a PI calf for a cow generally depended on the pregnancy stage of infection, as shown in experimental studies. Overall, the probability across the whole pregnancy averaged 0.11 to 0.29. As for horizontal transmission, model builders were facing lack of experimental data to calibrate these probabilities.

2.9.1.4 Model validation

Model validation was not always reported. The use of existing data to validate models should be enhanced, although comprehensive quantitative validation with observed data seems difficult as data describing the follow-up of herd infection are highly biased (e.g. early extinction of the infection is not traced whereas confirmed infection generally results in intervention to remove PI animals). An alternative validation strategy can be to separately validate the different assumptions of the model with selected data.
Surprisingly, although there have been considerable research effort on BVDV modelling, especially in Europe, few results of simulation studies were published to document the efficiency of BVDV control programmes. A few questions were addressed either to better understand the virus transmission in a herd, or to assess effects of herd management and some disease control actions. Nevertheless, published results are not sufficient to provide decision-makers with relevant information to define a control strategy adapted to the particular context of different herds of concern. Further simulation studies of existing or improved models should be performed.

2.9.1.5 Information necessary for improving existing and future models

The necessary information to improve existing within-herd epidemiological models can be listed by identifying assumptions in the models where biological evidence is absent or scarce. Moreover, sensitivity analysis allows for identification of key parameters where uncertainty about the parameter value is likely to strongly influence conclusions drawn from model outcomes.
Sensitivity analysis mainly focused on parameters with high uncertainty such as transmission parameters. Models are not or slightly sensitive to the coefficient describing direct transmission by PI animals (Innocent et al., 1997, Viet et al., 2004, Ezanno et al., 2006). By contrast, when a contact structure is represented with higher risk of virus transmission within a group than between groups, model outcomes are highly sensitive to between-group transmission coefficient for all shedding animals (including transiently infected) and also to the coefficient for within-group transmission for transiently infected animals.

Information is also required to define relevant scenarios for further simulation studies. This includes both information on farm structure or management decisions which are likely to influence the virus spread (e.g. herd size, structure of the herd and contacts between animals of different age groups, existence of a grouped calving season) and necessary information to define and quantify the expected effects of control actions (e.g. for vaccination, duration of immunity, protection induced in vaccinated animals against shedding and against foetal infection) in a precise manner. To assess BVDV control programmes, different risks of virus re-introduction in a herd also have to be considered. Moreover, production effects need to be more documented if outcomes of epidemiological models are intended to be used for economic models.

2.9.2 Between-herd models

Understanding the dynamics of BVDV transmission between herds is important to evaluate the impact of control measures. The latter are only effective if they on average prevent transmission from an infected herd to a susceptible herd. At first sight one may expect that between-herd modelling is an extension of within-herd modelling at a higher level. However, the specific characteristics of between-herd transmission of a disease, makes the understanding of the dynamics of this transmission more complex.
A methodology for modelling infection dynamics at an individual level can be based on the *SIR* model described by Anderson and May (1991), where it is assumed that individuals in a population can be classified according to their infection status (Susceptible, Infected, Recovered). As a herd will rarely be totally immune, more than momentarily, this can be reduced to a *SI* model. Transmission between herds can be expressed as a reproduction ratio $R_{h,}$ which is defined as the average number of susceptible herds that are infected by one infectious herd. R_h is a time-dependent ratio of the number of herds that become infected in a next time-point (t+1) divided by the number of herds that are infectious in this time-point (t). Measures to control between-herd transmission of BVDV are effective is they result in $R_h<1$.
Modelling R_h has been described for several diseases as, e.g. classical swine fever (Stegeman et al., 1999) and bovine herpesvirus 1 (Graat et al., 2001). Typically, all these studies model the disease dynamics starting from a unique introduction of the infection in a totally susceptible population This approach is not useful for modelling the dynamics of BVDV, since it may be endemic in a region. However, data available from a systematic repeated sampling scheme in which herds can be identified as recently infected or harbouring infectious animals can be used for modelling the disease dynamics. In this case the number of infectious and number of recently infected herds can be obtained and R_h can be roughly estimated
Still, the transmission of an infection between herds is determined by the infectivity of the herds upon infection, the susceptibility of non-infected herds and the contact structure between herds. Therefore a more accurate R_h can be obtained by accounting for these determining factors. The infectivity of an infectious herd can be estimated by within-herd dynamics models, with outputs of number of persistently and transiently infected animals over time, as well as number of dams pregnant with PI foetuses. The infectivity is also related to the probability of transmission associated with such animals. The susceptibility of non-infected herds can be estimated by identifying the immune status of these herds. The contact structure can be divided into the type of contact, the rate at which contacts occur and the number of herds that are connected.

2.9.3 Recommendations

Within-herd models for dairy herds are available, but should be further used to study possible results of control schemes at the herd level. Results cannot be extrapolated to beef herds and the existing model should be refined for this production system. Stochastic models are preferred. Models should take account of the contact structure in a herd, and represent possible horizontal transmission by transiently infected animals. To improve existing models, experimental or field information should be produced to justify assumptions for mathematical modelling on the force of infection and to estimate transmission parameters. The research efforts on modelling BVDV so far tend to produce models that progressively take important features of the herd dynamics and the infection into account in a better manner. The use of such models is a promising approach to study the opportunity of BVDV control programmes in the very different epidemiological contexts that exist for BVDV in Europe, and should be encouraged.

To our knowledge, modelling the between-herds transmission dynamics of BVDV has not been performed so far. Still, countries in which a long-term systematic control programme has been implemented for many years should have the appropriate data available to perform these kinds of studies. By modelling the between-herd transmission dynamics, the impact of control measures can be quantified by estimating R_h in time and this may be a considerable gain of knowledge. Also here, BVDV could serve as a model for infectious diseases that share the same risk factors.

2.10 BVDV data sources in Europe and their research potential

This section deals with what is currently known about BVDV in Europe from the literature, and the usefulness of such information. We also discuss what data are available to assess the impact of BVDV on production, fertility and animal health across Europe, and the potential in joining such data.

2.10.1 Literature data on BVDV infection status in Europe

2.10.1.1 Prevalence data

A series of investigations aimed at assessing the prevalence of BVDV infection have been performed in Europe, from the late seventies and into the 21st century.
Initially, prevalence surveys were performed by testing individual animals (Table 6). During the last decade, however, the prevalence has often been estimated at the herd level, based on serological samples from targeted age groups (spot samples) or antibody levels in bulk milk (Table 7). The general picture is that in many countries without systematic control in place, or before such measures were implemented, the infection has been/is endemic at a high level with 60-80% of the animals being antibody positive and 1-2% being persistently infected. In many countries, surveys indicated that almost all herds had antibody carriers and approximately half of them had PI animals. However, a few countries had quite a different picture with much lower prevalences (Figure 5). This heterogeneity in the presence of BVDV infection in the absence of systematic control is likely to reflect the distribution of risk factors for new BVDV infections and for persistence of the infection in the respective countries.
It can be noted that information on BVDV prevalence is still lacking from a number of EU member countries.

Table 6. Published European surveys for determination of prevalence of bovine virus diarrhoea virus (BVDV) infection in Europe based on individual tests for antibodies and/or virus (last updated June 1, 2005)

Country/ Region	Study period	Sampling frame	Sampling method		Sample size		Prevalence (AB)		Prevalence (Virus)		Vaccination	Reference
			Herds	Animals	Herds	Animals	Herd level Number (%)	Animal level, Number (%)	Herd level Number (%)	Animal level, Number (%)		
Belgium	…	Southern Belgium, Belgium White Blue and Friesian Holstein	Some herds suspicious or had prior diagnosis (42.5%)	All animals in herd	61	9685	61 (100)	6344 (65.5)	27 (44.3)	73 (0.75)	Some vaccination (not considered important)	Schreiber et al., 1999
Denmark	1988	Jutland in Denmark Dairy herds	Representative NPE	All per farm	19	2570	19 (100)	1655 (64.4)	10 (52.6)	35/28 (1.4/1.1)*	No vaccination	Houe and Meyling, 1991
Germany	…	Northern Germany. Breeding animals	Exporting herds	Pregnant NPE	>1000	2317	-	-	-	21 (0.9 (viraemic))	…	Liess et al., 1987
Germany	1993-94	Lower Saxony	NPE	Up to 3 years	329	20,253	-	-	149 (45.3)	425 (2.1)	Some vaccination	Frey et al., 1996
Lithuania	1997-2001	27 regions	Some suspect herds	Some suspect herds	147	3798	103 (70.1)**	2211 (58.2)	-	-	No vaccination	Mockeliuniene et al., 2004
Nether-lands	…	9 Herds participating in BHV1[a] vaccination trial >100 involved in international trade	…	Random	>100	1798	-	1169 (65)	-	-	…	Kramps et al., 1999
Norway	1984-86	Wide geographic representation. Norwegian red cattle	Representative, NPE	Random >2years	187	1133	52 (28)	210 (18.5)	-	-	No vaccination	Løken et al., 1991
Poland	…	Bulls at artificial insemination centres	-	> 6 months old	-	175	-	150 (86%)	-	-	…	Polak and Zmudzinski, 1999
Poland	…	Do	-	Do	-	219	-	-	-	5/2* (2.3/0.9)	…	Do
Scotland	1992-93	South West Scotland Breeding bulls on dairy, beef of mixed farms (5 bulls from dealers)	…	Random	78	109	-	85 (78)	-	-	…	McGowan and Murray, 1999
Slovakia	2000	6-12 mo. old	...	Random	45	1295	...	894 (69.0)	-	-	Animals not vaccinated	Vilcek et al., 2003

Table 6. Cont'd

Country/ Region	Study period	Sampling frame	Sampling method		Sample size		Prevalence (AB)		Prevalence (Virus)		Vaccination	Reference
			Herds	Animals	Herds	Animals	Herd level Number (%)	Animal level, Number (%)	Herd level Number (%)	Animal level, Number (%)		
Slovakia	2000	6-12 mo. old	Herds with 70-98% seropositivity	Random	13	462***	-	-	...	6 (1.3)	Animals not vaccinated	Vilcek et al., 2003
Slovenia	1996	5 regions Breeding herds	…	All animals in herd	274	6892	-	1144 (16.6)	-	-	…	Grom et al., 1999
Spain	1994	Castilla-León	...	...	51	3496	-	-	13 (26)	26 (0.7)	...	Source: Eduardo Berriatua
Spain	1997	Asturias region. Dairy herds	Random/stratified NPE	> 1 year old 20 herds: all animals. 8 herds: Random	28	529	24 (86)	112 (21.1 (CI: 17.8-24.6))	-	-	No vaccination	Mainer-Jaime et al., 2001
Sweden	…	11 counties in different parts of Sweden	NPE	Breeding heifers	114	711	-	292 (41)	-	12/9 (1.7/1.3)*	No vaccination	Alenius et al., 1986
Sweden	1987	County of Kopparberg. Dairy herds	Random	All lactating cows	15	413	11 (73)	190 (46)	-	-	No vaccination	Niskanen et al., 1991
Switzerland	1994-1995	Canton of St. Gallen	Random	Cows and heifers (all)	95	2892	95 (100)	2421 (83.7)	-	-	…	Braun et al., 1997
Switzerland	1995	Canton of St. Gallen, 7 Alpine pastures. Swiss Braunvieh cattle. Dairy herds	Invited by cantonal veterinary officer	Animals prior to pasture; 98% were replacement cattle. NPE	149	990	-	627 (63.3)	-	9 (0.9)	…	Braun et al., 1998
Switzerland	1993-1994	Dairy herds	Random (at least 5 cows)	All cows	113	1635	112 (99.1)	1174 (72)	-	-	…	Stärk et al., 1997
United Kingdom	1974-75	England and Wales	3 herds in each county	12 per herd representing a range of ages	133	1593	-	988 (62)	-	-	…	Harkness et al., 1978

Table 6. Cont'd

Country/ Region	Study period	Sampling frame	Sampling method		Sample size		Prevalence (AB)		Prevalence (Virus)		Vaccination	Reference
			Herds	Animals	Herds	Animals	Herd level Number (%)	Animal level, Number (%)	Herd level Number (%)	Animal level, Number (%)		
United Kingdom	1980-1985	…	…	Beef calves 2-4 m. Cows 2-3 y. Gnotobiotic calves NPE	-	924	-	-	-	7 /4 (0.8/0.4*)	…	Howard et al., 1986
United Kingdom	1985-86	England and Wales	-	Submissions of more than 10 samples to Central Veterinary Laboratory	-	18,759	-	12175 (64.9)	-	-	…	Edwards et al., 1987
United Kingdom	1986	Central Veterinary Lab.	-	Do	-	3151	-	-	-	57 (1.8 (viraemic))	…	Do

Note: Some numbers may have been calculated from percentages given in publications.

General legends and abbreviations in tables:

- Information not measured or not applicable.

. . . Information not available in the paper.

NPE: No past evidence, meaning that herds were *not* selected based on past evidence of infection (unknown BVD status)

AI: Artificial insemination centres

[a] BHV: Bovine herpes virus

* First number: Viraemic. Second number: Known to be PI.

** Not all animals in each herd are tested (i.e. herd prevalence is underestimated)

*** Only 84 antibody negative tested.

Table 7. Published European surveys for determination of herd level prevalence of bovine virus diarrhoea virus (BVDV) infection based on samples on bulk milk or from targeted age groups (spot samples). *For countries that have implemented systematic control, the table includes surveys performed before or in the beginning of the schemes.*

Country/ Region	Study period	Sampling frame	Sampling method	Sample size (herds)	Sample	Herd prevalence, AB Number (%)	Herd prevalence Virus/act. Inf Number (%)[a]	Vaccination	Reference
Austria	1996-98	Nieder-Österreich. All breeding herds	Stepwise: A: milk, B:Spot test and C: All animals NPE	A: 5,024 B: 512 C: 154	Milk Spot test All animals	-	50 (1.0) (PI animals were identified)	…	Rossmanith & Deinhofer, 1998
Denmark	1994	Dairy herds	All herds	16,113	Bulk milk	-	6284 (39) (suspected to have PI	No vaccination	Bitsch& Rønsholt, 1995
Estonia	1993-95 1997-98 1999-00	Dairy herds with >=20 cows	Representative random sample	328 363 351	Bulk milk and/or young stock test		152 (46) 59 (16) 65 (18) (suspected to have PI	No vaccination	Viltrop et al., 2002
Finland	1993	Dairy herds	All herds (>98%)	34,115	Bulk milk	342 (1)	-	…	Nuotio et al., 1999
England and Wales	1996	9 regions Dairy herds>40 cows	Systematic random	1070	Bulk milk	1021 (95.4) (OD>=0.135)	701 (65.5) (OD>=0.9)	No vaccination	Paton et al., 1998
Northern Ireland	1999	Dairy herds	From the largest milk processor	929	Bulk milk	920 (99) (OD>0.04)	461 (49.6) (OD>= 0.55)	…	Graham et al., 2001
Norway	1993	Dairy herds	All herds	26,430	Bulk milk	9779 (37) (OD>=0.05)	1877 (7.1) OD>0.55	No vaccination	Waage et al., 1997
Sweden	1993	Dairy herds	Majority of dairy herds	14,463	Bulk milk	-	7376 (51%) (OD>0.55)	No vaccination	Alenius et al., 1997

[a] Note that the antibody detection methods vary between countries as does the cut offs when a herd is considered to have antibody carriers or PI animals. Prevalences are therefore just indicative of the level and not directly comparable between countries.

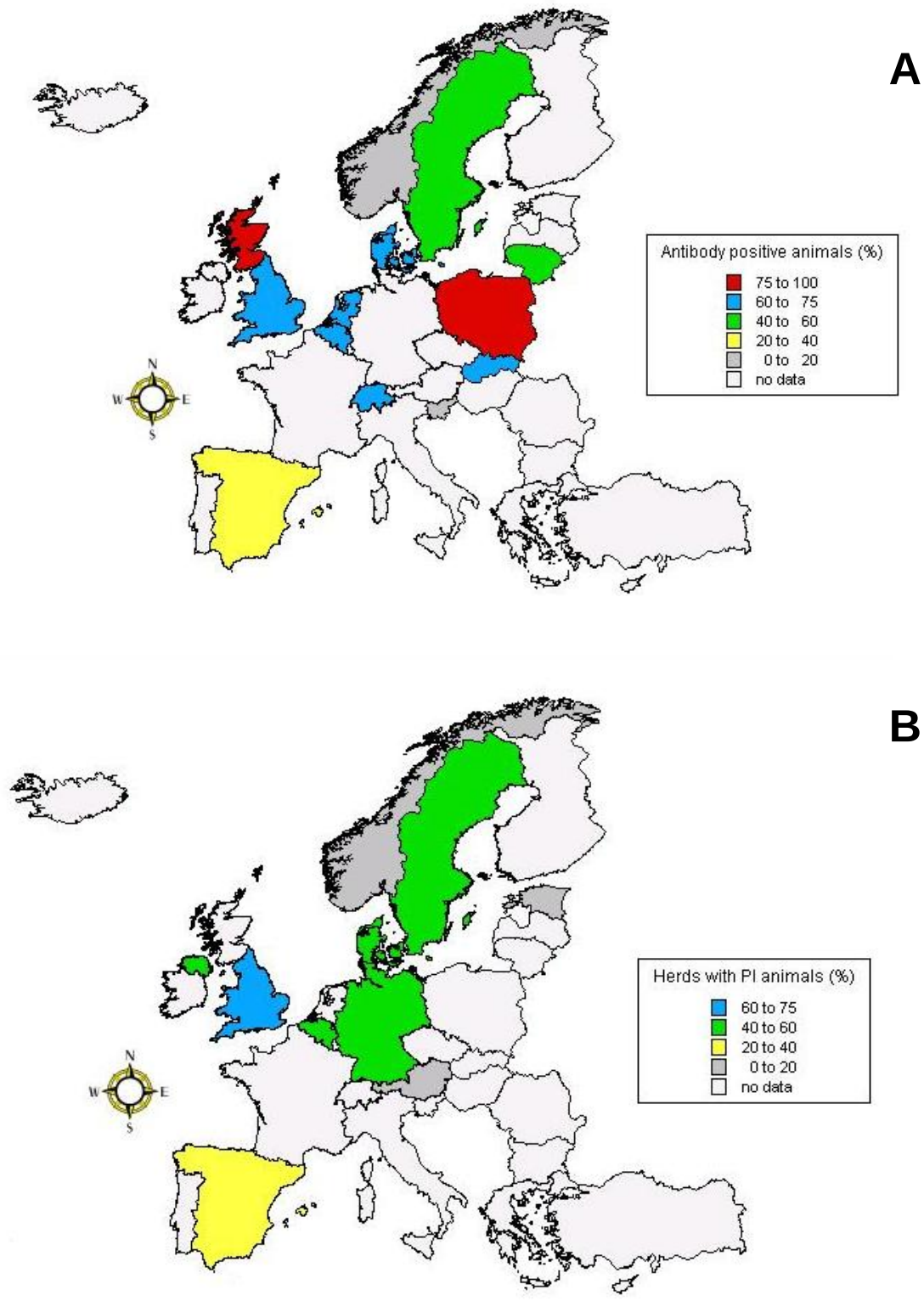

Figure 5. Literature data on prevalence of BVDV antibody positive cattle (A) in 13 European countries/regions and prevalence of cattle herds with virus positive animals (B) in 10 European countries/regions without systematic control schemes in place, or before such schemes were implemented.

Serological surveys performed to date have not typically distinguished between BVDV genotypes. From virological surveys it can, however, be concluded that to date the

predominant genotype in Europe is type 1. Type 2 BVDV has so far been identified in Germany, Belgium, France, the Netherlands, Austria, Slovakia, Italy and United Kingdom.

2.10.1.2 Comparability of prevalence data

It is desirable to compare results from different countries and over time within specific areas. This implies, first and foremost, that there is some sort of random procedure underlying the sample selection and that the sampling frame is representative of the target population. Moreover, the correct classification of an animal or herd as being infected highly depends on the performance of the diagnostic test that is used. All diagnostic tests are imperfect and therefore introduce a certain level of misclassification bias. Therefore only 'true' prevalence estimates which are corrected for the performance of the diagnostic tests (Rogan and Gladen, 1978) should be considered for comparison. Violations of these demands will limit the ability to extrapolate results to the population in question.
Unfortunately, several of the surveys listed in Tables 6 and 7 have not adhered to the above-mentioned practices, they have sometimes been performed on selected populations e.g. those with previous suspicion on BVDV infection, or on non-representative populations like AI-centres. In many surveys, prevalence estimates were not corrected for possible misclassification bias. It is therefore difficult to directly compare surveys from different areas and countries. To increase the usefulness of the information, it is desirable to also have covariate information on such as herd type (dairy/beef), herd size and geographical area. Prevalence estimates should always be reported with their confidence intervals.

The methods used for estimating prevalence in the past have largely followed the concurrent development on the diagnostic side (from individual to herd level tests), and this is also reflected in how the prevalence has been expressed over time, i.e. in what measures have been used. Thus, prevalence measures used in the literature can be divided into individual level and herd level estimates. Estimates at the individual level aim at describing the population prevalence of either antibody or virus positive individuals, whereas herd level estimates are aimed at describing the prevalence of herds with infection, a measure that may be more relevant from a control perspective. Some herd level measures have been directly based on individual level measurements – such as "prevalence of herds with at least one antibody positive animal" or "prevalence of herds with at least one virus positive animal". Others are based on herd level screening procedures (spot tests and tests on bulk milk) were the aim is to measure the prevalence of herds with a high probability of harbouring virus positive animals. The diagnostic tools used for this purpose include serological tests and PCR on bulk milk.
It is important to use prevalence measures that are relevant from an epidemiologic point of view, and reflect presence/absence of the infection. The measure "Prevalence of herds with at least one antibody carrier" should be avoided, because it will can reflect very different situations due to the long-lasting antibody response to BVDV. Herds without active infection may have antibody positive animals present although the infection is not present, and the measurement will be a mix of herds with and without infection. If such information is used, a better approach is one where the distribution of within-herd prevalences is reported (number/proportion of antibody positive animals). Ideally, the within-herd prevalences should be given by age group.
It should also be noted that cross-sectional surveys based on antibody detection may be affected by animal movement patterns. Animals that are antibody positive may have been purchased, and are thus non-representative for the herd they are in. The use of vaccines is another source of misclassification of herd status when it is based on serology. Therefore, all types of studies on BVDV have to be designed so that such misclassification errors can be avoided/reduced.

During the 90's, systematic eradication schemes were launched in a number of countries. These are so far the only areas where the changes in BVDV status over time have been followed in a coherent manner. This has resulted in more detailed prevalence information and also herd incidence data (incidence of new herd infections), which has been very scarce historically.

2.10.1.3 Incidence data

Measuring incidence implies that there is knowledge about the population at risk, i.e. what individuals/herds are initially free from the infection. Therefore, the current knowledge on herd incidence of BVDV infection comes mainly from areas where the infection is being controlled in a systematic manner, i.e. where there is monitoring of herd status in place. The case definition used differ slightly depending on the system that has generated them. For example, in Norway, a positive spot sample on young stock will have lead to restrictions, which has been the basis for their incidence calculations. In Denmark the herds have been classified according to status, and their case definition has been a shift in status from 1 (free) to 3 (presence of PI or high antibody in bulk milk). As comparison, in Sweden, a herd has been considered a new case only when the presence of virus positive animals has been confirmed. A positive scheme sample (e.g. high antibody in bulk milk) would only constitute a suspect case. Consequently, all measures are epidemiologically relevant, but the criteria for classifying a herd as a new case differ in strength of evidence, and this has to be considered in the interpretation.
Herd incidence risk is one of the most important parameters when estimating the cost-benefit of control measures. The experiences from the above-mentioned schemes indicate that the risk of new infections/reinfection has been overestimated in past calculations – however, relevant information from other areas than Scandinavia and Austria is lacking.

2.10.2 Databases of potential use for BVDV research

Secondary data collected for purposes such as breeding, milk recording, disease recording and slaughter house administration can be used to assess the impact of BVDV on production, fertility and animal health. This implies that there is also data available on BVDV status, at the herd level. Studies using such data have been performed, but only on a national basis, covering only a limited number of production systems, and therefore limiting the usefulness of the results. If equivalent data could be combined across countries, and analysed within the same study, it would be possible to get more system- and country specific estimates of effects of BVDV infection, which would provide a more accurate basis for cost-benefit analyses.
A number of countries in Europe have relevant data, being most complete for the countries that have regional or national schemes in place.
There are international collaborations where large quantities of cattle production data are streamlined to ensure comparability and joint analysis. One example is Interbull, the international centre for sire evaluation which is located in Sweden. Data are also shared within an ongoing Nordic project for harmonised breeding evaluation (NAV). Another, but different example is the International EpiLab in Denmark, a centre for epidemiological research focused on using secondary Danish data for investigating issues of interest both to Denmark and to the community as a whole, with help from international experts in the field.

One of the objectives of this Work package has been to establish a system for collecting information on BVDV data sources in Europe and to evaluate the research potential from combining such information. It can be seen from enquiries performed within the network that

data on BVDV research and control are, or have been, collected in about every Member State but that they are mostly unknown to research groups who want to investigate BVDV issues at an EU level. Therefore, an effort has been made to collect information about data sources on BVD and also relevant demographic data in Europe. The aim has been to make an inventory of data sources and to make it available through the website of the Thematic Network. The network partners have been warmly invited to provide input to the database to make it a valuable source of information to colleagues in the area. At current the database is accessible through www.bvdv-control.org.

2.10.3 Demographic data

Detailed demographic data allows more detailed estimates of disease occurrence for smaller regions in the EU. These estimates can be the basis for identifying region-specific risk factors for BVDV occurrence.
Member States may have detailed demographic information for different regions within their territory, but it may be cumbersome to compile this information from all Member States for EU-wide BVDV research. The Eurostat office has complete relevant demographic data available at Member State level. It also maintains a demographic database for the geopolitical entities within the Member States but for on average 50% of these entities data are missing.

2.10.4 Recommendations

Although many European countries have performed investigations into BVDV, information on prevalence is still lacking from a number of EU member countries. Incidence estimates is lacking from most of them. Also, surveys published are difficult to compare due to differences in design and in choice of measure. We therefore recommend that a comprehensive herd level survey to assess BVDV status is performed, preferably in areas where it is still poorly understood. In parallel, we suggest that monitoring systems are set up so that incidence of BVDV infection can be estimated in other regions of Europe, also in areas without other control, so that more accurate estimates of the potential of control measures in reducing risk of introduction can be obtained.

We also recommend that researchers designing prevalence surveys use measures that have a true epidemiologic meaning in terms of presence/absence of infection, and consider the risk of animal/herd misclassification inherent in test strategies based on serology.

Each Member State has installed an animal identification and registration system. If such data are compiled at an EU level, they could become a valuable resource for demographic cattle data.
We recommend that the community should support research where precollected data are joined across countries, to increase the power of the analyses and to make the results more applicable to the community as a whole. A Centre for Epidemiological Research on Infectious diseases should be established, where such data are stored, merged and made accessible for researchers.

2.11 Summary of research needs

2.11.1 Risk factors for BVDV and their relative importance in different regions

Means for mitigating risk factors for BVDV infection can be summarised under the term biosecurity. Biosecurity as it pertains to BVDV control has got a wider application and could be a model for many infectious diseases where the main driver is livestock movements/contacts and where attitudes/traditional behaviour among stakeholders have to be targeted to reach disease control objectives. Research should be targeted towards understanding the drivers and constraints for stakeholders with respect to biosecurity uptake, across Europe.

2.11.2 Methods for identification of risk factors in the late phase of control

There is a need for further research on the significance of identity and disparity, i.e. the validity of molecular epidemiology as a tool for tracing sources of new infections and identifying low frequency risk factors. This research will be greatly facilitated by improvements in the scientific infrastructure proposed by WP1, such as the creation of a genome database where protocols for submission are standardized.

2.11.3 Risks of re-infection in freed areas

New research suggests that virus persists in animals that have undergone an acute infection for longer periods than previously thought. It is still not known for how long and if virus can be reactivated. Other reports suggest that BVDVs exhibit strain differences in the affinity to embryos, and that current risk management procedures may be inadequate. This highlights the needs for continuing research into the various ways by which BVDV can survive and be transmitted between animals and herds, as well as the relative significance of different routes.

2.11.4 Health and production effects of BVDV under different production settings

There is a great need for research into the contextual effects of BVDV infection, in particular how the production system affects the type and magnitude of negative outcomes, but also the significance of differences in virulence and the effect of co-infections. Efficient research within this area calls for an upscaling based on the use of existing data bases, a process which would be highly facilitated by the establishment of a dedicated research centre.
BVDV can “hide” under many other infectious conditions and this has implications for priority settings, both for reducing antibiotic usage and for improvement of animal welfare. The contribution of BVDV infections in this respect should be an area for future research.

2.11.5 Methods for infection dynamics modelling

To improve existing models within-herd models, there is still need for experimental or field information should to justify assumptions about the force of infection and to estimate transmission parameters. Apart from providing insight into the effect of control measures at the herd level, within-herd models can generate input data for between-herd models. By modelling between-herd transmission dynamics, the impact of control measures at a larger scale can be quantified. Such modelling has not been performed for BVDV even though the preconditions in terms of necessary data are very good.

Future development is towards meta-population models that focus on the spread between regions and countries, and where heterogeneities that increase or reduce transmission can be incorporated. The effect of contact structure on the consequences of disease introduction, and consequent prospects for control is another, related, area of current and future interest. Similar to what is said in section 2.11.1, BVDV could serve as a generic model disease for such studies.

2.11.6 Research potential in joining BVDV information within Europe

The primary potential in combining data sources (both related to BVDV infection status, to cattle demographics and to production data) would be the power to get more system- and country specific estimates of effects of BVDV infection. This would, in turn, provide a more accurate basis for cost-benefit analyses. Such data could also be of value for investigating transmission and validating input for between-herd modelling. The maintenance of a transnational research database for livestock diseases is a long term project, and such a task would preferably be assigned to and established within a centre with appropriate epidemiological and administrative skills.

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Vaccines and vaccination strategies

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3.1 Executive summary

Bovine viral diarrhoea (BVD) occurs worldwide in practically all regions where cattle are raised. Up to about 20 years ago, it was thought that effective control or even eradication of the infection was therefore futile. A paradigm shift occurred when the Scandinavian countries successfully commenced to eradicate BVD by implementing a strict test and removal policy for animals persistently infected (PI) with BVD virus (BVDV) that was accompanied by movement restrictions for infected herds. Vaccination against BVDV was banned. Some other European countries are following the Scandinavian strategy. However, most other countries hesitate to adopt this control approach, because of adverse conditions, e.g. high cattle density in conjunction with high BVD prevalence, intense trade and/or lack of clear legal rules. In such cases, the test and removal strategy, with its fundamental elements of biosecurity, removal of PI animals and monitoring of herd status, in combination with systematic vaccination, is a promising alternative for an efficient BVD control leading to a crucial reduction of PI animals and infectious pressure. When used in the framework of a systematic control programme, this approach can serve as first step towards eradication of the infection.

3.2 Recommendations

a. With respect to the antigenic diversity of BVDV, data concerning the efficacy and safety of BVD vaccines should be clearly available to all users and – if necessary - expanded.
b. Vaccines and vaccination protocols with explicitly high foetal protection should be defined and further developed
c. Efficacious marker vaccines should be developed for use in control programmes progressing towards eradication.
d. Strategies for vaccination in conjunction with the identification and removal of PI animals could be refined for regional use for BVD control programmes. This will be important in those areas where there is either only a voluntary programme and potentially limited uptake by farmers or in the initial stages of a national programme, where there is concern to prevent BVD disease breakdowns in ‘clean’ herds.
e. Establishment of a virtual surveillance system in order to monitor the prevalence of BVDV-2 and other potentially emerging ruminant pestiviruses in Europe and a possible expansion of the present national data base should be considered. The efficacy of existing vaccines to induce protective immunity against BVDV-2 should be examined and reported. Any failures in preventing the development of PI animals should be noted. Based on these results the development of BVDV-2 vaccines may be taken into consideration.
f. Legislative support for BVD-free countries should be considered to support the status in intracommunity and international trade.

3.3 Objectives

The objectives of work package 3 of the Thematic network on BVD control have been;

- To evaluate methods and guidelines provided for vaccine trials
- To evaluate methods and strategies for the use of vaccines as part of a systematic control strategy and as part of zoo-sanitary control
- To evaluate safety precautions and systems to ensure safety for vaccines

3.4 Introduction

The concept for controlling of bovine viral diarrhoea (BVD) infection has changed since the first description of the disease almost 60 years ago. This change reflects the growing insights in the pathobiology, the economic impact of the infection and the development of suitable control tools. When Olafson and coworkers (1946) described a transmissible disease of cattle they named it "bovine viral diarrhea". This inconspicuous term did not reflect the enormous damage caused by BVD virus (BVDV) infections. Even when Ramsey and Chivers (1953) described the highly fatal “Mucosal Disease” (MD) it took some years to find out that MD too was somehow caused by BVDV (Gillespie et al., 1960). More than two decades later the link between immunotolerance, virus persistence and the two biotypes of BVDV, i.e. noncytopathogenic (ncp) and cytopathogenic (cp), was discovered (Brownlie et al. 1984, Bolin et al. 1985). Other pathogenic features of BVDV infections, e.g. immunosuppression, intrauterine infection with all its sequelae and involvement in haemorrhagic disease were also only recognised over time (Ward, 1969; Brownlie 1991; Pellerin et al, 1994)). With each new insight the full economic damage inflicted by BVDV infections on the cattle industry became clearer. It is this growing understanding of the widespread damage caused by BVDV to both cattle rearing and production that has catalysed the regional and national campaigns for BVD control and eradication.

3.4.1 Brief history of BVD control

In the 1960’s, when BVD vaccines first became generally available, they were used in single herds, i.e. in ‘non-systematic control’ programmes, and not within strategic frameworks of eradicating reservoirs of infection under implementation of good biosecurity. Thus, prophylactic vaccination was used only in order to prevent economic losses and no attempts were made to eradicate the ubiquitous BVDV systematically on either a regional or national basis. Even though the crucial epidemiological and economical importance of animals persistently infected (PI) with BVDV was known, such attempts were considered futile, because there were either no or only unsuitable diagnostic tools at hand. . The availability of new laboratory methods for serological and virological mass screening of cattle changed the situation. Laboratory methods used were newly developed enzyme immunoassays (ELISA) to detect antibodies in bulk milk samples and later the detection of PI animals was facilitated by antigen capture ELISAs. More than ten years ago, the Scandinavian countries and Finland designed the first national schemes for the systematic eradication of BVD. These programmes were based on the identification of herds with active BVDV infections, tracing and removal of PI animals and movement restrictions as well as other zoosanitary measures. Vaccination was banned (Bitsch and Ronsholt, 1995; Lindberg and Alenius 1999). These programmes

have been very successful; and these countries are now free or almost free of BVD (Sandvik, 2004).
In the meantime several European states and regions, e.g. Austria, Shetland Islands (UK) and the Italian province of Bolzano have adopted the Scandinavian approach for systematic BVD control.

Another early attempt to control BVD, though different from the Scandinavian approach was undertaken in the German federal state of Lower Saxony.The structure of the cattle industry was complex and local cattle densities exceeded 150 animals per km^2 with seroprevalences ranging from 50% to close to 100%, with a prevalence of PI cattle ranging between 1 and 2% (Frey et al., 1996; Bendfeldt et al., 2004). In 1985 the "Tierseuchenkasse Niedersachsen", a partially government-financed livestock insurance, redrafted its statutes and for the first time the search and removal of PI cattle became eligible for compensation. The new regulation came into force after notification by the EU Commission in 1988 and was designed to improve the health status of individual herds. The participation in the programme was entirely voluntary as there was no legal requirement for participation, and funds for an overall approach to eradicate BVDV were not available. An obvious disadvantage of the programme soon became evident, when herds free of PI cattle turned seronegative in an environment where BVDV was almost ubiquitous. In response the statutes of the "Tierseuchenkasse" were amended in 1992 and complete vaccination of all female cattle in herds that had been cleared of PI animals was recommended. The purpose of vaccination was to protect cleared herds against reintroduction of BVDV and to prevent the emergence of new PI animals. A third amendment in the year 2000 ruled that the costs of the vaccine would be paid for by the "Tierseuchenkasse" (Anonymous, 2000). The concept of the complete removal of PI cattle combined with the protection of herds free from PI animals using vaccination was adopted by the German federal government and in November 2004 BVD became a notifiable disease, and a directive aiming for the nationwide systematic control of BVD is in preparation.

3.4.2 Brief history of BVDV vaccines

The first BVDV vaccine described was from the USA in the 1950's (Baker et al. 1954). The first commercial BVDV vaccine was described later (Coggins et al., 1961). Since that time, it has become the most represented component within bovine multi-valent vaccines; in the Compendium of Veterinary Products, the USDA have currently licensed more than 160 vaccines with either BVDV alone or in combination with other products. It is interesting to note that the first vaccine described by Baker et al (1954) was a modified live vaccine (MLV), developed following the serial passage of NY-I after 75 transfers in laboratory rabbits. Moreover, in the 21 vaccines most recently licensed by the USDA (between 2000-2003), all but two were also MLVs whereas the remaining two were inactivated vaccines (Ridpath, 2005).

As it is estimated that between 70-80% of cattle producers in North America use vaccines containing BVDV antigens, it can be seen that BVDV vaccines have been widely used for a long period of time, and a large number of BVDV vaccines have been available worldwide. In most cases vaccination was used on a herd basis, i.e. not in the context of a systematic control/eradication programme. However, there is controversy about the benefit of vaccination against BVDV.

The original purpose of BVDV vaccination included a number of indications, e.g., respiratory disease, reproductive failure and diarrhoea and, to this end, it was included in most respiratory

multi-component vaccines. However, in the last 20 years, a further aspect of protection against BVDV infection has been shown. BVDV can be vertically transmitted to the next generation, via the creation of a PI animal. This means that long-term control hinges on the protection of the breeding herd and prevention of the birth of new PI animals. Meanwhile vaccine developers and users have focused on this problem and there are vaccines and vaccination protocols available that confer intrauterine protection against BVDV 2. (Brownlie et al., 1995; Paton et al., 1999; Frey et al., 2002; Oguzoglu et al., 2003). However, in light of the antigenic diversity between and within the BVDV species a full appreciation of the extent and duration of effective immunity is not feasible.

3.5 BVDV Vaccines available in EU

The EU pharmaceutical legislation has evolved over the past 35 years with harmonisation of veterinary medicines beginning in 1981 (Directives 81/851/EEC & Directives 81/852/EEC). Although immunologic veterinary products were initially excluded, in 1993, there was a Directive to include all vaccines within a harmonised legislation (Directive 90/677/EEC). Contingent with this legislation has been the formation of the European Pharmacopoeia; this in turn has commissioned some 75 vaccine monographs (Pastoret and Falize, 1999). One of these monographs deals with veterinary vaccines, including BVDV.

3.5.1 Modified live vaccines

BVDV field infections induce a strong and long-lasting immunity in cattle, based on humoral and cellular responses (Bolin and Ridpath, 1995; Beer et al., 1997; Fredriksen, 1999; Collen et al., 2002). The essential aim for developing MLVs is to reduce, preferably eliminate, the virulence of the live strain in order to prevent any disease in the vaccinated animal or any possible onward transmission of the vaccine virus to in-contact hosts. There are various mechanisms whereby this can be achieved. The most successful one has been the continual *in vitro* passage in cell culture of the pathogen over time. Viruses have been shown to attenuate by the process of selection of mutants that grow better in culture than *in vivo.* It commonly takes 40-90 passages for the virus to lose virulence for the host and to be safely used in field conditions. Foetal protection can be considered high. Similarly, most MLVs, except temperature sensitive mutants, replicate in the animal thereby inducing solid immunity (Cortese et al., 1998; Kovacs et al., 2003). Since the nature of attenuation of live BVDV vaccines is rarely known, it may be suspected that vaccination is followed by some transient immunosuppression, and potential short-lived viraemia, as observed in natural infection (Roth and Kaeberle, 1983). However, there are no published field observations to back up this assumption.

Typically, live virus vaccines are highly efficacious, cheap to produce and have good duration of immunity. Their disadvantages are the theoretical potential for reversion to virulence, including the ability to recombine with field strains and the ever-present possibility for contamination of vaccine strains with field strains. This last possibility is a real threat for BVDV vaccines, and where bovine foetal calf serum is used as a cell culture growth supplement it holds for all live cattle vaccines. When applied improperly, i.e. during pregnancy, MLVs induce a transient viraemia and can cross the placenta, resulting in PI calves or other reproductive disorders (Orban et al., 1983; Liess et al., 1984). Many live vaccines are based on cp BVDV since this biotype seems not to be able to cross the placental barrier (Brownlie et al., 1989), however, many vaccines, although primarily a cp BVDV, will

be a combination of both biotypes. When administered to PI animals there is a high risk for the animals to develop either acute or late onset MD. The latter is likely to develop when the antigenic makeup of endogenous ncp and exogenous cpBVDV differs. In these cases, a late form of MD may develop after recombination of ncp and cp viruses (Fritzemeier et al., 1997; Löhr et al., 1998). Due to the severe welfare consequences, measures should be taken to avoid vaccination of PI animals with cp live vaccines.

A further attenuation method has been the development of a temperature-sensitive BVDV mutant that had only limited replication at the respiratory mucosal surface, therefore having lost its ability to become viraemic and thereby unable to cross the placenta (Lobmann et al 1984). However, this vaccine was also shown to be able to induce MD in PI animals (Becher et al., 2001), and the immune response after repeated vaccination was shown to be poor (Frey et al., 1999).

3.5.2 Inactivated Vaccines

There are a number of mechanisms for inactivating viruses, many used for disinfection and sterilisation. The essential rationale for inactivating viruses for use in vaccines is to preserve the maximum antigenicity whilst eliminating all infectivity. For this to occur, it is advantageous to inactivate the nucleic acids (DNA/RNA) whilst preserving the protein viral coat. For BVDV, this is often by use of nucleic acid denaturants such as β-propriolactone (BPL), acetylethyleneimine (AEI) or ethyleethyleneimine (EEI). Alternatively, alkylating agents such as formaldehyde and glutaraldehyde. Both nucleic acid denaturants and alkylating agents have been used in the inactivation of BVDV vaccines.

Inactivated vaccines primarily elicit a humoral immune response that is somewhat weaker and of shorter duration compared to live vaccines. However, the incorporation of saponins, as adjuvants for inactivated vaccines, does provide both humoral and cell-mediated immunity, thereby widening the efficacy of the protective immunity (Morein, 1990). Inactivated vaccines are safe compared to live vaccines and they may be administered at any stage of gestation. Whereas some BVDV inactivated vaccines give good foetal protection following dam vaccination (Brownlie et al., 1995) some vaccines illicit a poor foetal protection (Zimmer et al., 2002). Depending on the product revaccination in 6 to 12 months intervals are required. In the field, the duration and extent of foetal cross-protection, in particular against heterologous strains, is not clear (Gaede et al., 2004; Graham et al., 2004; Laven et al., 2005).

3.6 Use of vaccines in EU

Europe is divided in the use of BVDV vaccines. For some countries, e.g. Scandinavian countries and Finland there is no availability of vaccines and even a prohibition on their use. In others, e.g. France, Germany and Spain there are several vaccines, both modified live and inactivated available. In the UK and Ireland, only inactivated BVDV vaccines have been licensed for use. The take-up of vaccines in countries, where they are registered, is commercially sensitive information and prevents accurate collection of usage. There is little doubt that it will vary between countries; our survey would indicate that across Europe BVDV vaccines are used, on average, in about 20% of livestock units; this is far less than the 80% usage in North America. In the EU countries, there are also different protocols for vaccine incorporation.

A recent questionnaire to the members of the BVDV Network has provided some interesting comparisons of those vaccines available, and used, in the different European countries (**Appendix A**). The differences in usage are not easily explainable on scientific grounds; it is more than likely to be cultural or commercial reasons.

3.7 Limits and problems of vaccination

The implementation of vaccination in the control of BVD has met some scepticism. In many countries vaccination against BVDV had been used for at least four decades without any noticeable overall reduction of BVD prevalence (O'Rourke, 2002). It might even be hypothesised that widespread vaccination using live BVDV-1 vaccines promoted the spread of BVDV-2 first in North America and later in Europe. Considering the widespread use of vaccines in the last four decades in countries with a high BVD prevalence, the question arises as to why vaccination has failed to reduce the incidence of BVD. The issue of vaccination and its limitations has been reviewed extensively by van Oirschot et al. (1999). Thus, before implementing vaccination in a control/eradication scheme, vaccination related problems must be carefully analysed. These problems include the failure of properly undertaking vaccine protocols correctly (Quaife, 1996) and the failure of vaccines themselves.

3.7.1 Antigenic variation

BVDV display quite a diversity of antigenic variants, although there are no distinct serotypes and there is cross reactivity throughout all genetic groups and BVDV species (Dubovi, 1992; Hamers et al. 2002). This antigenic variation may interfere with the efficacy of vaccination, since immunity in vaccinated cattle is strongest against the homologous vaccine strain(s) and less pronounced against field strains of differing antigenic makeup. The higher the homologous immune response the higher the degree of cross protection may be expected. Therefore any vaccination against BVDV should induce an immune response as high as possible. Frequent revaccinations and/or the use of MLVs may be suitable measures in order to keep immunity high.

3.7.2 Incorrect use of live vaccines

The first BVD vaccines were modified live preparations of the cp biotype of BVDV. In general these vaccines yielded satisfactory results, however, it took several years before the risk of *in utero* transmission of vaccine virus to foetuses was properly appreciated. Despite the fact that cpBVDV apparently does not cross the placenta (Brownlie et al., 1989), foetal infections after vaccination were observed. Most probably they were attributable to ncp contaminants of the vaccine. Incorrect use of MLVs in pregnant animals and the possibility of vaccine virus to be shed by vaccinees and transmitted to pregnant cattle discredited this type of vaccine and led to the increased development of inactivated vaccines.

3.7.3 Goals of vaccination

With evolving control concepts goals of vaccination changed. For a long period after the registration of first BVD vaccines the prevention of clinical signs, e.g. diarrhoea and respiratory disease, was the purpose of vaccination. When testing vaccines, challenge infections were used to observe the vaccinee's reaction in terms of fever and possibly viremia. However, in terms of control of BVD infection the disruption of the infectious cycle is important, i.e. prevention of the birth of PI animals. The relative inadequacy of many vaccines

and vaccination protocols became apparent, when foetal protection was explicitly required by veterinarians and farmers. Where vaccination becomes part of a systematic control programme the best possible foetal protection will then be the only and most important goal of vaccination.

3.7.4 Failure to elicit an adequate immune response

When goals of vaccination changed from the rather unspecific claim to prevent clinical disease to the very clear postulate to prevent BVDV-related reproductive failure, it became clear that a number of registered vaccines did not fulfil the requirements. There are doubts whether many current vaccines and vaccination protocols are suitable to prevent completely *in utero* transmission of the virus. In this context van Oirschot et al. (1999) deplore the lack of reliable in depth studies on BVD vaccine efficacy. Intensity and mode (humoral, cell-mediated) of immune response and duration of immunity after vaccination are salient issues. The present view is that varying levels of protection can be reached using BVDV vaccines but that immunisation against BVDV may not confer a full protection against intrauterine infection in all field situations (Kelling, 2004)

3.7.5 Failure to remove PI animals in a systematic manner

Most non-systematic control attempts do not require the removal of PI-cattle. On the contrary: PI animals were considered to be cheap means of "vaccinating" herds. In addition it was thought that most of them would die anyway within a short time after birth. These strategies have never been proven to be successful. In addition experience suggests that a policy of systematic vaccination alone, i.e. without prior removal of PI animals fails in the long run to reduce the overall BVD prevalence of a larger cattle population. Apparently PI animals exert such an enormous infectious pressure, that vaccine protection can fail and the infection continues to persist in the herd.

3.7.6 Failure to adhere to control strategies

As with other infectious disease control programmes, a half-hearted (non-systematic) approach can never be successful. Full commitment to biosecurity routines and adherence to an efficacious vaccination programme would be essential for their success. The observation that farmers and veterinarians often do not correctly adhere to vaccination strategies might be an additional interfering factor for the failure of vaccination to reduce the overall BVD prevalence (Quaife, 1996). In one large survey in Pennsylvannia, only 27% of BVDV vaccines were used correctly in the field; this would have profound effects of efficacy of any vaccine. Likewise frequent movement of (unmonitored) cattle interferes with control efforts considerably.

3.7.7 Spread of BVDV infections by injectables and vaccines against other viral infections

It has been shown that injectables contaminated with BVDV have the potential to be vehicles for BVDV transmission from infected to non-infected herds (Niskanen and Lindberg, 2003). Although the amount of virus may be small, it is sufficient when the natural barrier is overridden. Risky products in this context are those that are extensively used both on groups of animals where PI animals may be present, as well as on dams in early pregnancy, such as sedatives, analgetics, killed vaccines etc. Recently, BVDV was spread in The Netherlands

through live, contaminated BHV-1 vaccines. The economical impact of this incident was considerable and so was the loss of confidence among veterinarians and farmers in using live vaccines for disease control (Barkema et al., 2001). Since most biologicals in veterinary medicine are manufactured using foetal calf serum originating from different parts of the world, BVDV strains exotic to Europe may be introduced by this route.

However, despite all shortcomings there is evidence that vaccination in conjunction with the identification and removal of PI animals on a herd basis is suitable to prevent accidental reintroduction of BVDV (Thibault et al, 1993), particularly where there is still a high regional prevalence of BVDV infection, Thereby BVD related economic damage including PI animals can be prevented (Eicken et al., 2004).

3.8 Today's requirement for BVD vaccine safety and efficacy

The requirements for safety and efficacy have been set out in the European Pharmacopoeia monographs for veterinary vaccines. The relevant paragraphs are outlined below.

Safety

Inject a double dose of the vaccine by a recommended route into each of two cattle of the minimum age recommended for vaccination and that are free from bovine diarrhoea virus and antibodies against the virus. Observe the animals for 14 days. No abnormal local or systemic reaction occurs.

Inactivation

Carry out a test for residual infectious bovine diarrhoea virus by inoculating not less than 10 doses onto cells known to be sensitive to bovine diarrhoea virus; passage the cells after 7 days and observe the second culture for not less than 7 days. No live virus is detected. If the vaccine contains an adjuvant, separate the adjuvant if possible from the liquid phase by a method that does not interfere with the detection of possible live virus.

Potency

Use not fewer than twenty heifers that do not have neutralising antibodies against bovine diarrhoea virus. Vaccinate not fewer than thirteen animals using the recommended schedule. Keep not fewer that seven heifers as non-vaccinated controls. Keep all the animals as one group. Inseminate the heifers. Take a blood sample from non-vaccinated heifers shortly before challenge. Between the 70th and 90th days of gestation, challenge all the animals by the intranasal route with a non-cytopathic strain of bovine diarrhoea virus. Non-vaccinated animals that show antibodies against bovine diarrhoea before challenge and animals that are not pregnant at the time of challenge are excluded from the test. The test is invalid if fewer than ten vaccinated animals or five non-vaccinated animals remain at the time of challenge. Observe the animals clinically from challenge until the end of gestation. If abortion occurs, examine the aborted fetus for bovine diarrhoea virus by suitable methods. Immediately after birth and prior to ingestion of colostrum, examine all calves for viraemia and antibodies against bovine diarrhoea virus. Transplacental infection is considered to have occurred

if the virus is isolated from fetal organs or if virus is detected in fetal blood or if antibodies are detected in precolostral sera. The test is invalid if transplancental infection fails to occur in one or more controls. The vaccine complies with the test if there is no transplacental infection in 90 per cent of vaccinated animals.

Reviews of published reports on BVDV vaccine efficacy have been published (van Oirschot et al., 1999; Kelling, 2004). In these reviews a number of vaccines has been compared with respect to their range of protection.

3.9 Vaccine use in control/ eradication programmes

The accomplished or forthcoming eradication of some important human and animal viral diseases was greatly facilitated by the use of systematic prophylactic vaccination. On a global scale smallpox, polio (Andre, 2003), and rinderpest (Roeder and Taylor, 2002) are examples for the potential of systematic vaccination. On a regional or national basis vaccination made possible the elimination of foot-and-mouth disease, classical swine fever (CSF) and Aujeszky's disease (Müller et al., 2003; Terpstra and Tielen, 1976).
Taking into account the problems associated with BVD vaccination (see above) it should nevertheless be possible to utilise effective vaccines and implement adequate vaccination protocols in the control of the infection.

3.9.1 Rationale

In the context of this paper control is defined as a systematic approach to reduce disease incidence and prevalence of BVDV infection in a defined geographical area to acceptable economical levels. Subsequently adequate measures for the eradication, i.e. the zero incidence of disease and the absence of BVDV, should be considered. The successful control/ eradication programmes in Scandinavia have proven that the removal of PI cattle accompanied by strict zoosanitary measures including movement restrictions are suitable procedures to eventually eradicate BVDV. On the way to reach eradication of BVDV there are several crucial factors to be considered:

- Prevalence of BVDV infected herds in the area considered.
- Structure of cattle industry including cattle density, intensity of trade, monitoring of herds and animals.
- Information to and commitment by stakeholders (especially farmers and veterinarians) involved in the programme.
- Legal basis and compensation for control measures.
- Diagnostic services.

The Scandinavian example may not apply for all regions or countries of the EU since one or more of the above factors do not favour the direct approach. In cattle dense areas with intense animal trading BVD prevalence is usually high and PI cattle provide dangerous reservoirs for continuous reinfections of susceptible cattle. Lack of compulsory regulations for BVD control make voluntary and non-systematic control efforts in such environments face a constant risk of reinfection of cleared herds, thus adding excessive and unnecessary costs to the farmers. When one or more of these conditions apply it is proposed to implement systematic vaccination of cattle against BVDV in initial stages of control/eradication programmes. Herds that have been tested and are free from PI animals should be vaccinated systematically in

order to maintain a high level of immunity against BVDV. The goals and benefits of vaccination are:

- Prevention of accidental reinfection of herds that are free of PI animals and thereby reduction of direct and indirect losses caused by acute infection
- Provision of foetal protection in pregnant animals in order to prevent the genesis of new PI animals
- Regional/national reduction of susceptible herds/animals and thereby reduction of circulation of field virus and infectious pressure in cattle populations, respectively

In later stages of the control programmes when the incidence of PI animals is negligible there is the option to discontinue vaccination in order to reach a fully BVD-free status.

3.9.2 Strategies

Based on historical experience, vaccination as a stand-alone tool is not suitable for the successful control of BVD. First and foremost, a biosecurity programme preventing introduction of PI animals and dams pregnant with PI foetuses is needed. Identification and elimination of PI animals must precede vaccination and all female animals in cleared herds must be protected by vaccination in order to prevent the generation of new PI animals, i.e. foetal protection should be as complete as possible.

Proponents of a strategy including vaccination argue that in high density cattle areas with high BVD seroprevalences the risk of reinfection of seronegative herds is unacceptably high, thus impairing success and increasing the costs of the programme. In fact the risks of spread of BVDV and the risks of reinfection have been assessed several times (van Schaik et al. 2002; Alban et al., 2001). Essentials for a combined test-and-removal/vaccination strategy are:

- Removal of PI animals before vaccination must be a compulsory element.
- Promotion of safe trade, i.e. all herds can trade depending on their status. In any case reintroduction of the infection into recently cleared herds and to non-infected herds must be prevented.
- The immunity conferred by vaccination must induce the broadest and most enduring foetal protection possible.
- Vaccination of female cattle must be systematic, comprehensive, and performed in a way that is safe for pregnant cattle.
- A group of young animals in epidemiological contact with the main herd from six months of age must be kept unvaccinated. They should be monitored for BVDV antibodies so that biosecurity and/or vaccination breaches can be rapidly detected.
- The risk of spreading BVDV with injectables that are used in both infected and non-infected herds should be acknowledged and avoided.
- The best possible compliance of all stakeholders.

3.9.2.1 Immunisation protocols

Effective vaccination should provide protective immunity without any adverse risks from vaccination. The choice of vaccine should be based on its level of safety and efficacy. For the terms of reference of this paper the primary goal of vaccination against BVDV is to protect

pregnant animals and their foetuses. However, the data concerning efficacy are often insufficient and conflicting. A constant review of current evidence is therefore required. Time of vaccination is crucial. In any case the protection of cattle in early pregnancy has to be ensured, i.e. vaccination must be performed before insemination.

It is vital that breeding cattle are virus-negative and receive primary immunisation before first service. Heifers can be batched as yearlings and receive the primary course in good time before the commencement of service. Thereafter single booster doses are recommended before subsequent service periods to ensure optimal immunity is present at the stages of greatest potential risk i.e. service period and early to mid pregnancy.

Immunisation with a primary course of vaccine for the whole breeding herd will be most applicable in the following situations: Negative and thus naïve herds where there is a risk of virus entering the herd and/or where the value of the stock warrants an insurance policy, herds of high genetic worth and those herds carrying out embryo transfer work, herds that are experiencing ongoing loss associated with BVDV, e.g. early embryonic death, poor conception, abortion, enteric disease, immunosuppression.

The alternative route forward is a progressive approach during and after removal of PI animals, starting with the heifers and building up each year towards a fully vaccinated herd; this is particularly relevant where the adult herd has been widely exposed to natural infection and vaccination would add little benefit. However, for the young replacement stock, this is not the case. Heifers are the building blocks of the future herd. These are normally the animals on the farm into which the greatest level of genetic investment has been made. Increasingly, heifers may be reared away from the main herd and as such may have a very different disease status. In the first year bulling and first calved heifers can be vaccinated with a primary course. In the following year, these animals are given a booster dose and the next group of bulling heifers receive a primary course. With time, this leads to a fully vaccinated and protected herd.

3.9.2.1.1 Live vaccines

Attenuated live BVD vaccines bear the inherent risk of all live cattle vaccines, i.e. contamination with BVDV from foetal calf serum used in the production process. It might be difficult to distinguish the attenuated live from the contaminating BVDV, and the contaminating virus could induce major damage to the vaccinees and/or their foetuses Last but not least a possible shedding of vaccine virus to non vaccinated animals has to be considered (Brownlie, 1996). On the positive side live vaccines, if administered properly induce after one application a good and relatively long lasting immunity and a high degree of foetal protection. However, the evidence for the longevity of protection needs further definition. They are typically applied in young animals with no detectable maternal antibodies and not later than 8 weeks before the first insemination.

3.9.2.1.2 Inactivated vaccines

Inactivated vaccines are safe and the time of immunisation is not critical from the safety point of view. However, as with modified live vaccines they should be administered in order to protect animals in their early pregnancy. All inactivated vaccines have to be given at least twice for the priming schedule, i.e. a basic immunisation has to be followed by a booster injection about 4 weeks later. The primary course should be completed before young breeding

animals are accepted into the breeding programme. Yearly revaccination is required by most of the recent BVDV vaccines claiming *in utero* protection.

3.9.2.1.3 Combined use of live and inactivated vaccines

In search for an efficacious vaccination regime that would meet the requirements of a BVD control programme, two-step vaccination procedures utilising inactivated and modified live vaccines have been proven to be suitable. Inactivated vaccines are used for the first immunisation and four weeks later the modified live virus vaccines are administered. Analysis of the immune response of vaccinated cattle has displayed a remarkably high and long lasting humoral immunity against BVDV-1. Also, with a regional prevalence of 1-2% of BVDV-2 it was reassuring to find that two-step vaccination achieved foetal protection against a challenge with heterologous BVDV-2 (Frey et al., 2002). Three years after immunisation there were still significant neutralising titres against BVDV-1 strains (80-320), however, immunity against BVDV-2 had reached a critical low of <100 by 18 months post vaccination (Oguzoglu et al., 2003). These findings stress the need for regular revaccination. For revaccination inactivated vaccines are used.

A disadvantage of this programme is the strict requirement for two different vaccines (inactivated and live) to be given in the correct order and, within the prime/boost initial programme, both before the breeding programme.

However, two step vaccination is currently a well accepted vaccination procedure in Germany and it can be expected that it will play a major role in the first phase of the forthcoming compulsory BVD control programme. Vaccination will most likely be banned in the second and last phase of the programme after clearance of the majority of herds from PI animals.

3.10 Future threats

In contrast to CSF virus (CSFV), a closely related pestivirus, BVDV displays a broader genetic and antigenetic diversity. Initially only one genotype of BVDV was known of. First reports of a BVDV-induced acute infection, often with extensive fatalities, came from New York State, USA (Rebhun et al., 1989). From these cases a ncpBVDV was isolated that showed marked genetic and antigenetic differences when compared to the BVDV so far known. Consequently the terms BVDV genotype 1 (old) and 2 (new) were introduced (Ridpath et al., 1994), and in 1997 the genotypes were assigned the taxonomic status of species (van Regenmortel et al. 2000). It is now evident that BVDV-2 isolates can cause both fulminant disease and inapparent infections in the field; much as is seen with BVDV-1 isolates. Both BVDV species are now fairly well characterised in terms of genetic properties and their distribution in the cattle population.
The prevalence of both species is variable: Whereas BVDV-2 represents around 50 percent of the isolates in North America, BVDV-1 is the predominant species in Europe, with only a few percent of BVDV-2 present (Luzzago, 2001; Cranwell, 2005; Tajima et al. 2001). The origin of BVDV-2 and the reason for the disproportionate occurrence of the two species in Europe and North America are not clear. In order to monitor the future emergence or re-emergence of BVDV isolates with peculiar pathogenic and/or antigenic features in Germany a genome database has been established (see WP1).
Most BVDV isolates are well adapted to cattle and many acute (i.e. transient) infections go unnoticed provided that the virulence of the strain is low and that there are no complicating conditions. However, since BVDV virulence may vary and infection is accompanied by

transient immunosuppression there is a complex of diseases attributable to BVDV, ranging from respiratory and enteric conditions to lethal haemorrhagic disease (Baker, 1995).

3.10.1 Future spread of pathogenic BVD variants e.g. BVD-2; role of vaccination?

Unless precautions are taken, e.g. development of vaccines efficacious against BVDV-2 and /or efficient control measures with the goal of rapidly eliminating BVDV infection, there is always the threat of spread of BVDV-2 in Europe. Without the availability of efficacious vaccines this could jeopardize attempts to control and eventually eradicate BVDV.

3.11 Marker vaccines

Marker vaccines have the advantage that immunised animals can be distinguished from field virus infected animals using appropriate serological tests. Thus this type of vaccine could be particularly useful when there is an intent to enter an eradication programme but permit the strategic use of vaccination or for emergency vaccinations after outbreaks or break-downs in densely populated livestock areas. It was expected that the use of marker vaccines might reduce the necessity for pre-emptive culling of animals in the perimeter of an outbreak (e.g. Foot-and-mouth vaccine zone control).

3.11.1 Need for marker vaccines

There is a need for a marker vaccine against BVDV. In those regions and areas in Europe, and further afield, where control programmes include the initial use of vaccines, there would be considerable advantage to have the possibility to use protective vaccines without compromising any subsequent control/eradiciation programme. With respect to technical aspects as well as some disease control modalities there is some analogy with CSF control: CSF was at the brink of eradication in the EU when the non-vaccination policy against CSF in the EU was introduced effective by December 31, 1990. If any vaccine against CSFV were to be licensed thereafter, it would have to be an efficacious marker vaccine. A first generation of marker vaccines was developed and two products were licensed and are commercially available. Both vaccines were subunit vaccines based on the viral envelope glycoprotein E2 expressed by baculoviruses. The vaccines were safe and efficacious, however, when compare to modified live CSFV vaccines they were inferior with respect to onset of immunity after vaccination and foetal protection of pregnant animals. The accompanying test was suitable on a herd basis for the detection of field virus infections in a vaccinated environment.

In order to improve the speed of immune response and the safety of foetal protection a second generation of live marker vaccines is being developed. According to the current legislation the use of marker vaccines is possible under emergency situations and post vaccination restriction may be reduced after the use of marker vaccines vs. conventional MLV. So far emergency vaccination was never used during the various CSF epizootics of the last 15 years in Europe, neither with conventional nor with marker vaccines. The reluctance to use the newly developed marker vaccine for CSFV may be based on its performance in comparison to the conventional MLV, the initially poor performance of the diagnostic test and its higher price.

Paradoxically, although needed under European conditions, there is no on-going and widespread market for such a CSFV vaccine. It is a classic ‘chicken-and-egg’ situation and has commercial disincentives for development for a European market. This would certainly

not be the case with BVDV, where most probably there will be still a market for an improved and 'marker' directed vaccine.

3.11.2 Types of marker vaccines

With respect to the close relationship among the members of the pestivirus genus all approaches for the development of a marker vaccine against CSFV has valuable lessons for marker vaccine development against BVDV.

1. Subunit marker vaccine based on expression of viral E2
2. Vector vaccines
3. Avirulent chimeric pestiviruses expressing marker antigens, e.g. CSFV specific epitopes
4. DISC vaccines (Disabled infectious single cycle), (Reimann et al., 2003)

With respect to the GMO-based vaccines (3-4) there is a general *caveat*: It is not clear whether the consumer will accept the use of these vaccines in the food chain.

3.11.3 Possible use of marker vaccines against BVD

Although marker vaccines may be more expensive than conventional preparations, it is likely that they will be considered valuable in a systematic control programme. Within a voluntary regional scheme, there may be value for giving protection to herds that are vulnerable to reinfection but wish to undertake total herd control. On a single herd basis, where there is no intention for eradication, there may be little or no benefit distinguishing vaccinated from infected animals.

In an organised regional or national eradication effort marker vaccines might be advantageous, provided they offer a best possible foetal protection and the accompanying discriminatory test is suitable to discriminate vaccinated from infected animals. Especially in cattle dense areas with a high initial infectious pressure the use of marker vaccines in conjunction with a systematic control effort might be useful for the monitoring of progress.

However, taking the experience with marker vaccines against CSF into account, it may be concluded that the development of a marker vaccine against BVD will need to pay proper attention to developing sufficient foetal protection in order to have any real field or commercial value. There is little doubt that there is 'ample room for improvement' of both efficacy and safety of BVDV vaccines and it is expected that better vaccines to include 'marker vaccines' will be launched in the future' (van Oirschot et al 1999).

3.12 Conclusions

1. There are a number of MLV and inactivated vaccines on the European market. None of them contains BVDV-2.
2. Unsystematic vaccination, i.e. vaccination alone, without elimination of PIs, on an individual or a herd basis has done little if nothing to reduce the overall prevalence of BVD.
3. The importance of foetal protection as result of vaccination is recognised by all stakeholders.

4. Foetal protection can be achieved using vaccination. However, due to the wide antigenic variation of BVDV and according to published evidence, it is difficult to achieve a full foetal protection under all field conditions.
5. Although BVD has been eradicated from Scandinavian countries without use of vaccines, vaccination used in combination with removal of PI animals may offer additional security against reinfection of BVD-free herds.
6. In regions or areas where not all farms are included in BVD control, e.g. in voluntary schemes, there may be value for vaccine use to protect susceptible herds free of PI animals.

3.13 References

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TABLES - EU THEMATIC NETWORK – WORK PACKAGE 3 - VACCINES

OBJECTIVE 1

Country	**Evaluation of methods and guidelines for vaccine trials** *Comments on BVDV vaccine monograph*
Austria	None
Belgium	It is important to find the same monograph for live BVDV vaccines. I find reasonable to accept a BVDV vaccine if the protection observed against tansplacental infection is 90% or higher and also to accept that all the control animals could not be infected.
Denmark	The number of animals in the safety and potency study is relatively low. In the paragraph of potency it could be more explicitly stated what is meant by 'harvest of foetuses at 28 days', i.e. is it 28 days post challenge? How is harvesting done?
England	The demands of the trial (to ensure 15 out of 20 animals pregnant in one oestrus period & to have 90% protection in vaccinated animals) are daunting for anyone undertaking experimental trials – I know!
Finland	None
France	We also need to have quantitative estimates of level of protection of vaccinated animals and of their foetus in field conditions. Results are likely not to be 100% so we need estimate and "reasonable" confidence interval.
Germany	I think that the monograph should be redrafted. It is too imprecise when it comes to time of challenge, type of virus (in relation to the vaccine virus) to be used. One can debate the 90% protection, but only in conjunction with the above issues.
Ireland	The number of animals involved in the trials is low. Paragraph describing potency trial lacks detail, especially in terms of challenge with BVDV (strain type/amount etc), why the option to terminate 28 days post challenge or carry to term? I appreciate it is difficult to achieve, but as the aim of the vaccine is to prevent foetal infection and PI animals, a goal of 100% protection is desirable. Why is batch potency testing not carried out routinely?
Italy	I do not have any further comments. It seems to me that a 90% protection against the generation of a PI animal seems reasonable.
Netherlands	I would prefer besides measuring transplacental transmission, also the vaccine protection of within herd transmission to be measured in an additional challenge test. We should be working toward marker vaccines.
Northern Ireland	1. Batch potency test – given that the magnitude/duration of detectable antibody response post vac is variable (particularly by ELISA, rather than by VN), the use of serology to determine potency may not be sufficient. This might be usefully supplemented/replaced by measures of CMI. 2. The monograph does not address the issue of strain heterogeneity. I am not sure how best this should be done – perhaps it should recommend a range of options, including: homologous challenge; heterologous challenge with a vaccine of the same serotype, but belonging to a different subtype (eg 1a/1b); heterologous challenge with a different serotype (type I/II). 3. Potency. Given the primary goal of these vaccines is to prevent the birth of VI calves, I would prefer to see 100% protection being required for compliance.
Norway	None
Portugal	None
Scotland	None
Slovenia	I have no experience with vaccines against BVDV.
Spain	None
Sweden	I think that the potency test is not adequate. I suggest that 100% of the vaccinated animals must be protected from transplacental infection and that the challenge should be performed at least ten months after the last vaccination. Furthermore, I think that the duration of immunity as presence of neutralisation antibody titres against at least two different BVDV reference strains should be shown after both the initial vaccinations and after revaccination. The primary aim with a BVDV vaccine must be to prevent congenital infection against different antigenically diverse strains and so far no inactivated vaccine has, to my knowledge, been demonstrated to meet that requirement.
Switzerland	None

OBJECTIVE 2 (cont)

Country	BVDV Vaccines Available			BVDV Vaccine Use					Rationale for Use					
	Company	**Vaccine Name**	**Type**	**0-20%**	**21-50%**	**51-75%**	**76-100%**	**Estimated from:**	**Improve reproductive performance**	**Protect naïve herds**	**Improve calf health**	**Prevent resp. disease**	**Prevent mucosal disease**	**Other**
Austria	Pfizer Merial	Rispoval RS/BVD Mucobovin	Live BVDV & BRSV Killed, strain Aveyronite/New York	✓				Personal guesstimate						✓
Belgium	Merial Intervet Pfizer	Mucobovin Bovilis Rispoval	Killed Killed Live, combined with BRSV	✓				Other				✓		✓
Denmark				✓				Not specified						
England	Novartis Intervet Pfizer	Bovidec Bovilis BVD Rispoval 4	Killed NCP type 1a Killed CP type 1a Killed CP and NCP type 1 viruses & IBR, RSV & PB	✓				Personal guesstimate	✓	✓		✓		
Finland				✓				Not specified						
France	Intervet Merial Merial Pfizer	Bovilis Mucosiffa Mucobovin Rispoval BVD	Killed, strain C86 Live, strain Oregon C24V Killed, strains New York/Aveyron Live, strain RIT 4350	✓				Personal guesstimate	✓			✓		✓
Germany	Bayer Intervet Merial Merial Pfizer Pfizer	Bayovac Bovilis BVD Mucobovin Vacoviron Rispoval BVD/MD BVD/BRSV	Killed, Oregon C24V (sold to Prizer) Killed, strain C86 Killed, strains New York/Aveyronite Live attenuated, strain Oregon C24V Live ts mutant, strain RIT 4350 Live, attenuated, strain RIT 4350 in combination with BRSV		✓			Not specified	✓	✓				
Ireland	Novartis Intervet Fort Dodge Fort Dodge	Bovidec Bovilis Triangle BVD Triangle 5	Inactivated non-CPE strain Inactivated CPE strain C-86 Inactivated Inactivated	✓				Personal guesstimate	✓		✓	✓		
Italy	Intervet Merial Merial Gellini Pfizer Pfizer Pfizer	Bovilis Mucobovin Mucosiffa Hiprabovis 3 Rispoval BVD Ripoval RS-BVD Cattlemaster 4	Inactivated Inactivated Live Inactivated (IBR & P13) Live Live (BRSV) Killed 9BRSV, IBR, P13)			✓		Rough data from Industry	✓					
Netherlands	Intervet Novartis	Bovilis BVD Bovidec BVD	Inactivated, cytopathogenic strain, C86 Inactivated, non-cytopathogenic strain	✓				Personal guesstimate		✓				To prevent reintroduction in a herd free from PI animals
Northern Ireland	Intervet Novartis A H	Bovilis BVD Bovidec	Inactivated cpBVDV C86 Inactivated ncp BVDV	✓				Personal guesstimate	✓	✓			✓	

OBJECTIVE 2 (cont)

Country	BVDV Vaccines Available			BVDV Vaccine Use					Rationale for Use					
	Company	Vaccine Name	Type	0-20%	21-50%	51-75%	76-100%	Estimated from:	Improve reproductive performance	Protect naïve herds	Improve calf health	Prevent resp. disease	Prevent mucosal disease	Other
Norway				✓				National survey						
Portugal	Merial Intervet Novartis Fort Dodge Hypra Pfizer Pyramid	Mucobovin Bovilis BVD Bovidec Triagulo 3, 4 & 8 Hyprabovis 4 Rispoval 4 Fort Dodge	Killed Killed Killed Different pathogens in the vaccines: BVDV (killed), IBR, P13, BRSV, Leptospira BVDV (killed), IBR, P13, BRSV BVDV, IBR, P13, BRSV (killed) BVDV live			✓		Regional Survey	✓		✓	✓		
Scotland	Novartis Intervet Pfizer	Bovidec Bovilis BVD Rispoval 4	Killed NCP type 1a Killed CP type 1a Killed CP and NCP type 1 viruses & IBR, RSV & PB		✓			Personal guesstimate	✓			✓		
Slovenia	Pfizer	Cattlemaster	Inactivated	✓				Personal guesstimate			✓	✓		
Spain	Syva Intervet Bayer Bayer Fort Dodge Fort Dodge Fort Dodge Fort Dodge Fort Dodge Hipra Hipra Ovejero Pfizer Pfizer Iven	Respivac Bovilis Bayovac Combo IV Bayovac IBR-BVD Triangle-9 Triangle-4-PH-K Triangle-3 Triangle-4 Pyramid 4 Hiprabovis-3 Hiprabovis-4 Immubov Rispoval D Cattlemaster-4 Rinoparadia PP	Inactivated Inactivated Inactivated Inactivated Inactivated Inactivated Inactivated Inactivated Live Inactivated Inactivated Inactivated Live thermosen Inactivated Inactivated		✓			Personal guesstimate	✓	✓				
Sweden				✓				Not specified						
Switzerland	Veterinaria Graub	Bovilis MD Rispoval BVD/MD	Inactivated vaccine Live vaccine	✓				Personal guesstimate	✓				✓	

OBJECTIVE 2 (cont)

Country	Are there strategies for use of vaccines within control schemes			
	Local	**Regional**	**National**	**Strategy Reference?**
Austria	No	No	No	No
Belgium	Yes – If a vaccination strategy is followed, it corresponds to the protection of the herd against the reintroduction of a virus carrier after the elimination of PI animals. Vaccine companies (Intervet) participate in the first phase of this control programme supporting partially the financial costs of the detection tests	No	No	No
Denmark	No	No	No	No
England	Yes – within individual veterinary practitioner/ farmer schems (for individual farms). Usually based on either of two strategies: • Removal of all PI's and vaccinate all breeding cattle (control within 2-3 years) • Target just heifers and first calving animals with test for PI and vaccination (control within 5-7 years)	No – Regional schemes (as in Scotland with Shetlands & Western Isles). BVDV control is part of the Cattle Health schemes but only voluntary schemes and relatively few farmers have joined. Schemes are: • HiHealth – SAC (George Gunn) • Premium Cattle Health Scheme – SAC (George Caldow) • Herd Care – Biobest Lab (David Snodgrass)	No	No
Finland	No	No	No	Yes – BVDV control without vaccination: Voluntary BVDV control programme 1994 by Ministry of Agriculture and Forestry (only available in Finnish or Swedish), during this spring act of BVDV control will be in our legislation together with the voluntary BVDV control programme
France	Yes - Vaccine alone (or vaccine plus integrated biosecurity	Yes - Vaccine + biosecurity	No	Yes in some regions (farmers organisations
Germany	Yes – on the farm level several motives are valid for vaccine use, depending on the goals of the farmer or the veterinarian	Yes – there are voluntary control schemes including vaccination, in order to protect herds from reintroduction of BVD virus (Federal States)	Yes – there are voluntary control schemes including vaccination, in order to protect herds from reintroduction of BVD virus (Federal Guideline)	German Federal and State Legislation, voluntary guidelines
Ireland	No	No	No	No
Italy	No – vaccine is usually used without any further measures aimed to the detection of PI animals	No	No	No
Netherlands	Yes – vaccination alone sometimes with additional biosecurity but more often biosecurity does not play a significant role. Under the protection of the vaccine biosecurity may even become less of an issue	No	Yes – a control programme from the Animal Health Service including removal of PI animals, monitoring young stock and animal movement surveillance. Vaccination does not interfere with the programme.	The control programme is in principle based on the Scandinavian eradication scheme.
Northern Ireland	Yes – typically farmers use vaccine as a stand alone strategy, although in some cases consideration will also be given to biosecurity	No	No	No

OBJECTIVE 2 (cont)

Country	Are there strategies for use of vaccines within control schemes			
	Local	**Regional**	**National**	**Strategy Reference?**
Norway	No	No	No	No
Portugal	No – vaccines are used alone, in schemes adopted by the farmer itself, sometimes under veterinary supervision. Many technicians for different background training (mainly agronomic) tend to recommend the use of vaccines to solve fertility and/or production problems at the dairy herds.			No
Scotland	Yes – but only within the National (voluntary) scheme.	Yes – again usually within a National (voluntary) scheme. usually permitted in regions of high levels of virus, after blood testing and removal of PIs. Vaccination	Yes – 3 National (all voluntary) schemes	Yes – 3 schemes - Technical bulletins: 1. Premium Cattle Health Scheme 2. Herd Care 3. Hihealth
Slovenia	No	No	No	No
Spain	Yes – 3 scenarios: 1. Vaccine alone (herds with or without PI Animals. 2. Identification and elimination of PI animals and vaccination. 3. No vaccine, no PIs and testing bought in animals to avoid introduction of PIs.	No	No	No
Sweden	No	No	No	No
Switzerland	Yes – Mainly advise on regular vaccine plus integrated biosecurity on animal	No	Yes – A national concept on BVDV-control exists, but it hasn't been applied, so far. The concept does not contain vaccination.	No

OBJECTIVE 3

Country	**Evaluation of safety precautions and systems to ensure safety of BVDV vaccines** Comments or reference to any publications about vaccine safety
Austria	None
Belgium	None
Denmark	None
England	No comment – there appears to be some reluctance to use modified live BVDV vaccines for fear of contaminant infection. The authorities have licensed three killed BVDV vaccines – published data from some of these vaccines has shown extremely good protection.
Finland	Our main concern regarding BVDV and vaccines are the possible BVDV contaminations of any viral vaccine intended to be used for cattle. However, at the moment there are no viral vaccines for cattle on the market in Finland.
France	Questions are raised about possible drift of virus strains or selection of particular str5ains resulting from use of vaccines. This was observed in the past in France with another pestivirus, classical swine fever, when vaccination of pigs was compulsory.
Germany	Oguzoglu T C, Frey H R, Eicken K, Grummer B, Liess B, Moennig V. Dtsch Tierarztl Wochenschr. 2003 Jan; 110(1):14-7. Frey H R, Eicken K, Grummer B, Kenklies S, Oguzoglu T C, Moennig V. J Vet Med B Infect Dis Vet Public Health. 2002 Dec; 49(10):489-93
Ireland	None
Italy	None
Netherlands	We have to look at the US experiences. Recently in Davis (BVDV in the Americas symposium) it was concluded that: "We have been vaccinating the passed 15 years and it seems that we have been running around in circles". It is very important to find proper combination between sustainable control programmes in combination with vaccination.
Northern Ireland	None
Norway	None
Portugal	None
Scotland	None
Slovenia	None
Spain	Most farmers in Spain use dead vaccines and they are advised to give initially three doses, as the third dose will increase ten times the concentration of neutralising antibodies. Most antibody tests used detect the NS3 antigen
Sweden	Several publications show that the live vaccines against BVDV are not safe and that the vaccine virus can recombine with virus carried by PI animals. Furthermore, the live vaccines have not been shown to be safe in well-controlled field trials and they may induce disease or immunosuppression in vaccinated cattle. The vaccine virus may also spread to unvaccinated cattle under natural conditions. I think it is high risk that the present use of live vaccines may lead to the development of "new" more pathogenic BVDV strains that even may post a threat to human health. Therefore, I think that live vaccines against BVDV should not be allowed to be used to vaccinate cattle that may be PI with BVDV. It is also clear that there is a strong association between the use of live vaccines and the presence of type 2 BVDV strains in cattle populations. In summary: live vaccines give rise to safety problems and inactivated vaccines show poor efficacy, therefore BVDV is a great problem in eg USA and Germany despite the use of vaccines for several decades. Better safe vaccines, only strictly used in combination with diagnostic testing may be useful in the future. However, the experience from the Scandinavian countries shows that BVDV can be eradicated from highly infected areas without the use of vaccines and in a very cost effective manner. I am totally convinced that this can be done in all countries in the EU. A prerequisite is that the farmers and veterinarians received adequate education and information and that the control schemes are well designed.
Switzerland	None

Socio-economic aspects of BVDV control

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4.1. Executive summary

In this position paper, the current knowledge on socio-economic aspects of the control and prevention of Bovine Virus Diarrhoea (BVD) is compiled and evaluated. The work was carried out against the background of future decision making, particularly for farmers and countries which still harbor the virus.

First, the existing scientific literature was reviewed. A categorization into 5 groups was made, according to the aim of the studies involved.
Several studies report the financial-economic consequences of initial outbreaks of BVDV. A large variation in losses was reported, ranging from € 19 to € 600 per cow present. It should be stressed that these reports refer to incidental cases. However, it can be concluded that in case of introduction of BVDV in naïve herds, the financial-economic losses can be large.

Various studies were carried out on the average financial losses for cattle herds. The estimations range from € 30 to € 60 per average cow present. This figure can be interpreted as the maximum benefits achievable from eradication of BVDV from the herd. However, risks of re-infection were not considered, and hence the associated losses with re-introduction neither. These can be considerable, particularly if the herd has become naïve for BVDV again after a couple of years. Hence, in most cases the average long-term benefits will be lower than maximum achievable, particularly in cases of relatively high risks of re-introduction. Nevertheless, annual losses due to BVDV on farms in areas with risks of exposure to BVDV can be considerable.

At the level of the national livestock sector, studies indicated a loss due to BVDV under endemic conditions of € 15-20 per cow present. Compared to other production diseases such as mastitis and lameness, the financial-economic importance of BVDV can be considered as ‘moderate’. However, in contrast to the other diseases, eradication of BVDV, be it from individual farms or complete livestock sectors, is possible. In other words, the potential gross benefits of eradication of BVDV might be larger than those of other diseases. These studies however did not include the net benefits, i.e. costs for eradication, costs for biosecurity and risks (and consequences) of re-introduction.

The studies mentioned so far were based on empirical data. Also, simulation studies on the economics of BVDV at the herd level have been carried out, using computer models. The advantage of such approaches is that the whole system can be studied in an integrated way, provided that sufficient information for input is present. These studies are somewhat contradictory in answering the question: is eradication of BVDV at the herd level

economically sensible. However, all studies emphasize the risk of re-introduction of BVDV on the farm after eradication as a very important decision making factor. Therefore, in low risk areas, eradication could be feasible, but in high risk areas, eradication could be questionable: either because of losses associated with re-introduction or the extra costs for increased biosecurity.

Two studies were reviewed which focused on nation-wide eradication of BVDV: a model study for France and an ex-post evaluation of the Norwegian program. The first study indicates that nation-wide eradication is possible and the second is based on the actual eradication of BVDV from the Norwegian cattle population. The costs of such programs can apparently vary quite a lot, thereby affecting their Benefit/Cost-Ratio (BCR). The Norwegian study shows positive financial-economic effects (i.e. a BCR larger than 1) already after a few years, in contrast to the French study where it took approximately 15 years to reach break-even. It should be noted that these two examples applies clearly different control schemes. However, no single advice applicable for all situations exist. Specific conditions could determine the profitability of nation-wide programs.

The second part of this position paper deals with conceptual and theoretical considerations on endemic disease control in general and BVDV in particular. A general framework for the decision making process is described. Various distinct steps in the decision making towards implementing control programs are described. The framework can be used for various levels of decision making, ranging from the farm level to the national sector. Furthermore, the various levels of decision making and their respective decision making criteria are described. It is emphasized that, beside financial-economic criteria, also other criteria are important, e.g. animal welfare and ethics, regional and national economic impacts and veterinary impacts. The degree of importance depends on the level of the decision makers, but also on the preferences of the latter. The complexity of economic decision making in a broad sense is illustrated. This framework could be used in future decision making on control and prevention of BVDV.

In the third part, the financial-economic considerations with respect to BDVD are explored in a qualitative way. It has been shown, that changing the status of BVDV from the level of a production disease to the level of sector or national importance will affect the economic impact of presence of the disease at various levels of the economy. E.g., in case BVDV gets an official OIE-status, countries which are free of the disease could receive favorable trade conditions. Loss of this status due to re-emergence of BVDV could have negative economic effects due to trade restrictions. The economic impact of such an event is determined by the type of products involved (animals, semen, or other products) and the importance of these products for a national cattle sector. At this moment, this impact cannot be predicted.

Based on the review and inventory made, some conclusions on the economic aspects of control and eradication of BVDV can be drawn:

- Occurrence of BVDV can cause great financial-economic costs in naïve herds;
- On average, at the sector level BVDV can be regarded as an important livestock disease, however less important than mastitis and lameness;
- BVD can be eradicated from individual farms as well as within an entire country;
- Since BVDV in principal can be eradicated, the gross avoidable losses approach the current average losses observed (this is in contrast to e.g. mastitis);
- For the net financial-economic effect of eradication of BVDV, the following should also be taken into account: (1) the probability of re-introduction, (2) the associated losses with

this event (which can be high if the herd is naïve), and (3) the biosecurity measures required to reduce this probability. In the literature, these issues have been disregarded in most cases; this hold both at the level of the individual farm and the livestock sector;
- It can be observed that various countries have given priority to national eradication of BVDV (e.g. the Nordic countries), and some literature show a BCR larger than one; however, not all relevant factors were included in these studies, hence a comprehensive financial-economic justification for such decisions should be further investigated;
- In situations with a high risk of re-introduction of BVDV after eradication, on-farm control of BVDV does not seem to be not sensible from a financial-economic point of view;
- Provision of an official status to BVDV (e.g. OIE-listing) could have adverse financial-economic consequences for farmers in countries not officially free from BVDV, even if the farm itself if BVDV-free; the magnitude of these effects particularly depend on (1) the products involved and (2) the possible consequences of harboring BVDV.

For individual farmers and national livestock sectors that are still facing the decision whether or not to eradicate BVDV from their herd(s), scientific based decision support is important. The current state-of-the-arts in financial-economic literature on BVDV is not unequivocal, i.e. a science-based decision in favor of controlling BVDV in countries not yet free of the disease (mandatory control programs) cannot be taken on the available knowledge currently present. This holds also for individual farms. However, it should be realized that other criteria can be of importance too, such as animal welfare, socio-ethics, etc. Moreover, conditions can change over time, e.g. eradication in adjacent countries or farms could reduce the probability of re-introduction, which increases the likelihood of the long term benefits of eradication of BVDV.
Several gaps of knowledge, i.e. requirements for future research have been identified. Particularly the following are of importance:
- In case of absence of 'outside' pressure, i.e. in case of continuing voluntary programs for individual farms, decision support tools (i.e. computer models) which simulate alternative scenario's for on-farm BVDV control from a whole farm management perspective are required; these tools should be adaptable to specific regional and farm conditions which vary between and within European countries;
- In areas with a high prevalence, and therefore with a high risk of re-introduction, the impact of a collaborative (regional) approach should be studied, which should include the development of regional decision support tools (on top of the one already mentioned); these tools should provide insight in the between-herd spread of BVDV in case of various collaborative control efforts;
- In case of 'outside' pressure, insight in the trade impact of occurrence of BVDV for the whole sector is a must, because also non-infected herds could be economically affected; insight in this aspect requires sector-wide economic modeling of various livestock commodities which could be affected by the presence of BVDV.

4.2. Recommendations

a. A first recommendation would be, to bring clarity about the future official status of BVDV: will there be an official status of the disease, and if so, what will be the consequences of not being BVDV free at the level of the national livestock sector and for individual farmers. This is important, because such a status could be a major driving force with a financial-economic impact for the stakeholders.

b. At this moment, there is no sufficient scientific evidence that supports a decision from a mere financial-economic point of view to control BVDV in any case or in any country. More insight in the pros and cons for various countries and regions therefore is required. Therefore, country and farm specific conditions should be studied.

c. Considering three levels of decision making, the following recommendations are suggested:
Farming conditions with regard to BVDV can vary considerably, both between farms within a country or region, and between regions and countries. Hence, for decision support at the **farm** level (i.e. a voluntary approach), farm specific conditions have to be accounted for. Farm specific decision support tools have been developed for specific conditions (e.g. for The Netherlands). Adaptation to other countries and conditions is recommended. Furthermore, adaptations that take the whole farm business into account (and are not restricted to mere BVDV) are advocated.
Specific **regional** conditions (e.g. high prevalence) have an impact at both individual farmers and the region itself. Considerations on a regional approach should be supported by research specifically focused on that region. The development of decision support tools, focused on decision making options at this level is therefore recommended. Such pc-based tools should take account for (1) the various control options possible, and (2) the impact of monitoring of BVDV on rapid detection of new cases (re-introduction) and the ability to eradicate new cases quickly.
If decisions have to be made at the **national** level (e.g. as a result of an official status of BVDV), insight in the consequences of (re-)occurrence of BVDV for the entire livestock sector is required. Research on the impact of e.g. trade restrictions therefore is recommended.

4.3. Objectives

The overall objective of work package 4 of the BVDV control network has been to compile and evaluate the current knowledge on socio-economic aspects of decision making on the control and prevention of BVDV, with special reference to the European situation.

More specifically, the objectives were as follows:

- To evaluate the socio-economic aspects of different control strategies and criteria in the process of deciding upon a strategy;
- To evaluate methods and data requirements appropriate for describing and analysing the attitudes and decisions of farmers, stakeholders and other key actors in one or several member countries;
- To evaluate methods for incorporation of the sociological context into the decision and management process of BVDV in particular, and endemic infectious diseases in general.

4.4. Introduction

Bovine Virus Diarrhoea (BVD) is a viral disease of cattle. A large range of clinical signs are associated with BVDV infection, from sub-clinical manifestations to severe clinical disease. In the latter case, the direct disease effects include fever, inappetence, respiratory and gastrointestinal symptoms, infertility, increased embryonic mortality and foetal death, mummification and abortion (Baker, 1995) As a consequence, these direct effects cause

reduced production performance. In young stock, this includes increased mortality rates, reduced growth rates and increased culling rates (Lindberg, 2003). In adult cattle, performance effects are, for example, reduced conception and pregnancy rates, increased abortion rates and a reduction in milk production, and increased replacement rates (Lindberg, 2003). BVDV can also cause indirect effects, e.g. a higher probability of mastitis resulting from immuno-suppression (Lindberg, 2003; work package 2).

Obviously, both the direct and indirect disease effects of BVDV cause financial losses for the primary producers. In turn, less-efficient use of resources results in losses for society (Dijkhuizen and Morris, 1997). Moreover, the occurrence of BVDV causes impaired animal welfare due to increased morbidity and mortality, adverse side-effect or intangible loss. Impaired animal welfare causes 'loss' to Society as a whole (McInerney, 2004) i.e. it is an 'externality' of animal production. BVDV may cause additional externalities, for example reduced efficiency of food production associated with infertility and leading to otherwise avoidable environmental degradation (Garnsworthy, 2004) Despite their detachment from the farm business, such externalities can have financial implications for farm businesses perhaps through reduced demand for livestock products and hence reduced output prices and/or through restrictions imposed by society on farm businesses in an effort to limit the negative externalities. Such restrictions may increase in future now that farm subsidies have been decoupled from production and their receipt or level may be conditional on conformance to specific standards of farming practice aimed at safeguarding animal health, animal welfare and the environment ('cross-compliance'). Finally, occurrence of BVDV within a population, endangers efforts to improve the general level of animal health status, a self-proclaimed aim within the European Union.

Within Europe, prevalence of BVDV varies enormously. The Scandinavian countries (Norway, Sweden, Finland and Denmark) are almost free of BVDV, whereas in other countries such as The Netherlands and The United Kingdom sero-prevalence estimates exceed 50% (Lindberg, 2003; Moen, 2004; work package 2).

Different approaches in controlling and preventing BVDV between European states can be observed. In Nordic countries such as Norway, Sweden and Denmark, authorities are active in promoting and supporting BVDV control programs, resulting in programs that are almost mandatory. In contrast, in most other European countries, e.g. The Netherlands and The United Kingdom, authorities are more reluctant, leaving BVDV control to the livestock sector. In both these countries, control programmes exist, but participation is voluntary for the producers and only some participate.

Successful, socially and financially sustainable control and prevention of BVDV depends on various aspects. For the **individual producers**, the most important are: the economic impact of BVDV on the farm (i.e. the financial losses (s)he can avoid by eradicating BVDV), the costs of control and subsequent prevention, and the likelihood of re-occurrence of the disease (which depends amongst others on the BVDV prevalence in the broader environment). For the **livestock sector** (i.e. the collective cattle producers within a country), a major additional point for consideration is the question whether or not in the future BVDV occurrence will result in trade restrictions for livestock products and/or animals. This would be the case if biosecurity demands applicable to BVDV was to be included in the OIE Terrestrial Code. Such restrictions would not only affect diseased herds, but also herds within a country free of BVDV. Depending on the type of restrictions, this issue could have considerable financial-economic welfare implications for the society if the sector is net-exporting for e.g. live

animals (Saatkamp et al., 2000). For **society** as a whole, additional aspects play a role, such as losses due to inefficient use of resources and animal welfare. These externalities may be 'internalised' in future as explained earlier at which point they directly affect decisions of the individual producer.

Currently, questions on how to proceed with BVDV control and prevention are discussed. Norway and other Scandinavian countries are strong supporters of BVD to be regarded as an OIE listed disease (Anonymous, 2002), a point of view which is not shared by some other EU member states.

Given the differences between European countries with regard to current prevalence of BVDV, preferences of producers and society as well as other environmental conditions (e.g. prices and costs for BVDV programs), questions on BVDV control and prevention should be dealt with on a country specific basis. The main questions in this respect are: (1) is control and prevention of BVDV economically feasible or not from a farm and/or sector point of view both in the short and in the long run, and (2) if so, which approach or strategy would be most suitable to achieve and maintain the BVDV-free status. The main aim of this paper is to address these issues.

The economic literature with respect to BVDV is fragmented and scarce, country-specific and predominantly focused on the losses caused by the virus at the farm level. Within the near future, this is unlikely to change. Therefore, the main aim of this position paper is to give a comprehensive overview of all issues related to decision making on BVDV control and prevention. In this way, guidelines will be provided and knowledge gaps indicated. Finally, requirements for further socio-economic research with regard to BVDV will be listed and discussed.

4.5. Overview of existing economic literature on BVDV

This literature review includes approximately 30 publications, not all of them being original. Quite some variation between these publications exists with regard to aim, scope, approach and methodology used and factors included in the research. Moreover, the existing literature sometimes is rather country and/or situation specific. All this makes extrapolation of the results to other conditions and generalization of the conclusions questionable. A comprehensive review of the economic literature on BVDV can also be found in Houe (2003). In this overview, however, the number of studies has been extended. Moreover, particular attention has been paid to the potential use of the publications in economic decision making on control and eradication of BVDV.

Below, a categorization of the papers into 5 groups has been made, depending on the aim of the study. In turn, the publications are of two major types. Those discussed in sections 4.5.1, 4.5.2 and 4.5.3 all refer in some way to the estimation of losses, whereas the publications discussed in sections 4.5.4 and 4.5.5 focus more on decision making. In section 4.6, the main findings of these publications are drawn into the general framework of economic assessments and put into the broader perspectives of decision making on the control and prevention of BVDV.

4.5.1. Financial-economic losses due to initial outbreaks cases of BVDV

A number of publications deal with the financial-economic losses due to initial BVDV outbreaks in apparently BVDV naïve or free herds. These herds had no immunity or protection developed against BVDV at the moment of introduction of BVDV in the herd. Hence, the observed impact of the disease can be regarded as a worst case scenario, and the losses associated as a kind of possible maximum over a limited period of time (i.e. several months up to one year).

The basic approach which all these studies more or less had in common was, that the clinical observations made with regard to mortality, morbidity and sometimes also the impact on production, was transferred into monetary values using market prices. (The potential dangers of using market prices in this context are highlighted by Bennett and Ijelpaar (2003) who used border prices instead.) Moreover, only the direct effects of BVD were included, leaving indirect effects such as increased occurrence of other diseases unconsidered.

Bennett and Mawhinney (1999) calculated the losses due to an initial BVDV outbreak at £ 9,065 for a 100-cow British dairy herd, i.e. € 137 per cow present in the herd.

Duffell et al. (1986) estimated the financial loss incurred from an initial BVD-MD infection in a 67-cow British dairy herd to be between a minimum of £ 1,720 and a maximum of £ 4,115, depending on the way the died or culled animals were replaced (as calves or down calving heifers respectively). These figures imply values between € 39 and € 92 per cow present.

Pritchard et al. (1989) reported a case of a combined initial infection with BVDV, Leptospira hardjo and Coxiella burnetii in a 183-cow dairy herd in Great Britain, and estimated the total combined financial-economic losses to be over £ 50,000, i.e. € 410 per cow present.

A BVD outbreak in a Dutch 100-cow dairy herd was reported by Stelwagen and Dijkhuizen (1998), which resulted in losses of over DFl. 96,000, i.e. € 455 per cow present.

Wentink and Dijkhuizen (1990) reported the financial-economic effect of BVD outbreaks at several Dutch dairy herds to vary between € 19 and € 130 per cow present.

In Denmark, Houe et al. (1994) calculated the losses due to initial cases of MD only occurring on 8 relatively large dairy farms as being between € 30 and € 89 per dairy cow present.

Finally, a rough estimation of the financial-economic losses due to acute outbreaks in Canada at 7 dairy herds made by Carman et al. (1998) showed that these losses were between $ 40,000 and $ 100,000 for the whole herd, i.e. approximately € 240 and € 600 per average cow present.

When comparing these figures, the large variation in estimated losses immediately becomes clear: a minimum of € 19 and a maximum of € 600 per cow present. Various causes can be mentioned, e.g. the severity of the outbreak itself, specific farm and regional conditions, items included (e.g. only loss and replacement of animals or also other losses such as reduced milk production, treatment costs, etc.), whether or not other diseases also interfered, etc. Therefore,

a comparison between these studies in order to estimate an overall or 'typical' figure does not make much sense.

A point of methodological critique is, that in all studies financial-economic valuation was based on market prices instead of opportunity costs. This might have led to a slight overestimation of the losses. However, on the other hand, indirect disease effects were not included either.

Another issue which should be realised is, that these losses are incidental, and refer to a limited time period (several months up to one year); a positive side effect is namely that herd immunity is acquired, which makes the herd less vulnerable in the years after the outbreak. Moreover, the actual probability of incurring these losses, i.e. the probability of introduction of BVDV into a largely or completely susceptible herd, seems to be quite low (but not zero) in countries where BVDV is still endemic.

However, despite the fact that criticism is possible on these studies, the figures quite clearly show, that without any doubt initial infections of BVDV in naïve herds can cause large financial-economic losses for individual farmers.

4.5.2. Average financial-economic losses due to BVDV at the herd level

Several studies dealt with estimating the average financial-economic losses due to BVDV at the herd level. In contrast to the previously described cases, account was taken, or an attempt was made to do so, of a more or less continuous level of infection, or at least a continuous risk of infection.

To enable this, some kind of economic modelling was performed. However, different approaches can be observed, varying from Partial Budgetting (PB) to complete system simulation. All approaches had in common, that first the disease situation and its consequences were estimated, either by data collection and subsequent statistical analysis, or by simulation. Thereafter, the epidemiological outcomes were transferred into monetary terms by putting financial values on the various disease cases. In the latter, mostly market values instead of opportunity costs and border prices were used (see methodological comment above).

Chi et al. (2002) randomly collected blood samples from 90 dairy herds in Eastern Canada to obtain an estimation of the number of herds and animals infected with BVDV, bovine leucosis virus, Mycobacterium avium subspecies paratuberculosis, and Neospora caninum. Subsequently, these disease data were included in a Partial Budget model to estimate the average direct financial-economic losses and treatment costs due to an infection with these diseases. This model was stochastic, to account for the natural variation of occurrence of the diseases. The total losses and costs for a 50-cow infected herd with BVDV were calculated at CDN$ 2,422, being € 34 per average cow present. The costs of treatment only made up 2% of this figure, hence the remaining 98% was due to losses due to BVD.

Gunn et al. (2000) estimated the yearly losses due to BVDV for British dairy herds over a 10-year period. In a stochastic Markov-Chain simulation model, the probability of (re-)infection was included, which made a calculation of the average yearly losses and costs more realistic. Their study showed a median loss due to BVDV over a 10-year period for a 50-cow dairy

herd to be £ 10,300 (range £ 5,200 to £ 21,200), i.e. € 31 per average cow per year. Depending on the milk price, this would imply a loss of 9 to 19% of the farm income.

For Scottish beef herds, a similar study showed an estimate of £ 37 (range £ 32 to £ 43), i.e. € 58 per average cow per year (Gunn et al., 2004).

Sørensen et al. (1995) developed a more analytical stochastic simulation model to study the impact of BVDV infections on farm net revenues (FNR) over a 10-years period. They demonstrated a marked effect of BVDV infection on FNR if new infections do not occur regularly, i.e. only during the initial years of simulation. With regularly occurring new BVDV infections (i.e. semi-continuous presence of PI-animals), the impact on FNR varied considerably only in the first 4 years; thereafter, the difference in FNR with herds free of BVDV was only very small.

Fourichon et al. (2004) estimated the financial-economic losses due to on-going BVDV infections on French dairy herds. They used estimated production effects of BVDV from epidemiological sources, and considered all product effects possible. Hence, they tried to include also the indirect effects of BVDV due to the increase of other diseases resulting from immunosupression. The disease data was used in a PB model, and the calculated effects showed a financial-economic loss varying from € 60 to €100 per cow-year for average and severely affected herds respectively.

Based on these studies, a rough estimation of the annual average costs per cow due to BVDV would be to lie between € 30 and € 60, a considerable amount. At first sight, it is very temptative to interpret these losses as the net benefits of eradication, i.e. these maximum losses due to BVD are also the total avoidable losses (McInerney et al., 1992). Disregarding the issue of discounting, this would mean, that a farmer could spend on average approximately € 30/cow/year on eradication, monitoring and additional prevention. For a single herd however, operating in a wider surrounding of other herds which are or could be a source of potential (re-)infection, there always exist the probability of (re-)infection. The associated losses, which could be high, particularly in case of complete susceptibility resulting from eradication after a couple of years (see the above described cases), should be taken into account as well. This implies less financial space for eradication than the € 30 originally suggested.

Nevertheless, the described studies show that if individual farmers are more or less continuously confronted with BVDV (i.e. an endemic on-farm situation), either because of continuous presence in the herd or because of regular new introductions from outside the herd, the total annual (avoidable and non-avoidable) losses most likely are considerable.
It is also interesting to note, that apparently continuous exposure to BVD virus results in far much lesser losses than irregular exposure (see: Sørensen et al. (1995)). In this context, it should be made clear that also under endemic situations continuous exposure is rare, as PI animals tend to be few (low within–herd prevalence) and regularly will leave herds due to death, for slaughter or for sale. In case of a relatively long period of non-exposure and a high replacement rate, the possibility exist that a considerable pool of susceptible animals emerges, resulting in a reduced herd immunity, simply because PI animals are not systematically/intentionally removed (Lindberg and Houe, 2005).

4.5.3. Financial-economic losses due to BVDV at the level of the national livestock sector

Several studies have been carried out to estimate the financial-economic losses and costs at the level of the national livestock sector. In all cases, first, based on epidemiological survey information, an estimation was made of the incidence of BVDV, divided into various relevant age and disease classes. Subsequently, the impact on production performance of the various age/disease combinations was included. Finally, monetary values were included to estimate the annual financial-economic costs of BVDV. The latter included both direct losses due to the disease in terms of expected output loss, costs for treatment and costs for prevention (Bennett et al., 1999). Hence, indirect losses and wider economic aspects were not included. Moreover, fixed market prices for livestock commodities were assumed.

Bennett et al. (1999) and Bennett (2003) developed a series of spreadsheet models to estimate the total annual output losses and input expenditure for various endemic diseases in Great Britain. Total financial-economic impact for BVDV was estimated at £18m for dairy and beef cattle together (range m£ 5 and m£ 30, due to incidence and disease effects considered); in Euros, these figures are m€ 27, m€ 7.5 and m€ 45 respectively. Compared to other endemic livestock diseases, BVD ranked 4th, after mastitis (m£ 121, m€ 182), lameness (m£ 48, m€ 72) and enteric disease (m£ 29, m€ 44). However, such comparisons must be interpreted with care. They represent the current cost of the disease, not what it could be if the total cost of the disease were minimised or the costs of achieving minimum cost status (McInerney, 1996). As different diseases are at different points with respect to their optimal economic position, direct comparison of diseases on the basis of their current cost is not valid. As BVDV is an insidious viral disease with no direct treatment options it could be argued that current BVDV costs tend to underestimate its true economic importance compared to other more tractable and/or less stealthy diseases.

Bennet and Ijpelaar (2003) presented an update of these estimations. They used border prices, i.e. prices at which the livestock commodities could be produced elsewhere (e.g. New Zealand or Australia) and included transport costs to Great Britain. Although slightly lower, these border prices reflect better the true economic value of these commodities. Moreover, they included aggregated animal welfare effects of the various diseases, based on estimation by experts. The results showed an increase of the estimated financial-economic impact of BVDV, being m£ 40 (m€ 60). The ranking of the aggregated animal welfare impact was 4th, after lameness, mastitis and infectious bovine keratoconjuctivitis.

Given the fact of approximately 3.9m calvings per year, these figures imply that the annual losses and costs due to BVDV for Great Britain approach £ 10 (€ 15) per head.

Houe et al. (1993) used a similar type of approach to estimate the total annual losses due to BVDV infections in Denmark, which showed to be m£ 13 (m€ 20) per million calvings, i.e. € 20/cow/year. These estimations were made before the onset of the national BVDV eradication program. Subsequent calculations assuming a BVDV strain with a high virulence showed that the estimated annual losses would increase up to m$ 57 (m€ 52), i.e. more that two-and-a-half times higher (Houe, 1999).

The first pictures that emerge from these studies is, that a rough estimation of the costs due to BVDV in presumed ‘normal’, endemic conditions with a moderate to high prevalence lies somewhere between approximately € 15-20 in Great Britain and Denmark (in the latter case

before the start of the eradication program). Since epidemiological studies show, that the endemic situation of BVDV in Great Britain is reasonably similar to that in most other EU member states, except for the Nordic ones, these estimates could be used as an approximation for these countries as well.

It is again tempting to interpret these estimates as the potential benefits of complete nation wide eradication of BVDV; in other words, the figure of € 15-20 represents the total avoidable costs. However, some remarks can be made in this respect.

First, a nation wide program would in most countries imply increased costs for monitoring and prevention, particularly if more strict legal regulation is required; Bitsch et al. (2000) point out, that this would be the case in most countries. In turn, this would reduce the avoidable costs (McInerney, 1996) and hence the net benefits of an eradication program.

Second, the risk of re-emergence of the disease should be taken into account. There is no literature available on the consequences hereof, but large incidental losses cannot be excluded, and should be subtracted from the avoidable costs. These potential losses would increase as the eradication scheme progressed and increasing proportions of the national herd became naïve to BVDV. At the same time, costs of finding remaining sources of BVDV infected livestock may increase as infected herds become rarer and restricted to farms that are in various ways less accessible. The risk of re-infection and how it is affected by the implementation of regional/sectoral control is discussed further in the position paper of work package 2.

Finally, the impact of nation wide eradication of BVDV on the supply of livestock commodities should be considered. For decision making at the farm level, fixed output prices can be used, because the impact of improved efficiency on the total supply is negligible. However, if an entire sector comprising millions of animals improves production efficiency by eradicating a livestock disease, a (temporary) increase in total supply cannot be excluded (Dijkhuizen and Morris, 1997). This holds even more, if several countries operating on the same market (i.e. the common EU market) eradicate BVDV. According to economic theory, a so-called shift in the supply curve ultimately would result in reduced commodity prices for producers, and hence a reduction in the avoidable losses. The magnitude depends on various factors, e.g. the size of the increased supply and the time span in which this will occur.

Despite these aspects, these estimations for the national livestock sector clearly show the economic importance of BVD in presumed ‘normal’, endemic conditions. Compared to the losses caused by diseases such as mastitis and lameness, the financial-economic impact of BVD should be regarded as ‘moderate’. However, when considering avoidable losses, the relative importance of BVD could increase: in contrast to the other diseases, BVDV potentially can be eradicated completely. The latter would also have an impact on the externalities of the disease, i.e. improved animal welfare (see: Bennet and Ijpelaar, 2003).

4.5.4. Economic modelling to compare decision alternatives at the herd level

The advantage of using computer based epidemiological-economic models for decision support is, that all relevant factors influencing the decision making can be included in one study. However, quite often, if not always, values of some of the key parameters are uncertain due to lack of empirical data. Moreover, there is always the risk of the model not completely

representing the real world. However, this approach showed in many occasions to be a valuable aid in decision support (Dijkhuizen and Morris, 1997).

Bennett (1992), amongst others, pointed out the relevant stages which should be included in the design of a general disease control decision support system (DSS):
- integration of relevant epidemiological and disease information into a disease model;
- combining the former with a production system model to simulate the effects of the disease on production performance;
- inclusion of other information, such as disease control options, to simulate the epidemiological impact of the various decision options;
- inclusion of a financial-economic module to evaluate the financial-economic impact of the various alternative decision options;
- incorporation of other relevant factors which affect the decision making, e.g. the decision makers' preferences and risk attitude, to support the decision making in ways most in line with the goals and preferences of the decision maker.

Computer simulation modelling has both advantages and limitations (Bennett, 1992; Dijkhuizen and Morris, 1997); on both, a lot can and has been stated. DSS offer the possibility to incorporate all relevant aspects to the decision problem, and study them simultaneously. In this way, a comprehensive analysis can be carried out, and e.g. interactions between different factors can be studied. Moreover, they can be built relatively easily, quickly and cheaply. Major limitations include the uncertainty of values of key parameters, and the danger of incorrectly representing the system which is studied. One of the outcomes of almost all simulation studies is, that they indicate scarcity of empirical data on one of more aspects relevant to the decision making process. Such outcomes can be used to criticise simulation modelling and its outcomes (which often is done). However, revealing such scarcities can be regarded as a valuable outcome too, also with regard to interpreting the results of empirical studies. Moreover, simulation modelling offers the opportunities, if carried out carefully, to partially deal with these uncertainties through sensitivity analysis and validation (see e.g. De Vos et al., 2005).

Perfect representation of the system studied by a simulation model is an illusion. However, careful validation (both internal and external) can reveal the usefulness and credibility of the outcomes. Thereby it should be kept in mind what the main purpose of the DSS is: support of making choices, not providing exact estimation of costs and benefits in any circumstance.

Finally, the use of DSS and model outcomes should be a part of the decision making process, i.e. they should not monopolize the decision making, thereby neglecting other aspects. Ideally, DSS should be used interactively with the decision maker to explore the full contents of the decision making problem and interpret outcomes within the right context.

Preferably, risky events (e.g. the chance of re-introduction of BVDV) and the decision makers' attitude towards risk should be included in the DSS as well (Hardaker et al., 1997).

Several studies regarding decision making at the herd level have been performed.
Pasman et al. (1994) described a state-transition model to evaluate economically the decision options 'no intervention' and 'culling carriers' in a BVDV-infected herd (re-infection from outside sources was not considered). It was calculated that the 'no intervention' option would result in almost complete immunity of animals having an age above 1 year. The 'culling carriers' option would result in high immunity and reduced losses because of less clinical

problems due to BVD, however, the expenditures for testing and culling was quite high and did not outweigh the benefits. Moreover, they simulated the economic impact during the first year after an outbreak of BVD in a completely sero-negative herd, which turned out to be DFl. 85,000 (€ 38,500), being € 385/cow present. It was concluded that out of both decision options, the 'no intervention' option should be preferred for financial-economic reasons.

Houe et al. (1994) performed a Decision-Tree Analysis (DTA) for herds with outbreaks of MD, including (1) no blood testing, (2) blood testing of animals within the risk group and subsequent removal of PIs, and (3) blood testing of the entire herd and subsequent removal of PIs. They concluded, that testing the risk group and removal of PIs in most cases would be the best option to control BVDV, provided that in this way the infection risk was reduced and precautions would be taken to prevent further reintroduction of BVDV in the herd.

Stott et al. (2003) used the Markov Chain-based Monte Carlo approach to simulate the effect of various levels of biosecurity on the within-herd spread of BVDV in a 100-cow Scottish beef herd. Biosecurity was defined in such a way, that the probability of BVDV introduction from outside sources was included as well. The results of these simulations was subsequently used as inputs for linear optimization using linear programming. The aim was to determine the optimal level of biosecurity, which satisfied the achievement of a certain (user defined) target income with the minimum of BVDV risk given the available resources and constraints; the latter were derived from user defined whole-farm characteristics. The results showed that particularly in fully susceptible herds total costs can be high if the risk of re-introduction of BVDV is also relatively high; total expected costs of approximately £ 35 per cow/yr (€ 53) were calculated for susceptible herds with low levels of biosecurity. Increasing the latter resulted in a reduction of the annual costs to below £ 25/cow/yr (€ 38), however on the expense of an increased variation (i.e. risk) of the latter figure. This clearly shows the potential of benefits resulting from investments in biosecurity in these susceptible herds. However, they also concluded that when whole-farm financial risk was taken into account, the optimal disease-control level might be different from the decision that minimises the expected total costs of the disease itself.

Groenendaal (1998) and Groenendaal and Horst (2000) developed a Markov Chain-based stochastic simulation model to carry out calculation of Cost-Benefit-Ratios (CBR) of various control scenarios for BVDV at Dutch dairy herds. This model was further developed and adapted to the current voluntary BVDV programme offered by the Dutch Animal Health service (Saatkamp et al., 2005). The possible scenarios included test-and-cull of PIs, increased biosecurity and vaccination. Basis for comparison between scenarios was the CBRs between a situation without control and one adopting a particular scenario. Preliminary results show, that particularly with relative high probabilities of re-introduction of BVDV from outside sources, control measures should not be favoured either because of a negative CBR or because the return of investment time is quite long. Vaccination as an additional prevention measure was not economically sensible under Dutch conditions.

These studies show some kind of contradictory results. Houe et al. (1994) and Stott et al. (2003) tend to be positive on the financial-economics of prevention and control of BVDV, whereas the other studies tend to be more critical. All studies have in common the emphasis to reduce the risk of re-introduction of BVDV: a high risk has negative consequences on the financial-economic feasibility of prevention and control of BVDV. Apparently, this risk seems to be a critical factor in deciding pro or con control of BVDV at the herd level. From these studies, it can be concluded that BVDV eradication at the farm level could be

worthwhile from a financial-economic point of view in areas where the natural risk of re-introduction of BVDV is low due to e.g. favourable natural conditions. If natural conditions are less favourable (e.g. in The Netherlands with a relatively high sero-prevalence amongst herds), the costs of additional measures to reduce the risk of re-introduction could become that high that eradication of BVDV is not worthwhile from a financial-economic point of view. This is particularly the case with vaccination.

4.5.5. Cost-Benefit Analyses of national livestock sector BVDV eradication programmes

Empirical evidence clearly show, that complete nation wide eradication of BVDV is possible. This implies that potentially all current losses can be avoided instead of only a part (McInerney et al., 1992).

Dufour et al. (1999) used deterministic computer simulation to evaluate ex ante the economic feasibility of eradicating BVDV in France. The study was carried out for a fictitious average population at regional level, representing approximately 1.2% of the total French cattle population. Annual base-line costs caused by BVDV in the absence of an eradication program was estimated at approximately mUS$ 1 (i.e. US$ 10.5 per adult cow). Within the BVDV eradication program, they assumed that annually 9,500 animals were introduced in the region and should be tested for BVDV. Moreover, besides monitoring based on general bulk tank milk Elisa, extensive serology and virology on individual animals at (presumed) BVDV positive herds was carried out in order to remove PIs. Costs for removal of PIs was included, and turned out to be approximately 30% of the total program costs in the first year. The total program costs for the first year were estimated at approximately mUS$ 1.8 (i.c. US$ 7.7 and US$ 19 per animal and adult cow present respectively). The prevalence of PIs reduced and became 0 after 10 years, resulting in a gradual reduction of the program costs to approximately mUS$ 0.5 in year 10 and mUS$ 0.35 in year 20. Apparently, the intensive testing for PIs did not result in a faster eradication of PIs than 10 years. They concluded that eradication of BVDV in France would become cost-effective only after 15 years, and therefore adaptation of such a program is questionable.

An extensive ex post CBA of the Norwegian BVDV control program was carried out by Valle et al. (2005). They used the actual program costs during the 10 years of operation as a basis. Benefits, i.e. reduced losses due to BVD, were defined as the difference between the expected direct losses without the program and the observed direct losses during the course of the program. Both data on costs and benefits were included in a stochastic simulation model for further analysis. An average loss at the onset of the program of NOK 77 (approximately € 11) per calving per year was calculated. A gradual reduction of BVDV prevalence was observed, which resulted in an almost complete eradication after 10 years. During the course of the program, benefits increased. A Net Present Value of the entire program over the entire period of mNOK 130 was calculated (range from mNOK 51 to mNOK 201), i.e. m€ 18 (range from m€ 7 to m€ 27). It should be noted however, that at the onset of the program, 75% of the herds were naïve to BVDV, which could imply high on-farm losses in case of re-introduction of BVDV; in turn, this would have an increasing effect on the programs' benefits. Also, strict biosecurity measures, involving a ban on purchasing animals by BVDV-free herds from herds that were not free, very much reduced the probability of re-infection of BVDV-free herds, and thereby increased the benefits. On the other hand, control and eradication costs could be kept

very low at approximately US$ 2.7 per adult cow. Main reasons for these were use of bulk milk samples as the basis for distinguishing BVDV-free herds from others and collection of pooled first-calver's milk samples by the farmer if the herd was previously tested positive. Hence, both benefits and costs were amplified in a desired way. From this study, it can be concluded that under certain conditions, sector wide eradication of BVDV is possible and cost effective, provided that re-introduction can be avoided.

Both studies came to quite different conclusions: Dufour et al. (1999) questioned the economic feasibility of regional eradication of BVDV, whereas Valle et al. (2005) were positive. A closer look reveals some of the probable reasons for this difference in outcomes. First of all, the estimated average yearly losses appeared to be quite the same: US$ 10.5 and 11 per adult cow respectively. Moreover, in both studies eradication of BVDV (i.e. PIs) was achieved within approximately 10 years. However, a very large difference can be observed in the program costs: US$ 19 and 2.7 in Dufour et al. (1999) and Valle et al. (2005) respectively, both during the first year. Valle et al. (2005) did not include costs associated with removal of PIs, which accounted for 30% of the program costs in Dufour et al. (1999). Even then, the difference in program costs is remarkable. Main reasons for this appears to be, that Dufour et al. (1999) used extensive blood testing on individual animals, which make up approximately 50% of the total program costs during the first year (note: Valle et al. (2005) do not provide a specification on this issue). In contrast, in the Norwegian program predominantly testing of pooled milk samples was used, which kept program costs low. Although a little speculative, approximately 80% of the difference in program costs can be explained in this way.
Hence, it seems likely that the difference in conclusion between both studies can be explained largely by the much higher program costs assumed by Dufour et al. (1999), resulting from extensive individual testing and (replacement) costs for removed PIs. A key question in this respect seems to be: are the assumptions made by Dufour et al. (1999) absolutely required to obtain eradication of BVDV under their conditions, or could a less intensive and therefore less costly program such as the Norwegian one also result in eradication of BVDV under French conditions? In other words: are less costlier alternatives for the approach by Dufour et al. (1999) possible, provided they would have the same eradicative effect on BVDV?
Given the available literature, these questions can not be answered, unfortunately. In comparing both programs, some key differences can be observed however which could justify higher assumed program costs in other conditions as those in Norway.
The average herd size assumed by Dufour et al. (1999) was 71 animals compared to 36 in Norway. In populations with relative small herd sizes, eradication of BVDV is believed to be easier, hence requiring less rigid and therefore less expensive control programs.
There was a considerable difference in initial sero-prevalence between both studies. Based on empirical observations, Dufour et al. (1999) assumed only 25% of the herds and 54% of the animals to be sero-negative, whereas 75% of the Norwegian herds were assumed to be naïve to BVDV. Moreover, whereas in Norway extremely strict legal-based biosecurity was applied with regard to e.g. trade of animals, it seems likely that this was not the case in France (e.g., Dufour et al. (1999) assumed 9,500 (4%) new animal introductions into the population annually). This would justify more intense sampling and testing of individual animals, with accompanying higher program costs. The latter holds also, if a more intense and less transparent trade pattern is assumed.
Finally, it is noteworthy that in both studies the risks of re-introduction of BVDV in the population after complete eradication is not considered. This would cause losses, and hence would reduce the BCR of the eradication program. Such a risk presumably will be lower in a rather isolated population like the Norwegian, compared to the French conditions.

Both studies show, that eradication of BVDV within a region or country is possible. However, the comparison of both studies also shows that the program costs can vary considerably, and in return can affect the BCR of the program. In future decision making in other countries beside those that already have adopted or completed an eradication program, careful ex ante studies aimed at comparing various different eradication programs is therefore absolutely required. Such studies should focus on (1) the ability of the programs to eradicate BVDV, (2) the course of BVDV prevalence and (3) the duration until complete eradication, and (4) the total financial-economic costs of such a program including costs associated with re-introduction after complete eradication, prevention and monitoring. Preferably, also the indirect losses caused by BVDV (i.e. indirect benefits) should be taken into account. Only then, an economic-sound decision can be made whether regional or national eradication is economically feasible or not. Examples of such approaches for other diseases exists, e.g. for IBR (Vonk Noordergraaf, 2002).

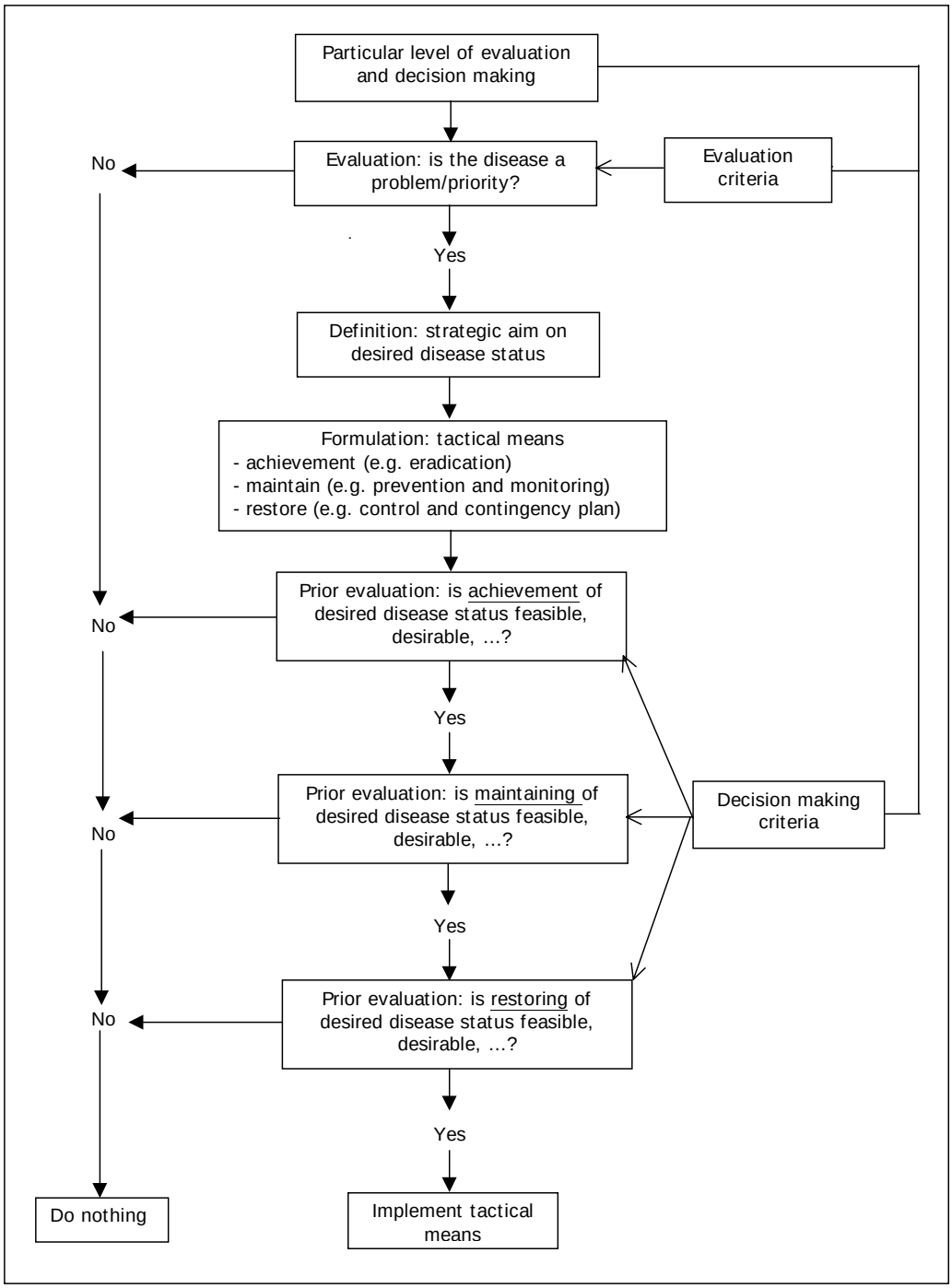
An important consideration before any regional or national disease eradication programme is to establish an appropriate partnership between and commitment towards the programme from all stakeholders concerned. This point is made in the Animal Health and Welfare Strategy for Great Britain (Defra et al., 2004). This may partly explain why BVDV can be successfully eradicated from a relatively cohesive and geographically isolated community such as the Shetland islands (Synge et al., 1999) but not from France or mainland Great Britain for example. It should be appreciated that farmers and the farming community are not the only beneficiaries of BVDV eradication due to the removal of considerable ‘externalities’. If the eradication programme is sufficiently widespread such that supply of animal products is significantly increased, then product prices are likely to fall to the detriment of farmers, particularly those who were free of BVDV in the first place. The major beneficiaries will then be consumers who pay less for animal products. This situation is explained in the context of hypothetical eradication of Johne’s disease from the USA by Losinger (2005).

4.6. Conceptual and theoretical considerations on endemic disease control in general and BVDV control in particular

4.6.1. General framework for decision making on disease control and prevention

In figure 1, a general framework for decision making on livestock diseases, currently present in a population, is presented. This can be applied at any level of decision making. Four distinct points of evaluation or decision making respectively can be seen.

Figure 1. General framework for decision making on livestock diseases currently present within a population.



The starting point is the definition of the level of evaluation and decision making, e.g. the farm, the livestock sector or society as a whole. For each level, particular criteria for evaluation and decision making can be derived, such as veterinary criteria, farm economic criteria and social criteria (for an elaboration: see Chapter 3).
Starting question is: can the disease be regarded as a problem and should this problem be given priority? Depending on the appropriate evaluation, their weights and consequently their ranking, this question can be answered either positively or negatively. In the latter case, i.e. if the disease is not regarded as a problem and/or a priority, then the status quo (i.e. do nothing) is the logical outcome. In contrast, a positive answer should be followed by the definition of a strategic aim, i.e. the desired disease status. Subsequently, formulation of the tactical means to achieve, maintain and, if required, to restore (e.g. in case of new disease outbreaks) this disease status should be carried out.
Next steps are prior evaluations of the following issues:
- is achievement of the desired disease status feasible and/or desirable given specific decision criteria;
- is maintaining this disease status feasible and/or desirable;
- is restoring this disease status feasible and/or desirable.
These prior evaluations should be subject to specific decision criteria. If all evaluations are positive, implementation of the tactical means, control and eradication of the disease, should follow. However, if one or more of the evaluations results in a 'no' answer, the ultimate result will be: do nothing.
It should be noted that several different strategies for eradication, prevention and control can be subject to these prior evaluations, out of which some can be suitable and some not.

From this framework, the following list of **requirements for economic decision making** can be derived:
- the **levels** of evaluation and decision making which can or should be considered;
- the evaluation and decision making **criteria** associated with these levels;
- a definition of the desired disease status (i.e. the **strategic aim**) per level for which the disease is considered to be a problem and/or priority;
- formulation of **tactical means** to achieve, maintain and if necessary restore the desired disease status, e.g. eradication and control strategies;
- **methods** for prior evaluation of these tactical means.

4.6.2. Decision making on control and prevention of Bovine Viral Diarrhoea

In this section, the requirements listed above will be elaborated for BVD as specifically as possible. In most cases, the same approach is applicable to other diseases as well. Part of the information used in this section results from discussions within the Thematic Network.

4.6.2.1. The levels of evaluation and decision making

With regard to BVD, the following levels of evaluation and decision making were identified:
- the farm level, with the farmer as decision maker;
- the livestock sector at the regional level, with some form of regional sector authority as decision maker, e.g. a regional farmers' cooperative or union;
- the livestock sector at the national level, with some form of national sector authority as decision maker, e.g. a national union or product board;

– the society, with the national government as decision maker.

Currently, in most EU countries the farm level is the predominant level of decision making: the farmer decides whether or not (s)he will participate in a voluntary control and prevention program, initiated at the farm level, or higher.
The regional sector is only applicable in larger countries, such as the United Kingdom (UK), Germany and France. In these countries, the livestock sector within the region has some kind of autonomy. With regard to the region, specific aspects can be considered, such as epidemiological isolation (e.g. the Shetland and Orkney Islands within the EU), socio-demographic aspects (e.g. in Brittany in France) or the political structure of the country (e.g. the Länder in Germany). Indeed, in some EU countries, evaluation and decision making on BVDV at the regional sector level can be observed, e.g. The Shetland Island and Orkney Islands in the UK and Brittany in France. Semi-mandatory eradication programs were carried out during the last couple of years.
In the Scandinavian countries Norway, Denmark, Sweden and Finland, BVDV is regarded as a problem of the national sector or even a priority for society (a clear distinction cannot be made in these cases). In these countries, mandatory control and prevention programs currently are running.
It can be observed that voluntary programmes are only applied if the decision making level is the farm level. At higher levels, (semi-)mandatory programmes eventually have to be applied, although there are examples where such large-scale programmes have been voluntary at the onset.

4.6.2.2. Evaluation and decision making criteria

4.6.2.2.1 Evaluation: is BVDV a problem and should control and prevention be given priority?

In Table 1, evaluation criteria for the four levels are presented. These evaluation criteria can be derived e.g. from (panel-) interviews or questionnaires focused on goals and preferences with groups of stakeholders, relevant for the particular level of concern. In principal, both evaluation and decision making criteria are not related to the disease as such, i.e. can be applied to any livestock disease; in the application of these criteria, the impact a disease has on the particular criteria is valued, as will be explained later.

Table 1. Levels of evaluation and accompanying evaluation criteria for BVDV.

Evaluation criteria	Evaluation level			
	Farm	Sector/region	Sector/national	Society
Veterinary	+	+	+	+
Farm economic	+	+	+	+
Sectoral/regional economic		+	+	+
Sectoral/national economic			+	+
National welfare economic				+
Ethical/animal welfare	+	+	+	+
Social		+	+	+
Food security and safety				+
International situation	+	+	+	+

Note: although food security and safety is an evaluation criterion for society, in the case of BVDV it is not applicable

At the farm level, primarily veterinary criteria (e.g. morbidity and mortality), economic criteria (e.g. losses due to BVDV, compared to losses due to other diseases) and ethical and animal welfare criteria are important.
At the sector level within a region, also (regional) social criteria can be of importance (e.g. because of a close link between the regional society and the livestock producers). Moreover, regional economic criteria should be included, mainly for two reasons. First, BVDV can have a negative impact on the regional cattle sector as a whole, i.e. all farms within the region are affected somehow. Second, if there is a variation in economic impact of BVDV on farms within the region, in some cases a collaborative approach can be regarded as the most appropriate way of dealing with the disease.
With regard to the national sector, the same holds as for the regional sector (note: in small countries like e.g. The Netherlands, there is no distinction between both), however also national sector economic criteria should be included.
Evaluation at the level of society as a whole should consider preferences of all members of society, i.e. also those not directly involved in livestock production. Hence ethical/animal welfare and food security and safety evaluation criteria should be included as well (note: with regard to BVDV, there is until now no evidence of BVDV endangering food safety and security, hence these criteria can be disregarded).
Self evidently, international requirements (e.g. requirements regarding freedom of BVDV if OIE listed) are an evaluation criterion at all levels.

4.6.2.2.2 Decision making on prevention and control of BVDV.

Decision making deals with allocating scarce resources in such a way that the maximum level of satisfaction is achieved. The latter is subjective by nature, because each individual has a different ranking of preferences or criteria which should be fulfilled. Hence, decision making deals with making choices (e.g. complete eradication of BVDV versus only reduction of the impact of the disease) and allocating resources to achieve that goal (e.g. participation in a control programme, either with or without use of vaccines, etc.)
'Decision maker' in this respect can be defined as: the person or body who owns the decision problem and is actually responsible for deciding what to do about it and in which way this should be done. In the case where several levels regard BVDV as a problem, probably the highest level of aggregation will be 'appointed' as the decision maker. However, it is also imaginable that a lower level is appointed, and facilitation from higher levels will take place.(This is the general thrust of the approach to endemic animal disease control in Great Britain set out in the Animal Health and Welfare Strategy (Defra et al., 2004)).
The goals or strategic aims will be elaborated in the next paragraph.

When it comes to decision making on animal health, usually these decisions affect various aspects of animal production, i.e. these are multi-criteria decisions. Each decision taker (i.e. the decision maker) or stakeholder however has different priorities and preferences with regard to these criteria, hence weighing between the various decision criteria is inevitable.
The following decision criteria can be identified (it should be realized that each criterion can be broken-down further into several so-called sub-criteria or indicators (Huirne et al., 2002), not described here):

- veterinary criterion: the ability of a strategy to (1) achieve, (2) maintain and (3) restore the desired BVDV status;
- farm-economic criterion: the ability of a particular strategy to be financially profitable and hence will contribute to the farms net profit (i.e. the benefit/cost-ratio of the strategy and the expected time to return on investment);

- welfare-economic criterion: the ability of a strategy to contribute to an increase in Gross Domestic Product (GDP), i.e. to enhance the efficiency of cattle production;
- international feasibility criterion: the likelihood that a strategy is in compliance with international (legal) obligations of a particular country, and if not, that implementation of that strategy would not have adverse effects for the country;
- international-economic criterion: the possible effects of a strategy in a particular country for other countries;
- ethical or animal welfare criterion: the ability of a strategy to improve animal welfare;
- ecological criterion: the effects of a strategy on the environment, nature and biodiversity;
- psychological criterion: the effects of a strategy on the mental situation of those affected;
- food security and safety criterion.
- distortion criterion: the possible adverse effects of a strategy on daily life, e.g. reduces mobility of people.

Not all decision criteria most likely will apply to every level of decision making. In table 2, an overview is presented of relevant decision criteria for separate levels of decision making.

Table 2. Levels of decision making and accompanying criteria for BVDV.

Decision criterion	Farmer	Regional sector	National sector	Government
Veterinary	+	+	+	+
Farm economic	+	+	+	+
Regional economic		+	+	+
Sector economic			+	+
National welfare economic				+
International feasibility		+	+	+
International economic				+
Ethical/animal welfare	+	+	+	+
Psychological	+	+	+	+
Ecological				+
Food safety and security				+
Distortion				+

4.6.2.3. Definition of desired BVDV status

Given the four levels of decision making distinguished above, the following strategic aims regarding the desired BVDV status can be defined:

- the individual farmer: if (s)he considers BVDV as a problem, the aim would be to achieve and maintain a BVDV-free status of the farm, preferably accompanied with a certificate. Alternatively, a farmer could also aim at merely a reduction in the impact of BVDV without complete eradication from the herd;
- the regional sector authority: if BVDV is regarded by all farmers within the region as a collective problem, or if a collective approach to BVDV would be more economical from a regional point of view, decisions on BVDV should be made by the appropriate regional

sector authority, aimed at eradication of BVDV throughout the region, either or not accompanied with some kind of official status;
- the national sector authority: the same as for the regional sector authority;
- the national government: if the (supra-)national society regards BVDV as a problem, the national government should aim at eradicating BVDV from the country, most likely supported by some kind of legislation, aiming at the status of officially free of BVDV.

A key issue in this respect will be the degree in which control of BVDV can be approached 'voluntarily'. Basically this will come down to the question: will freedom of BVDV be given a (semi-)official status, without which also other farmers beside the affected ones will be confronted with (e.g. trade restrictions at regional or national scale). The most profound way in this respect will be BVDV regarded as an OIE listed disease. If so, either the national sector or the government will have to take the initiative; if not, other levels of decision making also are possible.

4.6.2.4. Tactical means to achieve, maintain and restore the desired BVDV status

Tactical means refers to ways to control or eradicate, prevent and monitor BVDV. In practice, no clear distinction between these three is being made: all approaches include elements of each other. Moreover, all practically applied approaches include combinations of the single measures described below. However, a distinction should be made if the BVDV-status of a particular farm affects other farms within the region or country.

4.6.2.4.1 Means to achieve freedom from BVDV

Regardless of the level of decision making, prime focus should be on the individual farm because of the current endemic nature of BVDV. Throughout Europe, farmers practice different ways to achieve freedom of BVDV, either in co-operation or independently:
- participation in a test-and-cull based eradication program focused on culling permanently infected (PI) animals, as these animals are the prime source of maintaining BVDV within the herd;
- vaccination against BVDV, aimed at either eradication or at reducing the clinical impact of the disease (note: this latter option will not result in freedom of disease);
- enhanced bio-security of the farm, aimed at preventing BVDV being (re-) introduced on the farm.

4.6.2.4.2 Means to maintain freedom from BVDV

Basically, increased bio-security is the predominant way of trying to prevent BVDV from introduction once eradicated, be it at the level of the individual herd or at a wider level. This could be accompanied by vaccination, although this is not regarded as sufficient.
Monitoring the disease-free status is regarded as a necessary accompanying measure, particularly if this status is (semi-)officially recognized. Moreover, monitoring is a means to detect at a preferably very early stages re-introduction of BVDV.

4.6.2.4.3 Means to restore freedom from BVDV

In case of reintroduction of BVDV on a **farm**, the farmer can decide to re-start the same procedure as with achieving freedom of BVDV; this could take approximately one year. However, at regional or higher levels, the situation can be more complex, if the (semi-)official BVDV-status of the **region or country** will be changed after reintroduction of BVDV at only

one particular farm; this will be the case e.g. if BVDV is regarded as an OIE listed disease. If this change of status will result in e.g. trade restrictions or other adverse effects for not only the farm affected, lots of other, non-affected farms will also be confronted with adverse effects as long as this change of status remains in power. Both the magnitude of the adverse effects, as well as their duration, are determining factors in such cases. As a consequence, a rapid regional or national eradication of BVDV could be desirable, in which case more rigid disease control measures would be considered.

4.6.2.5. Economic methods for prior evaluation of means and strategies

In terms of methods for economic evaluation of means and strategies for control, a distinction can be made between methods focussing on a part of the decision making problem and those claiming to be more comprehensive. The former include issues such as diagnostic tools, vaccination, epidemiology and clinical trials to study the veterinary and zoo-technical impact of BVDV, all based on more or less real-life experimentation, veterinary-epidemiological data analysis and clinical trials. Other WorkPackages within the Thematic Network deal with these issues.
A comprehensive study primarily focused on decision making should integrate all these separate issues, and should include socio-economic aspects as well. Real-life experimentation in such cases becomes quite difficult. If real-life experimentation is undesirable or even impossible, costly or disruptive, and also if strategies or approaches have to be evaluated which have not been applied yet, computer simulation (i.e. veterinary-economic modelling of BVDV) is an attractive alternative (Dijkhuizen and Morris, 1979). Since fundamentally different situations can be distinguished, various integrated approaches should be applied, depending e.g. on the level of decision making (on-farm simulation models should include different aspects compared to e.g. sectoral models), the strategic aims (eradication, monitoring), etc.

4.7. Financial-economic considerations with regard to the eradication, prevention and control of Bovine Virus Diarrhea Virus

Despite the fact that decision making on BVDV can or should be regarded as a multi-criteria decision problem (see above), the financial-economic impact of BVDV is of utmost importance for all decision making levels considered. Therefore, particular attention should be given to this issue.

Starting from a current situation of endemic BVDV, be it on a farm or within a region, three distinctive periods should be considered, irrespective of the economic level:
- the period until achieving the BVDV-free status, be it on the farm, within the region, within the sector or the country;
- the period of maintaining the BVDV-free status;
- the period after possible reintroduction of BVDV until restoring the normal disease-free status.

The first period can be regarded as a period of investment, e.g. in BVDV eradication, monitoring, bio-security, etc. Financial-economic aspects of prime importance are: the costs of the eradication programme.
The second period can be regarded as ‘return on investment’, e.g. by increased production efficiency, higher product prices, etc. (although it is possible that prices may fall as explained

above, see Losinger (2005)). Basically, some kind of Benefit/Cost-Analysis (BCA) could provide insight into the economic impact of eradication of BVDV.
Additional to both periods, other costs should be considered as well: costs for monitoring and costs for increased bio-security. The first are usually an integral part of an eradication and control program, the latter can be regarded as 'fixed costs' to reduce the probability of re-introduction of BVDV.
With regard to the third period however, the economic impact very much depends on factors such as the economic level considered, the impact of the control measures, possible changes in status and accompanying trade restrictions, etc. E.g. for re-introduction on a farm only the farmer is confronted with the adverse consequences, whereas re-introduction within a region could have adverse consequences for all farmers within that region if trade restrictions are imposed. Moreover, crucial will be the types of products on which such restrictions are imposed.

The financial-economic impact of BVDV, particularly in case of re-introduction, largely depends on the following factors:
- the economic level considered;
- the definition of the 'normal' disease-free situation;
- the effect of reintroduction of BVDV on this normal situation, particularly for other farmers, i.e. will this result in some kind of trade restrictions and if so, which products will be affected (animals, products such as meat and dairy products, semen, etc);
the control strategy applied in trying to restore the normal disease-free situation.

In table 3, an overview of the financial impact of occurrence of BVDV in different situations in presented. The first column (BVDV present but varying in degree per farm) reflects more or less the current situation, i.e. BVD being basically endemic and not subject to control at a larger scale. In such a situation, economic theory explains that farmers affected face a loss, and those that are not have a comparable gain. Both consumers and society will have a comparable loss due to higher prices and less efficient use of resources.
However, if the status of BVD will be changed from an endemic disease to a disease which is eradicated in certain areas (can or will have consequences at a higher level, i.e. non-affected farmers within a region or country), some financial-economic consequences can change. This particularly depends on the type of measures imposed after re-introduction of the disease within that larger area to control BVD, i.e. either or not trade or transport restrictions, and the type of products included in such measures. Hence, it should be realized that collective measures for control/eradication could have financial-economic implications for non-affected herds.

Table 3. Financial-economic impact of BVDV in different situations with regard to economic level considered and (changes in) BVDV status.

Economic level	BVDV status, confirmation of this status and possibilities for trade restrictions			
	BVDV present but varying in degree per farm	BVDV-free within the region, present in the rest of the country	BVDV-free within the country	BVDV-free within the country
	Not or with farm certificate	Not or with (only regionally or nationally recognized) regional status	Not or with (only nationally recognized) national status	Officially recognized national status OIE-List B
	Only voluntary between-farm restrictions, based on BVDV-free certificate	Voluntary/mandatory within region between-farm restrict-ions, based on BVDV-free	Yes, within the country but no export restrictions	Yes, within the country and export restrictions
BVDV affected individual producer	A direct relation between degree of BVDV and economic losses.	Financial losses depend on control strategy, compensation payments and impact of BVDV.	Financial losses depend on control strategy, compensation payments and impact of BVDV.	Financial losses depend on control strategy, compensation payments and impact of BVDV.
BVDV non-affected individual producer	Financial advantage compared to BVDV affected producers.	Financial losses depend on the degree and impact of trade restrictions and products affected; in case no trade restrictions, financial advantage compared to BVDV affected producers.	Financial losses depend on the degree and impact of trade restrictions and products affected; in case no trade restrictions, financial advantage compared to BVDV affected producers.	Financial losses if trade restrictions are imposed, depending on the type of products involved, particularly in net-exporting countries.
Regional cattle sector	Due to price adjustment no relation between degree of BVDV and income of cattle farmers.	Financial losses depend on control strategy, compensation payments and impact of BVDV.	Not applicable	Not applicable
National cattle sector	Due to price adjustment no relation between degree of BVDV and income of cattle farmers.	Due to price adjustment no relation between degree of BVDV and income of cattle farmers.	Moderate loss, depending on control strategy, compensation payments and impact of BVDV.	Significant loss particularly for net-exporting countries, resulting from price drops on domestic market.
Agri-industry	Note	Note	Note	Note
Consumer	Economic loss due to less-efficient production and higher prices.	Hard to determine	Hard to determine	Incidental advantage if trade restrictions distort markets, particularly in net-exporting countries
National economy	Economic loss due to less-efficient production and less-efficient use of resources.	Hard to determine	Hard to determine	The aggregated effect is hard to determine

Note: it is assumed that price changes are passed on to the consumers fast and completely, therefore possible effects are not specified.

4.8. Discussion and conclusions

In this section, the main findings of the reviewed literature (4.5) are put into the broader perspectives of decision making (4.6) on the control and prevention of BVDV. This is done from two perspectives: the individual farm and the livestock sector.

4.8.1. Is BVDV an economic problem?

The case studies described in section 4.5.1 indicate that introduction of BVDV into naïve herds with unprotected animals can cause great financial-economic costs, i.e. large adverse consequences. Ahl et al. (1993) define risk as the probability of occurrence of an adverse event times the consequences of that event. However, neither the studies described in this section, nor others, provide an indication of the probability of occurrence. Therefore, in terms of decision making under risk, the value of these case studies is rather limited. What they do indicate is, that the potential economic danger of BVDV introduction on farms is great, and should not be neglected. In other words, BVDV is a potential threat or problem, which cannot be disregarded but should be studied further (see: Figure 1). Today, realistic estimates on the incidence of new infections can be retrieved from ongoing control programmes (see work package 2).

The average yearly on-farm direct losses estimated in the studies described in section 4.5.2 showed, that BVD is potentially an important economic livestock disease. Estimations of the direct losses for the national livestock sector, described in section 4.5.3, confirm this. However, this importance most likely is less than mastitis or lameness. The question remains if the direct losses estimated are avoidable or not. In contrast to e.g. mastitis and lameness, BVDV can in principle be eradicated, either on an individual farm or within the entire sector. This implies that in principle these losses are avoidable, provided the eradication is complete and lasting (i.e. no re-introduction of BVDV in the long run). In that case, these (avoidable) losses estimated should be set against the additional expenses required to obtain complete and lasting eradication, e.g. costs for eradication, monitoring and certification and prevention. In case re-introduction of BVDV cannot be excluded, the total costs of such a re-introduction (i.e. losses due to the disease and control costs) should be subtracted as well. On the other hand, possible reduced indirect losses due to reduced incidence of other diseases because of the eradication of an immunosuppressive agent (BVDV) should be taken into account as well. Hence, an estimation of the 'true' avoidable losses at the farm level is still lacking. Nevertheless, although the magnitude of this problem still is not completely clear, the studies described clearly indicate BVD as a financial-economic problem, both for farmers and for the entire livestock sector. In a broader economic context, not only these financial-economic aspects are part of the problem, but also (see: Table 1): veterinary aspects (morbidity, mortality) and animal welfare aspects; from the perspective of the livestock sector, also the international situation can be included if other countries are BVDV-free and possible trade restrictions could be the case if BVDV is still present. (Economics can estimate the financial impact of non-market goods such as animal welfare using a variety of techniques (e.g. Bennett, R., and Blaney, R. (2003) and these can then be included in the decision support CBA).

Based on the studies dealing with the estimation of losses due to BVDV, it can be concluded that BVDV is an economic problem for livestock owners and the sector as a whole, both for

financial-economic and other reasons such as veterinary and animal welfare. Sero-epidemiological evidence shows, that this most likely holds for most EU member states.
A clear indication of the magnitude of this problem, e.g. in terms of 'true' avoidable financial-economic losses, cannot be derived from these studies. However, the studies do suggest that it is reasonably safe to classify BVD as being one of the important livestock diseases after mastitis, lameness and fertility disorders in most of the EU member states.

4.8.2. Should BVDV be given priority from an economic point of view?

Considering BVD as an economic problem in the broader context, the next question which should be addressed (see: Figure 1) is: should solving the BVDV problem be given priority? In other words, is BVDV such a big problem to the individual farmer or the livestock sector, that allocation of scarce farm or sector resources to BVDV is justified above such an allocation to solve other problems, be it disease problems or others? This implies, that an BVDV control program with a BCR above 1 is not an economic justification of adopting this program, because other projects or investment could contribute more to the benefit of the decision maker. Based on the studies described in sections 4.5.1 to 4.5.3, the question raised above can not be answered, neither for the farm nor for the sector level. Other scientific literature addressing this issue could not be found either.

As pointed out earlier, ideally a MCA including the various decision options and criteria should be carried out to answer the above raised question. Alternatively, CBA at the farm level or Social Cost-Benefit Analysis (SCBA) for the sector or country (as proposed by Bennett and Done (1986)), could be carried out. Examples of such analyses have not been published so far.

What can be observed, however, is that in some countries the livestock sector has given priority to BVDV control. The Nordic countries and parts of Germany, Austria, Great Britain, France and Italy have started eradication programs. Apparently, these countries/regions perceived BVDV as such a big problem and/or threat, that priority could be justified. Arguments in favour were (see: e.g. Valle et al. (2005), Lindberg (2003) and Greiser-Wilke et al. (2003)): (1) the presumed economic losses based on CBA-studies, (2) the possibility of indirect veterinary and economic effects due the immunosupression, (3) the veterinary effects in terms of morbidity and mortality, and (4) the animal welfare effects. These programs have proven to be successful in eradicating BVDV in Norway, Sweden, Finland and Denmark. Nevertheless, a sound economic justification for allocating the scarce resources to BVDV instead of other problems of the livestock sector could not be found. Moreover, Dufour et al. (1999) concluded the opposite.
Also, it can be observed that individual farmers throughout the EU join voluntary BVDV control programs.
Hence, it can be concluded that eradication of BVDV has been given priority in quite some cases. However, a clear science-based economic justification can not be found in the literature, and should therefore be investigated.

4.8.3. Is achievement of eradication of BVDV feasible from a financial-economic point of view?

All studies reviewed agree on at least one thing: BVDV has adverse economic effects, i.e. the average losses associated with the disease are substantial, and in incidental cases outbreaks

can cause even large losses. It seems also safe to state, that in most cases, the costs associated with the eradication are less than the long term benefits in terms of increased production efficiency. This holds for both individual farms (sections 4.5.1, 4.5.2 and 4.5.4) and the sector level (sections 4.5.3 and 4.5.5). An important assumption to this statement is: re-introduction of BVDV is disregarded, and hence also the costs associated with reducing this re-introduction. This issue will be addressed in the next section.

4.8.4. Is maintaining of the BVDV-free status feasible from a financial-economic point of view?

After obtaining the status of BVDV-free, the pay-back period starts, and the longer this period is, the higher the BCR of eradication. However, both individual farmers and the livestock sector should face the possibility of re-introduction of BVDV. In order to limit this probability, additional bio-security measures are required, which have financial-economic implications. The latter can be quite county or region specific. In favourable, more isolated regions, these costs can be relatively low, e.g. in the Nordic countries and isolated areas such as the Shetland and Orkney Islands. Other, more continental areas, face a higher risk of re-introduction of BVDV, i.e. higher costs for prevention.
The existing literature does not explicitly address the costs for prevention of introduction of BVDV. However, Dutch studies (e.g. Groenendaal and Horst (2000) and Saatkamp et al. (2005), which focus on combined efforts to eradicate BVDV and maintain freedom of BVDV at the herd level, indicate that in these conditions, eradication and prevention at the herd level can be questioned.
This raises the question if a joint effort, e.g. at the regional level, to eradicate BVDV and maintain freedom of BVDV, is not a better solution. In the Nordic countries, such an effort proved to be rather successful. However, program costs and bio-security costs were relatively low. The question if this holds also for ‘less favourable’ countries cannot be answered based on the existing literature.

4.8.5. Is restoring the BVDV-free status feasible from a financial-economic point of view?

Facing the risk of re-introduction, the last question to be answered is: is restoring BVDV-freedom sensible in case introduction has occurred at a farm or in a region? Farm level studies for The Netherlands indicate, that if the probability of re-introduction is relatively high, the answer would be negative, particularly if the sero-prevalence at re-introduction is rather low. In such cases, the losses associated with re-introduction are quite high (see e.g. Groenendaal and Horst (2000) and Saatkamp et al. (2005)).
At the sector level, an additional criterion for consideration will be: what is the international situation? If all surrounding countries and/or trade partners will have a BVDV-free status, the pressure for regaining freedom of BVDV will be high. Also from a financial-economic point of view, because possible trade restrictions will caused additional economic losses on top of the production losses.
However, an explicit answer to this question based on the current literature cannot be given.

4.9. Requirements and availability of methods and data to evaluate control and prevention strategies/scenarios against Bovine Virus Diarrhoea Virus

With regard to future decision making, insight into two issues is important:
- Is BVD a problem and should it be given a priority?
- What is the veterinary and financial-economic impact of control/eradication, prevention and monitoring?

For both questions, of course, the level of decision making should be the start of the exploration.

4.9.1. Identification of the problem and priority setting

As described above, elicitation of evaluation criteria and their comparative weights can be useful in problem identification and priority setting procedure. In Tables 1 and 2, evaluation and decision making criteria for BVDV are listed. Particularly for evaluation and decision making levels higher than the farm level, these criteria should be more elaborated (inclusion of e.g. sub-criteria or indicators). Moreover, and this holds particularly for evaluation at the level of society and decision making at national level, weighing and ranking of these criteria is important. Only then, a comprehensive evaluation is possible.
For BVDV, such information is not available yet. However, because these criteria are not strictly disease dependent, use can be made of other studies. Huirne et al. (2002) described such an approach and data for FMD. Hence, basic methodology is available, and some basic data as well.
Such formal procedures are usually quite elaborative, however. At the farm level, interactive and implicit communication between farmer and advisors (i.e. his/her vet) is usually sufficient to reveal whether or not controlling BVDV should be given attention. At higher levels of decision making, a more explicit discussion involving all relevant stakeholders is the minimum which is required. Use of ‘check lists’ based on Tables 1 and 2 will be very useful.

4.9.2. Prior estimation of veterinary and financial-economic impact of BVDV

For questions regarding prior estimation of the impact of disease, integrated epidemiological-economic simulation modeling has proven to be quite useful (Dijkhuizen and Morris, 1997). However, different levels of decision making require different approaches.

4.9.2.1. Farm level

In case the prime interest is control and prevention at the farm level, simulation models that mimic within herd spread of BVDV and its financial-economic impact, subject to different control and prevention scenarios, is required. Several of such model are currently available for BVDV:
Gunn et al. (2004) described a model for Scottish beef herds, estimating the losses associated with BVDV. With this model, an indication of benefits and costs of BVDV control can be obtained;
Gunn et al. (forthcoming) adapted this model for Scottish dairy herds;

Groenendaal (1998) developed a decision support model estimating the B/C-ratio of BVDV control for Dutch dairy herds. This model was later adapted to new and more sophisticated BVDV control programmes (Saatkamp et al., forthcoming).
All these models focus only on BVDV control and prevention in an isolated way, i.e. they only deal with the single question: is BVDV control and prevention as such financially-economic beneficial or not. The aspect of on-farm resource allocation is not considered. However, from a total farm management point of view, this is quite important because of limited resources available, i.e. competition between farm activities. Stott et al. (2003) addressed this issue for Scottish beef herds, using a combination of simulation modeling and linear optimization, a so called MOTAD approach (Minimization Of Total Absolute Deviation) (see: Hardaker et al., 1997).
With regard to farm level evaluation and decision making, several different tools are currently available. For application to farm and region specific situations, these tools have to be adapted further, which is currently being carried out (Gunn et al., forthcoming)

4.9.2.2. Regional and sector levels

If the prime focus of interest is extended beyond the level of the individual farm, not only estimation of the impact of control and prevention of BVDV for individual producers is required. E.g., prior evaluation of a regional or even more wider scale program requires insight in (1) the impact on between-farm spread and (2) the 'quality' of monitoring programs. In terms of model output parameters, this means: an estimation of the R_h (basic reproduction ratio of between-herd spread of BVDV, which should be less than 1 for effective programs) and an estimation of the probability of detecting BVDV-positive herds and the time between (re-)introduction and detection.
Examples of such models applied to other diseases have been described, e.g. for *Leptospira hardjo* (Graat et al., 2001; Saatkamp et al., 2005) and paratuberculosis (Roermund et al., 2005). These models have a generic approach, in principle allowing for adaptation to BVDV.

4.9.2.3. National level

For a comprehensive socio-economic prior evaluation at the national level, two issues should be included additionally. First, the impact of BVDV on national economic welfare, and second a comprehensive multi-criteria analysis including all decision criteria.
To estimate the impact on national economic welfare of re-introduction and subsequent control of BVDV within a country, only approaches for highly contagious diseases such as FMD and Classical Swine Fever (CSF) have been described so far, e.g. by Mangen and Burrell (2001) and Berentsen et al. (1991). Although adaptation of these models to BVDV requires re-parameterization (i.e. additional data collection), in principle these approaches can be used within serious problems.
Huirne et al. (2002) presented a comprehensive evaluation of FMD control and prevention strategies for The Netherlands. They applied a Multi-Criteria Analysis (MCA), to take account for all relevant decision criteria, e.g. also less easily quantifiable aspects such as animal welfare and psychological aspects of the decision problem. Again, this basic methodology is in principle applicable to BVDV.

4.10 Future outlook, research agenda and conclusions

4.10.1 Current state of the arts

The available veterinary and economic literature quite clearly shows, that BVD can have serious consequences at the farm level: both from the veterinary, animal welfare and financial-economic points of view. Moreover, experiences in the Nordic countries show, that on-farm and sectoral/national eradication of BVDV is possible. Hence, striving to achieve and maintaining eradication should be considered seriously for countries which still have an endemic situation with regard to BVDV.

Generally, two approaches are possible: voluntary and (semi-)mandatory. Voluntary approaches are directed towards the farmer, and hence should be in his/her interest. At the moment, basic veterinary and economic methodology is available to support farmers in this decision problem. However, the existing models still are quite area and/or situation specific, and should be adapted to the specific conditions for application. Although this is not as easy as often thought, this is possible with relatively limited resources and within a reasonably short period of time. Hence, on-farm decision support on control, prevention and monitoring of BVDV is not a major future constraint.

Semi-mandatory approaches at regional or national level include more aspects, as was illustrated, e.g. between-farm spread during eradication and after re-introduction and possible welfare aspects. To decide whether it is in the interest of a particular region or country to eradicate BVDV, basic methods specific for BVDV are not available. However, for other types of diseases they are, e.g. for Aujeszky's Disease, Classical Swine Fever and IBR. BVDV-specific adaptation however requires quite some time and resources, particularly if various different conditions within the EU should be taken into account.

4.10.2 Driving forces in future decision making

Various driving forces in future decision making can be observed within the EU and beyond. First, official listing of BVD at the OIE list would require reconsideration of the BVD situation in countries in which the disease is currently endemic, i.e. the pros and cons of nation wide eradication. Besides mere disease specific aspects, also possible trade implications should be taken into account.
In some countries beside the Nordic countries, national eradication programs have started, e.g. in Austria. Although there is a common goal within these countries, possible trade effects are restricted within the country or between participating farmers.
In the remaining countries, BVDV is still dealt with on an individual basis, hence only farm specific arguments drive the decision on whether or not to tackle BVD or not.
From all three mentioned, the possibility of OIE listing is the major driving force in future decision making, and countries should anticipate on this, i.e. study the consequences of such a measure. To do such things properly, the outline of such a listing should be clear: what are the possible adverse consequences for farmers, regions and/or countries harbouring BVDV. Based on that, studies on the consequences and on the optimal ways of dealing with these can be carried out.

4.10.3 Main knowledge gaps

Given the above, particular emphasis should on studying the veterinary and financial-economic consequences of regional approaches to control BVD. This holds particularly for those countries in which the disease is still endemic and have not yet decided on going towards a sectoral or national eradication of BVDV, e.g. The Netherlands, Portugal and the United Kingdom.
Without 'outside' pressure (e.g. OIE listing), it should become clear for these countries what the consequences of either maintaining or improving the current BVDV situations are, and whether or not tackling BDVD should be given priority. Such studies should also facilitate decision making in anticipation of possible future changes in the international setting of BVDV.

4.10.4 Conclusions

From the above, the following conclusions can be drawn:

- BVDV can have a serious impact at individual herds: financial-economics losses, high morbidity and mortality, impaired animal welfare; this is particularly the case in naïve herds; hence, BVDV can be a serious disease problem from an economic point of view;
- Literature is less unanimous on the question whether BVDV is a such a big economic problem that addressing this problem is always justified; both at the herd and sector level, various studies conclude differently;
- Eradication of BVDV has been given priority in some countries (i.e. the Nordic countries) and has been successful in these countries; however, extrapolation of these decisions to other countries cannot be based on current scientific literature: in these countries, other conditions with regard to BVDV can exists, and other priority preferences might exist;
- A key question with regard to the decision to eradicate, maintain and eventually restore freedom of BVDV seems to be the probability of re-introduction; if this is rather low, or can be kept rather low at low costs, eradication programs will have a good chance to be economic feasible (hereby disregarding other investment allocation possibilities); however, if the probability of re-introduction is high and costly bio-security measures should be implemented to reduce this probability to acceptable levels, the financial-economic feasibility of an eradication program seems to be questionable;
- In areas with a high prevalence, a joint effort of all farmers to eradicate BVDV seems to be more sensible than efforts at the individual farm level; reduction of the risk of re-introduction of BVDV can be carried out at lower costs, whereas the benefits of this reduced risk will be for all farmers;
- Further research is required, particularly on the epidemiological and economics impact of BVDV control at the regional level; basic methodology is largely available, however adaptation to specific BVDV conditions is lacking.

4.11 References

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APPENDIX 1

Design and progress of BVDV control- and eradication schemes in Austria, Denmark, Finland, the Netherlands, Norway and Sweden

1. Aim of surveillance

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Aim of the surveillance:						
Control/eradication	Eradication	Eradication	Initially control, followed by eradication	Eradication	To get BVDV-free regions and finally Austria free of BVDV.	Eradication
Geographical extension (national/regional (name of region))	National	National	National	National	Lower Austria (LA), but programs are performed in all regions of Austria; data are available of LA only.	National
Disease level before the scheme started	10% with active infection	Seroprevalence of dairy herds around 1 % and of beef suckler herds 3,2 % in 1994.	herdprevalence between 80 to 90%	appr. 50% of herds with PI animals; appr. 100% with antibody carriers	60% Antibody positive herds	52% of herds had high antibody levels, 77% were antibody positive in bulk milk.
When was the scheme launched (year/month)?	December 1992	In 1994	April 1998	Volunteerly from early 1994. Officially from 1996 April	Lower Austria: January 1997	1 September 1993

2. Target population

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Target population:						
All/Beef/Dairy	All	All dairy herds and a sample of beef suckler herds are included in the surveillance	All	All	Organised breeders mainly dairy herds since 1997; since 2002 also not organised breeder take part in this voluntary program .	All herds with breeding animals. Specialised rearing units are not a primary target.
Size of target population at the start of the scheme	29 000 herds, 1 mill cattle	~ 34 200 dairy herds and ~ 3000 beef suckler herds in 1994	2.2 m. dairy cattle ==>28.000 herds, 1 m beef (mainly cow/calf operations) ==> 32.500 herds	Approximately 2.1 million cattle (16.000 dairy, 15.000 beef)	21,242 herds (522,118 heads of cattle) in LA.	18,500 dairy herds (518,000 cows), and 17,800 beef herds (cow/calf) (107,000 dams).
Size of target population 2003	23 000 herds, 940 000 cattle	20 577 dairy herds (including herds with 1-2 cows in 1.5.2002) and 1 274 beef suckler herds	1.6 m dairy cattle ==> 24.500 herds, 1m. beef ==> 30.000 herds	Approximately 1.7 million cattle (7.000 dairy, 18.500 beef)	16,619 herds (475,532 heads of cattle) in LA.	10,000 dairy herds (420,000 cows) and 13,000 beef herds (160,000 cows)

3. Organisation

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Organisation:						
Is there any legislation in support of the scheme?	Yes	Not at the moment, but in the future if BVD suspected /diagnosed. The control scheme will be voluntary also in the future	No	Yes	In preparation, will be put in force in March 2004.	Yes
If yes, given name and number of directives	1. Forskrift om bekjempelse av dyresjukdommer av 06.03.1995 nr 237. 2. Rundskriv M 31/94. BVD/MD-prosjektet, dekning av kostnader, grunnlag for oppheving av restriksjoner, informasjon. 3. Forskrift om soner for å hindre spredning av bovin virusdiaré virus (BVDV) hos storfe. Fastsatt av Landbruksdepartementet 03.04.2001 med hjemmel i lov 8.juni 1962 nr. 4 om dyrehelse § 3.	n.a	n.a	Government order, In Danish: "Bekendtgørelse 2002-09-05 nr 746 om BVD hos kvæg" issued September 5 2002.	"Entwurf einer Verordnung über ein Untersuchungsprogramm zur Bekämpfung der Bovinen Virusdiarrhoe und der Mucosal Disease bei Rindern (BVD-Verordnung)."	1. SJVFS 1993:42 Organiserad hälsokontroll av husdjur, kap 12. 2. SJVFS 2002:31 Obligatorisk hälsoövervakning avseende sjukdomen bovin virus diarré [BVD) i nötkreatursbesättningar
URL(s) to legislation	http://odin.dep.no/ld/norsk/index-b-n-a.html	n.a	n.a	?	?	**1.** http://www.sjv.se/download/SJV/forfattningar/1993/SJVFS1993-42/1993-042.pdf. **2.** http://www.sjv.se/download/SJV/Forfattningar/2002/2002-077.PDF
Administrative body(ies)	National Veterinary Institute	Ministry of Agriculture and Forestry, Food and Health Department	Animal Health Service	Danish cattle	Official veterinarians at the district offices, at the offices at the local governments, and at the office of the federal government.	Swedish Dairy Association (central) and the Regional Livestock Cooperatives (regional)

3. Organisation

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Organisation:						
Who takes samples?	National Animal Health Authority and private practitioners	Veterinarians	The practitioner does	Practising veterinarians. For bulk milk, the tank milk driver.	Milk recording assistants(milk), practical and official veterinarians (blood).	Bulk milk: Milk quality labs. Pooled milk and individual samples: AI technicians, large animal practitioners (and veterinarians at regional livestock cooperatives)
No. of laboratories involved in analyses	From the beginning: 6. Gradually reduced to 2.	One	AHS lab., results of other labs allowed.	Practically one (Danish Cattle Laboratory in Ladelund)	One in Lower Austria.	One. National Veterinary Institute
Who decides upon measures to be taken in infected herds?	The farmer.	Measures voluntary, but highly recommended by National Veterinary and Food Research Institute	In the end the farmer himself does decide. If he wants to continue to participate in the control programme he will have to stick to the rules and regulations laid out by the AHS.	A plan is made that must be approved by Danish Cattle. A BVD administration group under Danish Cattle approve the plans	Official and practical vets.	The scheme's rules dictates that affiliated herds **should** be cleared from the infection. **How** this is done is decided upon by the responsible vet, in dicussion with the farmer.
Who performs investigations in infected herds?	District vet. officer or private practitioner.	Municipal veterinarians	The AHS will coordinate, the practitioner does the sampling.	Practising veterinarians	Official and practicing vets.	Veterinarians at the Regional Livestock Cooperatives and large animal practitioners. Sampling may be delegated to AI technicians.

3. Organisation

Question	Norway	Finland	The Netherlands			Sweden
Organisation:						
How is the scheme financed? Describe who (e.g. farmer, industry, government) pays for what (e.g. administration, labour and analyses)!	By the government, the industry and the farmer in cooperation.	Administration payed by government, free herds farmer pays sampling and testing, in infected herds industry pays sampling and testing (via The Association for Animal Disease Prevention in Finland, ETT). (Voluntary scheme sampling and testing are payed by the farmer, but they can also use screening samples as a scheme sample and then farmer gets the result freely without costs.)	The farmer pays for everything: € 90 p.a. for administrative support and warning system (e.g. animal movement registration). Lab investication of pooled samples € 5.65 per head, sample collection costs € 4. 40 per sample, The farmer is not compensated for the costs of culling	Danish Cattle pay for bulk milk tests and administration. Blood samples ordered by the farmer, are paid by the farmer. If the herd is suspected of infection, the follow up samples are paid by Danish Cattle (both labour and analyses). If the herd is considered infected, Danish cattle will pay for analyses (testing of all calves), but not for labour. At the final testing 9 or 12 month after removal of the last PI animal, Danish cattle pays both labour and analyses. PI animals are compensated for but no other losses are covered.	Costs for sampling are paid from the farmers, administration and analyses are paid from the local government	All costs for monitoring are paid for by the farmers (labour, adm.,analyses). Annual affiliation fees are subsidised for beef herds. Labour costs for clearing herds are paid for by the farmers but analyses are subsidised by the Board of Agriculture. The BoA also pays for an annual bulk milk screening and administration (since 2004). Culling of PI animals is not covered, but there are some insurance companies that cover this.

3. Organisation

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Organisation:						
Describe the administrative system. For example, how do people who take out samples know when it is time to do so? How do farmers/field staff/staff at the central level get access to test results? How do farmers/field staff/staff at the central level get access to information on herd status?	A full time project manager runs the program. All test results are sent to the farmer and to the district veterinary officer.	Farmer himself is responsible for keeping his herd in the scheme. From yearly screenings information is passed to the municipal veterinarian, if BVD is suspected, the farmer and the municipal veterinarian concerned are informed immediately and measures strongly recommended. The information on the farms in the scheme is collected and passed on by municipal veterinarians to district veterinarians, who basicly keep records on the herd status. This is not working in practice. Our Ministry of Agriculture and Forestry is working in order to establish a large data management system, which should serve municipal, district and government veterinarians.	There is a centrally managed supportive certification system (COS). This system is connected to: the central Identification and Registration system I&R (animal movement, mortality and birth registration), AHS lab (pathology and lab test results are sent to COS), rules and regulations of the BVDV control programme are translated to functionalities in COS. Based on the information recieved from the sources mentioned, COS will generate the appropriate message. Farmers will receive lab results. With any change in status, based on lab results or violation of the animal movement rules, he will receive a new certificate indicating the present status of the herd. field staff/practitioners will receive lab results via email and sampling instructions by mail. Staff has access to overall results via computer. Farmers can log-in at www.ziezo.biz to see there status, and the status of other farms (if they approve).	Concerning necessary blood samples, the farmer gets a reminder 4-5 weeks before deadline for confirmation of status. It is the farmers own responsibility to call the veterinarian to take samples. The veterinarian gets status lists for the herds in the practice approximately every second week. The veterinarian can also get a list of recorded status for individual animals by contacting the BVDV administration group in Danish Cattle.	Reports from laboratory are sent to the farmers, to the veterinary practitioners and to the official vets of the district office. All results are in a data base and the official vets have access to this data base in their office. It is planned that also farmers can access their results in the data base. At this time farmers have only hard copies of their status in form of reports. With this help they can decide with vet practitioners and the milk recording assistants how to continue in the program. The official vets have the responsibility to decide if farms can be declared as BVDV-free (certified) and if animals are permitted for animal trade.	All information on BVD-status and test results, dates etc are in a central database. Based on this info the system generates sampling orders. Bulk milk sampling is ordered from the milk quality lab every third month. Sampling of herds on other test methods is ordered from the RLCs the month (?) before it is time to take the sample. If the sample is to be taken by a large animal practitioner, the order is forwarded to him/her by the RLC. The central database is on a UNIX platform and is accessible by staff in the central administration. A PC application with all info on herds within a RLC or a certain veterinary practice is available for everyone who works with BVD. It is updated twice weekly. Paper reports/work lists/alarm lists are also produced by the system and distributed to the responsible vet via the RLC. The farmer gets info on test results on paper, together with an interpretation.

4. Affiliation

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Affiliation – what applies to your country's scheme?						
Type of affiliation	Compulsory by law	Voluntary (i.e. the farmer decides himself if he wants to become affiliated to the scheme).	Voluntary (i.e. the farmer decides himself if he wants to become affiliated to the scheme).	The scheme is compulsory by law	Compulsory for participation on animal markets and common grassland. Voluntary or farmers not using common grassland and markets.	Primarily voluntary, but industry requirement since late 90's (dairy 1997, beef 1999). Compulsory by law since 1 July 2002 for those not yet in the voluntary scheme.
Does the affiliation procedure involve a written consent by the farmer (like a contract)?	No	Yes	Yes	No	Yes	Yes

5. Rules and regulations

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Rules and regulations applying to herds in the scheme – Biosecurity						
Purchase of animals	Herds with restrictions are allowed to buy animals	Without testing from other herds in the scheme, from outside the scheme only animals which have been tested both for ab's and virus with negative test results (compulsory in the scheme), not allowed to buy any pregnant animals from herds not in the scheme	Rules and regulations are laid down in: Reglement Certificering BVD bij Runderen 2002. Those herds in the scheme are advised to follow the "closed farmíng' concept. The status of the herd of origin is decisive. Outside the scheme only animals which have been tested both for ab's and virus with negative test , pregnant animals allowed, calf tested later > 4m.	BVD certificate (compulsory)	Animals are only allowed to be purchased from BVDV-free herds or they should be tested for antigen and antibodies with an negative result.	Farmers in the scheme can only buy animals from BVDV free herds (compulsory). Farmers of infected herds should avoid to purchase animals (recommendation).
Selling animals	Herds with restrictions are not allowed to sell animals	Not allowed to sell PI's (except for slaughter) (compulsory in the scheme)	Not allowed to sell PI's (except for slaughter) (compulsory in the scheme)	BVD certificate unless direct to slaughter or specialised slaughter calf producer (compulsory)	Farmers in the program are only allowed to sell BVDV-free animals. Pregnant animals can be traded only from BVDV-free herds, or they have to be tested with an antibody negative and antigen negative result. Calves under an age of 5 month have to be tested compulsory also from BVDV-free herds.	To sell animals as being BVDV free, the latest approved scheme test must not be older than 3 months (4 months for herds employing bulk milk as test method). Infected herds or herds under suspicion must not sell animals other than to slaughter or to rearing units where all animals are predestined to slaughter. Animals from inf. herds that are sold to rearing units have to be tested free from BVDV at an age of +12 weeks before they leave the farm. (all compulsory)

5. Rules and regulations

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Rules and regulations applying to herds in the scheme – Biosecurity						
Planned contacts with other herds	Herds with restrictions are not allowed to have planned contacts with animals from other herds	Only controlled contacts allowed	Manifistations are categorised: BVD free, BVD save (BVD vaccinated from non scheme farms are allowed) and other. Only animals from free herds or tested animals are allowed to have contacts.	BVD certificate (compulsory)	Only animals from free herds or tested animals are allowed to have contacts on exhibitions etc. On communal grassland only animals tested with BVDV-antigen negative result are allowed, or they come from a BVDV free herd.	In order to have planned contacts with other herds, the latest approved scheme test must not be older than 3 months (4 months for herds employing bulk milk as test method). Infected herds must not have any planned contacts. (alla compulsory) Animals returning from exhibitions should be put in quaranteen and tested 4 weeks after the return (recommended).
Unintentional contacts with other herds	Herds with restrictions should not have contacts with animals from other herds. If this happens unintentionally, it is up to the local vet to decide upon measures (if he/she is informed). Farmers and vets have recommendations on how to act in situations like this.	Contacts on pasture must be prevented	Farmers and vets have recommendations on how to act in situations like this.Testing is recommended	Testing recommended	Animals have to be tested for antibodies with an negative result after an unintentional contact.	A follow-up should be made (compulsory), either by checking that the contact herd has got a current scheme test, or by testing animals in contact (either on own animals: quaranteen and test 4 weeks after contact, or on contact herd's animal(s)).
Contacts with animals of other species	Herds with restrictions should avoid having contact with other ruminants and pigs.	No regulations	No rules	Recommended (sometimes) to test sheep and goats	Not regulated	Contacts with sheep of unknown status should be treated as contacts with cattle of unknown status, unless they belong to a farmer with a BVDV free herd and a current scheme test.
Visitors	In a coming (?) directive (Forskrift om hold av storfe), there is a demand that farmers should provide visitors with clothes to borrow.	No regulations for visitors on affiliation agreement at the moment, but in the future normal biosecurity rules probably included.	herds in the scheme ==> 'closed farming' concept	General hygienic procedures: don’t reuse utensils etc.	Not regulated	Provide visitors with boots and overalls to borrow (recommended)

5. Rules and regulations

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Rules and regulations applying to herds in the scheme – Biosecurity						
AI / embryo transfer	**Semen:** Bulls at AI stations are tested free from BVDV before entry and once per year during the stay. Imported semen is tested (one straw per batch) according to a special routine. **Embryos:** Recipients of imported embryos are tested for antibodies prior to ET and approx. 3 weeks after transfer to check for seroconversion.	No regulations in the old scheme, in the future testing of recipients if imported or in vitro embryos transfered, allowed to use semen only from approved AI-centres or after semen has been tested for BVDV.	No rules. The use of semen over 5 years of age is considered to be a riscfactor. Import semen and AI station should comply to 88/407/EU and recent changes (2002/0229). ET considered to be a riscfactor			**Semen:** Bulls at AI stations should be tested free from BVDV before and during the stay. Imported semen from outside Scandinavia semen is tested with PCR (one straw per batch) unless the bull is tested negative for antibodies after collection and where the semen has been tested once before. (compulsory) **Embryos:** Recipients of imported embryos and embryos collected in infected herds should be tested for antibodies 4-12 weeks after transfer to check for seroconversion. (compulsory)
Other regulations/comments			There are qualifications on animal and herd level: antigen, antibody positive, suspect. There is a description of the type of test to be used for different animal or herd status. There are rules for the introduction of new animals. There is a set of additional rules dealing with unintentional contacts Underlying all AHS programs is the regulation describing the general rules for participation in cattle health programmes. Some of the above aspects are taking care of by this regulation.			**Obligation to inform**: Farmers of infected herds must inform peers and other professionals about his herd's BVDV status. (compulsory) **Transports:** Animals from infected herds must not be transported together with animals from other herds to slaughter unless they are picked up last on the route. Otherwise they should have been tested free from BVDV or be born before the herd became infected. (compulsory). Animals should be delivered to the transporter outside of the barn (recommended).

5. Rules and regulations

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Rules and regulations applying to herds in the scheme – Biosecurity						
How are non-compliant farmers dealt with?			Farmers are simply k.... out. There can be several reasons however. If he is not sending in the right samples at the right time eg after introducing an animal from outside the scheme the herd will be placed underobservation from the moment our Identification & Registration system has detected this action (automatically his status changes in the COS and he will recieve a letter asking to sample. This will be repeated one more time after that he is evicted. In case he is not in compliance with the monitoring scheme (2x/yr 5 animalsfrom 8-12m.) the herd will be placed in observation. This is also an automated procedure. Another, obvious, cause can be lack of payment.	In the legislation non-compliance can be followed by a fine.Not known to what extend that has been re-inforced. However, it is perceived as being important that the possibility is there as veterinarians can put pressure on farmers having samples taken.		Farmers in the (original) voluntary scheme can be excluded. They will then automatically be included in the compulsory scheme. In the compulsory schemes there are no subsidies. Also, the dairy and beef industry has promised not to handle milk/animals from herds that are thrown out of the scheme. Extreme measures, such as forced testing (with police assistance etc) can only be taken on herds in the compulsory scheme.

6. Surveillance of free herds

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Test procedures used for surveillance of free herds (and herds on their way to being declared free)						
Frequency of testing	Once per year	All dairy herds and a sample of beef suckler herds yearly	**Intake procedure:** PCR on BTM, antigen ELISA on dry and young stock ≥4 m, all calves born within a 9 months period at the age of 4 months. **Monitoring**: two times per year, five animal between 8 to 12 months, antibody ELISA	Bulk milk 4 times a year. Free status must be confirmed within 12 months.	Every 5-7 month.	**Before certification:** Two tests with a 7 month interval. Three tests with a 7 month interval if it can not be excluded that the herd had unsafe contacts during the year preceding affiliation. **After certification:** once per year unless animals are to be traded as BVDV free or if there are planned contacts with other herds - the the latest test must not be older than 3 months (4 months for herds employing bulk milk).
Type of test	Indirect AB ELISA (SVANOVA)	Indirect AB ELISA (SVANOVA)	**Intake procedure**: PCR (in-house, modified Weybridge), antigen ELISA (IDEXX). **Monitoring:** antibody ELISA (CEDI diagnostics)	Blocking ELISA for antibodies in bulk milk and on individual samples. A blocking ELISA for virus detection is used in herds with infection.	Indirect AB ELISA (SVANOVA)	Indirect AB ELISA (SVANOVA)
Sensitivity and specificity of the test(s) at the individual level	Not investigated	Not assessed with Finnish samples	**Antigen ELISA:** relative Se = 100% (compared to other antigen ELISA), relative Sp 99.5 (compared to PCR). **Antibody ELISA:** Se: 98%, Sp: 99.2 (gold standard=neutralisation test)	The BVDV antibody ELISA has shown a sensitivity of 96.5 and specificity of 97.5 when compared with the virus neuralisation test (Rønsholt et al., 1996).	Not investigated.	Serum - comparison with SNT: convenience sample with known SNT titres (not field sample); Se 100%, Sp 96% (Juntti et al., 1987). Milk - representative field sample: 100% accordance with 84 serum positive samples, 91% accordance with 55 serum negative samples (Niskanen et al., 1989).

6. Surveillance of free herds

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Test procedures used for surveillance of free herds (and herds on their way to being declared free)						
Usage of tests (bulk milk, spot tests (what category of animals) etc.	Bulk milk, pooled milk from primiparous cows and pooled blood from 3-5 young animals (7-12 months)	Bulk milk samples of dairy herds taken by dairy industry, individual blood samples of beef herds taken at slaughter	Bulk milk, max 120 animals (practitioner) for PCR. Pooled PCR heparinized blood (max 36 animals) confirmation ag ELISA.	Bulk milk and blood samples from young stock older than 8 months. Pooling of blood samples is not used.	Bulk tank milk or individual milk samples from young cows(5) or animals in an age from 6-24 month(5) with an antibody negative result.	Bulk milk, pooled milk from primiparous cows and individual blood from 5-10 young animals (+12 months).
Interpretation of tests (what is regarded as an approved result, what is non-approved for each of the tests that are used for surveillance of free herds)	Approved results: Bulk milk: AB S/Pratio <0,250 (from 1998 <0,150), pooled milk from pp-cows: AB<0,100, pooled blood from young animals: AB<0,250	Samples tested using screening ELISA (without control wells) with cut-off-point given by manufacturer (0,1 for milk and 0,25 for serum samples). All samples positive in screening test re-tested with confirmation ELISA (with control wells). If OD over cut-off-point => suspicion on BVD	Detection of viral RNA/antigen during intake is non-approved. Detection of >= 2 antibody positive in a group of 5, non approved at AB >0.250. calves within the age group 8 to 12.	A herd is declared free if: Bulk milk less than 50% in blocking ELISA. Young stock antibody negative (at least 3 animals). At routine confirmation of status usually only 3 samples are taken, but at follow up usually more samples are taken.	Approved result of a bulk tank milk test: OD450 <0,24; or all individual milk samples of young cows(5) or all cows: OD450 <0,1; or all individual blood samples(5) of animals in an age from 6-24 month are under OD450 <025.	Approved result of a bulk tank milk test: OD450 <0.250 (BVD class 0 or 1); pooled milk OD450 <= 0.10; or all individual blood samples (5-10) of young stock+12 months old have OD450 <=0.20.

6. Surveillance of free herds

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Test procedures used for surveillance of free herds (and herds on their way to being declared free)						
Sensitivity and specificity of the test(s) at the herd level	Not investigated		PCR (compared to individual antigen ELISA results): Se = 95.2% , Sp = 100%	As indicator for presence/absence of PI animals: Bulk milk: HSE= 1 and HSP=0.62; Young stock test: HSE=0.93 and HSP=1. **Note:** determined on a limited number of herds meaning quite some uncertainty in the figures.		As indicator for presence/absence of PI animals: **Bulk milk:** HSP= 98% when used as a tool to monitor herds where bulk milk can be employed, i.e. not herds that have recently had the infection!!; HSE=98% - at a single occasion – this is because some of the new infections are introduced in non-lactating pregnant animals. However, as soon as these calve (and the test is repeated) the Se will be essentially 100%. Not so much because the test is applied repeatedly as because the test is applied to different strata with respect to stage of infection! (Lindberg, 2000); **Pooled milk:** No estimate available. **Young stock test**: HSP=1 (when used as a herd test by testing 5 young stock (sampling without replacement, target group in herd = 12 animals, prev. of seropositive 0.01-0.02). HSE=1 (when used as a herd test by testing 5 young stock (sampling without replacement, target group in herd = 12 animals, prev. 20-80%)

7. Measures in infected herds

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Measures taken in infected herds/herds under suspicion of having BVDV infection						
What evidence is required for a herd to become a BVD-suspect herd?	AB>0,250 in pooled blood from young animals	Antibodies found in any sample	If within the age group 8 to 12 month >=2 out of five test antibody positive	A rise in blocking Elisa of more than 20-30, presence of any antibody positive animals, that were anticipated to be antibody negative at the time of sampling.	1) Previously strictly seronegative herds get a positive bulk tank milk (OD450>0,1); 2) herds with former bulk tank milk results between OD450 0,1-0.24 the OD450 is now >0,24;3) any seroconversions in former negative animals; 4) contacts with animals from herds with unknown status or contacts with PI-animals.	1) Scheme test on bulk milk in BVD-class 2 or 3 (OD450 >=0.250) or 2) Scheme test on pooled milk from primiparous cows has OD450 >0.10 or 3) Scheme test on young stock: 1 or more animals with OD450 >0.20 in serum or 4) the herd has had contacts with animals from herds with unknown status/infected herds.
What evidence is required before a herd is confirmed as being BVDV-infected?	Detection of a PI-animal.	BVDV virus isolated or antibody profile of the herd indicates on-going BVDV infection or pregnant seropositive animals in the herd	If within the cohort age group from 4 to 16 month a PI is found.	Presence of virus positive animals or occurrence of antibody carriers in a pattern indicating presence of a PI animal.	Seroconversions of pregnant animals occurred or cannot be excluded in the time of pregnancy when a PI animal can be developed; birth or introduction of a PI animal.	Seroconversions in expectedly seronegative (young) age groups, detection of PI animals
Are infected herds put under restrictions?	Yes	Not yet, but in the future they will be	No	Yes	Yes	Yes

7. Measures in infected herds

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Measures taken in infected herds/herds under suspicion of having BVDV infection						
If yes, what type of restrictions?	Not allowed to sell animals, no access to common pastures, no exhibitions or gatherings or transport together with other herds.	Movement of animals into and from the herd prohibited (except for slaughter)	n.a.	Further testing must be done according to an approved plan. Isolation of PI animals. Movement restrictions (detailed rules about the necessary testing). Must inform all people coming into contact with the herd and also neighbours.	The farmer is not allowed to sell pregnant animals, non-pregnant animals have to be tested for BVDV-antigen with a negative result. All animals for communal pastures have to be tested for BVDV-antigen. In future when the legislative will be put in force it will be forbidden to bring PI-animals out of the stable; the PI animals have to be slaughtered within two weeks after the result of the lab.	The farmer is not allowed to sell animals other than to slaughter or to specialised rearing units where animals are predestined for slaughter. He should not have contact with any other herds with cattle, sheep or goats. Coming restrictions are 1) duty to inform, 2) demand to transport animals directly to slaughter (or picked up last) unless tested free from BVDV or born before the herd was infected. 3) only allowed to sell calves for rearing if they are tested free from BVDV at +12 weeks.
What other measures can be/are taken in infected herds?	Qualified information on risk for reinfection and of risk for infecting other herds	Farm has to offer protective clothing for all the herd visitors, has to inform AI technicians, veterinarians etc. of the infection, has to prevent unnecessary visits and contacts with other herds			n.a.	In problem herds a special action plan can be set, including test strategies, strategies for separating animals and immunisation strategies. The farmer has to adhere to this plan, otherwise he can be excluded from the voluntary programme (with subsidies) and included in the compulsory programme (without subsidies). The industry will not accept deliveries from farmer who refuses to adhere to the regulations. The exclusion rules applies to any farmer in the scheme who does not comply and still refuses to do so after reprimands.

7. Measures in infected herds

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Measures taken in infected herds/herds under suspicion of having BVDV infection						
Is it compulsory to take measures to get rid of the infection?	Not in the beginning, from 1999 it is compulsory.	Farmer decides on if and when to slaughter PI's, but the restrictive measures will not be lifted until the herd has been sufficiently tested to be sure that all the PI's are found and slaughtered	Only if the farmer decides to stay in the programme	Yes	The coming legislation will force the farmers to perform an eradication scheme in infected herds.	Yes, if you are in the scheme you have to clear your herd from the infection, and you have to slaughter PI animals within 2 months.
Is there any compensation scheme?	No	Association for Prevention of Animal Diseases (ETT) subsidises sampling and testing of BVD suspected herds, in the future government will finance sampling and testing and partly the value of the slaughtered PI's (this comes from the animal disease legislation)	There is no compensation scheme; the farmer can decide to have calamity insurance, however.			No.

8. Insurance

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Insurance						
Is insurance against BVDV infection available?	Yes (may be not only for BVD)	No	Yes	No	No	Yes
Private or public insurance?	Private	n.a.	Private	n.a.	n.a.	Private
What does the insurance cover?	I am not sure, but my impression is that the farmers are reasonably happy with the compensation.	n.a.	Usually the insurance is a general one (for all types of diseases or mishaps).	n.a.	n.a.	Partial compensation for PI animals if the herd is affiliated to the BVD scheme and the PI animal is slaughtered within 2 weeks (2000 SEK for animals older than 1 yr, 1000 SEK for animals <1 year.
What are the criteria for having access to such insurance?	No special criteria	n.a.	The total damage should reach a certain level and should be connect to a single proven cause.	n.a.	n.a.	Affiliation to the BVD scheme

9. Newly infected herds

Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Herds with new infections						
What is required for a herd to be classified as a new case of BVDV infection in the scheme?	AB positive pooled blood sample from young animals	Ab's found from a previously seronegative herd or from herd without known history of BVD	If the herd is in the scheme a positive cohort test (one or more PI´s detected) suffice. Occasionally a virus positive foetus is diagnosed	Previous free herd that get rise in bulk milk, or antibody positive young stock or virus positive - but note Denmark use the term getting "not free status" and not "case".This means that a harmless antibody positive animal can mean a herd get from free to not free.	Seroconversions of pregnant animals have occurred or cannot be excluded during the time of pregnancy when a PI animal can be developed; birth or introduction of a PI animal.	Positive virus isolation in the herd after it has been certified free from BVDV.
How are new cases of infection investigated?	Blood samples of all animals	Epidemiological investigation to find out the possible sources of infection and support for the suspicion and individual blood samples of all the animals > 3 months	By pooled serum testing,	A group in the dairy board makes individual plans for infected herds. So the intensity of follow up depend on an evaluation of the possible transmission dynamics in the herd. Unfortunately I don't have further details. But for example non-PI youg stock	The offspring born after the time of infection is tested. If the time of infection is not exactly known all animals of the herd are tested.	A positive scheme test is followed up to look for seroconversions among young stock/presence of PI animals. If findings are indicative of aactive infection all animals +12 weeks are sampled. The lab first runs ab analyses, and then virus isolation on those that are ab negative. After the inital herd screening, all calves born are tested as they reach an age of +12 weeks.
Is the source of the infection traced?			Occasionally farms are visited (farmers have to pay)	To some extent	Yes	Yes, if virus is isolated in a herd that has previously been certified free from BVDV, tracing has to be performed.
If yes, how?			We are in the process of putting together a questionnaire	Questionnaires have previously been send out - see Bitsch et al., 2000 - but it is not done systematically	The farmer is asked about his animal movement. If his animals can have nose to nose contact on a fence of a neighbouring farm etc. We have no check list to ask the farmers. Such a list could be helpful!!!!	The herd's veterinarian performs the investigation. First the time period during which it is likely that the herd became infected is established based on information on negative and positive scheme tests and on birth dates of identified PI animals. Then the farmer is asked about what contacts there have been during that period.

10. Certification

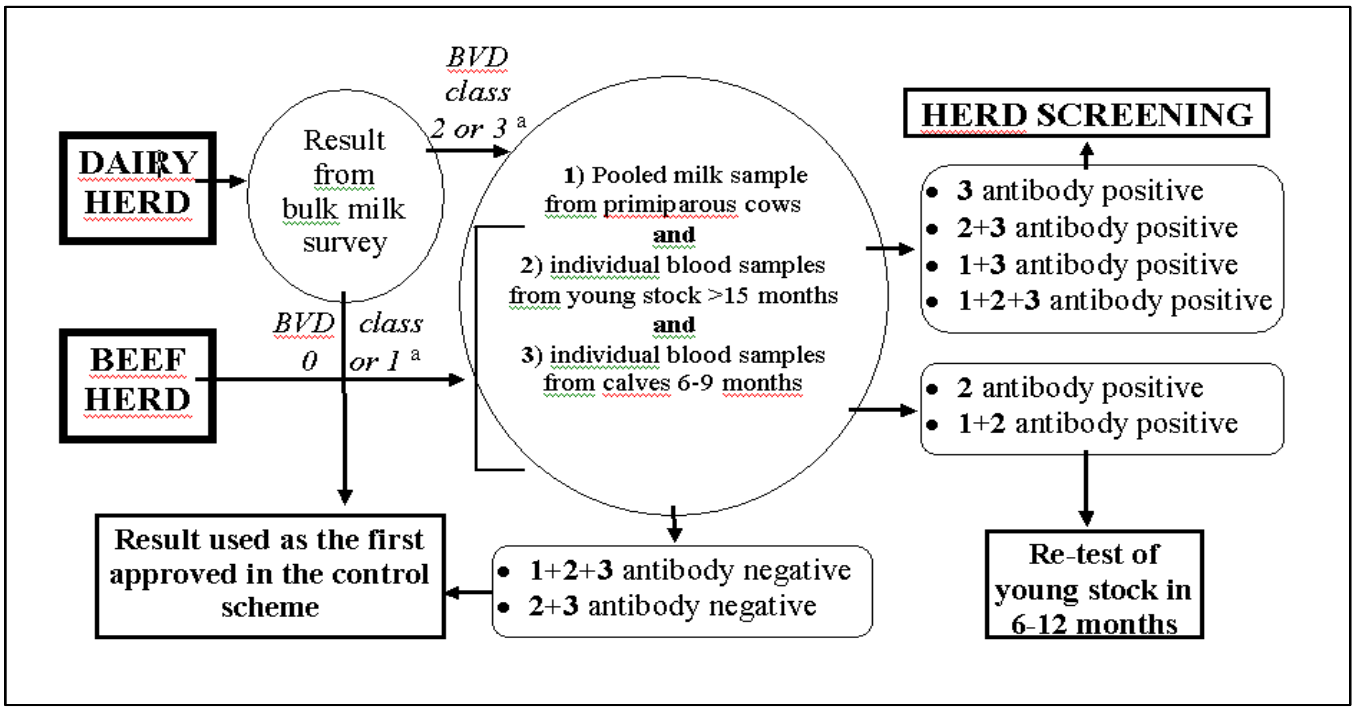
Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Certification/procedures for classifying herds as infected or non-infected						
Does there exist a formal procedure for certification of BVDV-free herds?	No	Yes	Yes	Yes	Yes	Yes
If yes; requirements to reach certification?	n.a.	Herd twice tested for ab's with 4-12 months interval and testing of purchased animals, test results negative for antibodies	The herd need to be free from PI animals	A herd is declared free if: Bulk milk less than 50% in blocking Elisa. Young stock antibody negative (at least 3 animals).	Approved herd level tests, Correct animal movement.	Two scheme tests with approved result with +7 months interval. If the herd has had unsafe contacts during the year before the first test, three scheme tests need to be taken.
*** Requirement to maintain certified status**	n.a.	Follow the rules of the scheme (especially trading and re-testing)	Spot testing of 2 x 5 animals p.a., testing newly introduced animals coming from a herd with a lower BVD status.	Confirmation within 12 months	Further herd level tests with approved results. Control of animal movement.	Retest within 18 months (the system issues orders for test every 11/12 months unless the farmer has asked for more frequent testing). In order to sell animals as BVDV free the latest approved test result must not be older than 3 months (4 for herds employing bulk milk as scheme test).
*** What rights and/or obligations does the status imply?**	n.a.	Animals of the herd have can enter animal exhibitions without testing, can sell animals as BVD-free	No specific rights, obligations are laid down in the regulation.	Movement of animals without individual testing is possible if the herd has been free for more than 24 months (superfree) and the last status examination is less than 4 months old.	To sell animals as BVDV-free, to bring animals on common grassland.	Right to sell animals as BVDV free, right to sell calves to rearing units without individual testing, right to have contact with animals from other herds, including trade, if the latest approved test is not older than 3(4) months.
*** What is required for certification to be suspended?**	n.a.	Neglecting the rules (formal certification is necessary, the farmer is the only one, who has on-line information of the events of the herd, he/she is the only one, who can effectively manage the risk of BVDV in association of trade/ET etc.	Non compliance with the regulation eg not testing newly introduced animals etc..	Previous free herd that get rise in bulk milk, or antibody positive young stock or virus positive. (non-compliance?)	Seroconversions, Contact with cattle of herds with unknown BVDV-status.	Positive scheme test or other suspicion on infection - temporary suspension of the certification until the situation has been investigated and resolved. If infection is confirmed the suspension will remain until the herd has been cleared from the infection. Certification can also be suspended if the farmer does not comply with the rules of the scheme.

10. Certification

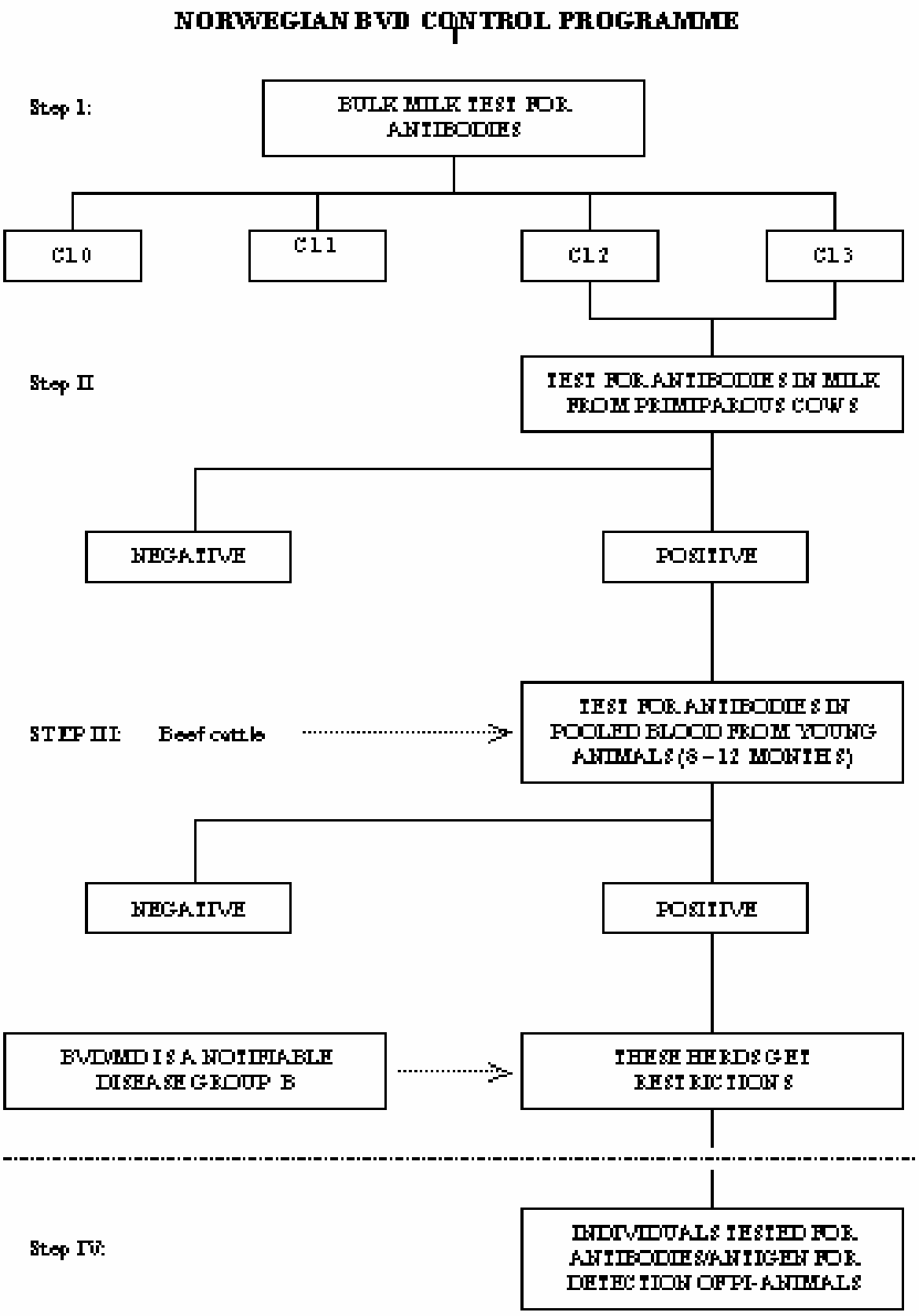
Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Certification/procedures for classifying herds as infected or non-infected						
If no; explain why a formal certification is not desirable/needed!	In Norway there is an opposite principle. A certification of freedom from disease is never given. All herds are free of diseases as long as they are not given restrictions.		n.a.	n.a.	n.a.	n.a.
Does there exist a non-formal systematic classification procedure of herds (e.g. as possibly infected or probably free, but without certification)?	No. (Work is being done to create a system with a classification of herds in a pyramid, with the herds with best status on the top and poorer status downwards. This will be a private system run by the organisations, but with some support from the authorities.)	Some veterinarians/farmers think that seronegative bulk milk is sufficient proof for the herd to be non-infected, in other words some people think herd is free without any involvement by the farmer	No	No	No	No.
If yes; how are herds classified?	n.a.	Just according the yearly screening test results	n.a.	n.a.	n.a.	n.a.
*** Requirements to reach a certain classification**	n.a.	OD values of the samples under cut-off-point of the ELISA	n.a.			n.a.
*** Requirement to maintain a certain classification**	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
*** Are the different statuses associated with different rights and/or obligations?**	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

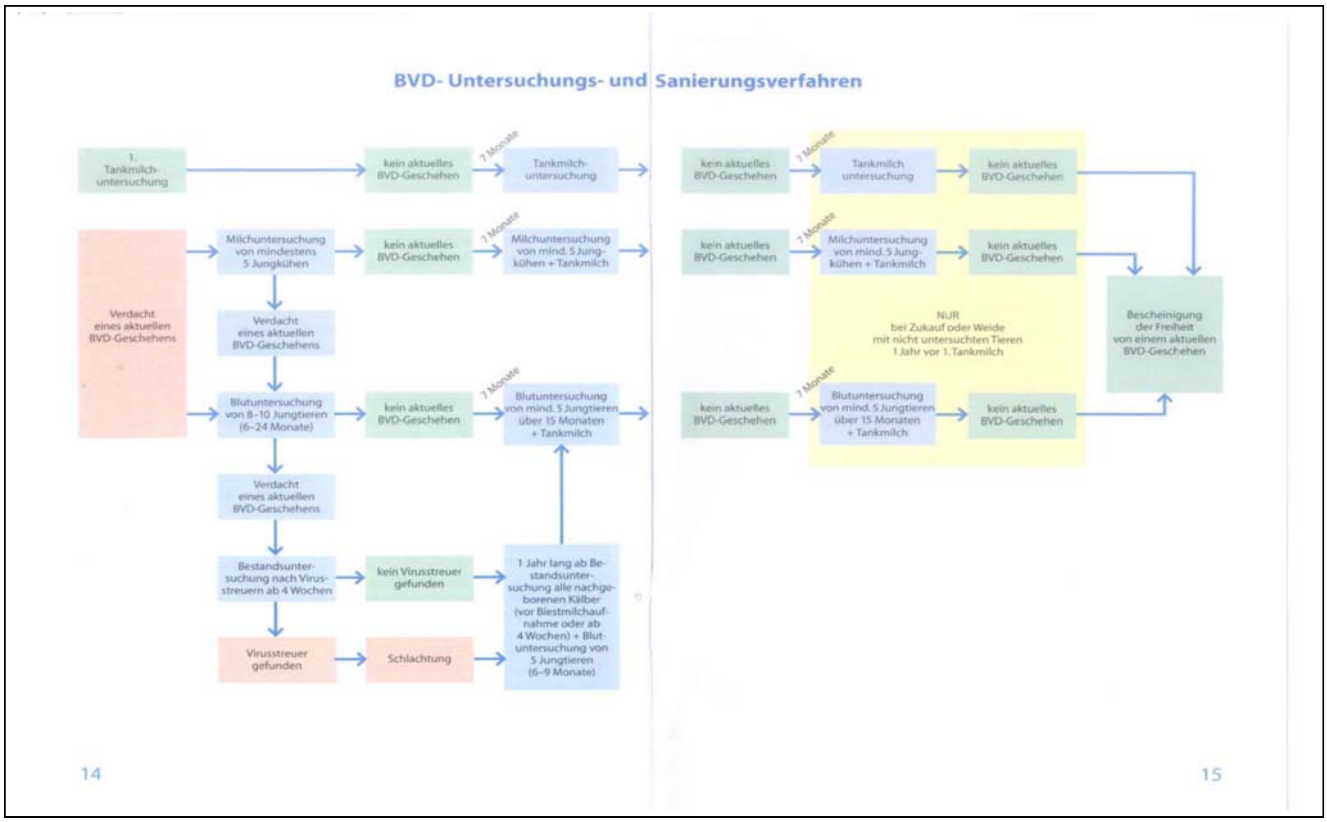
11. Scheme progress

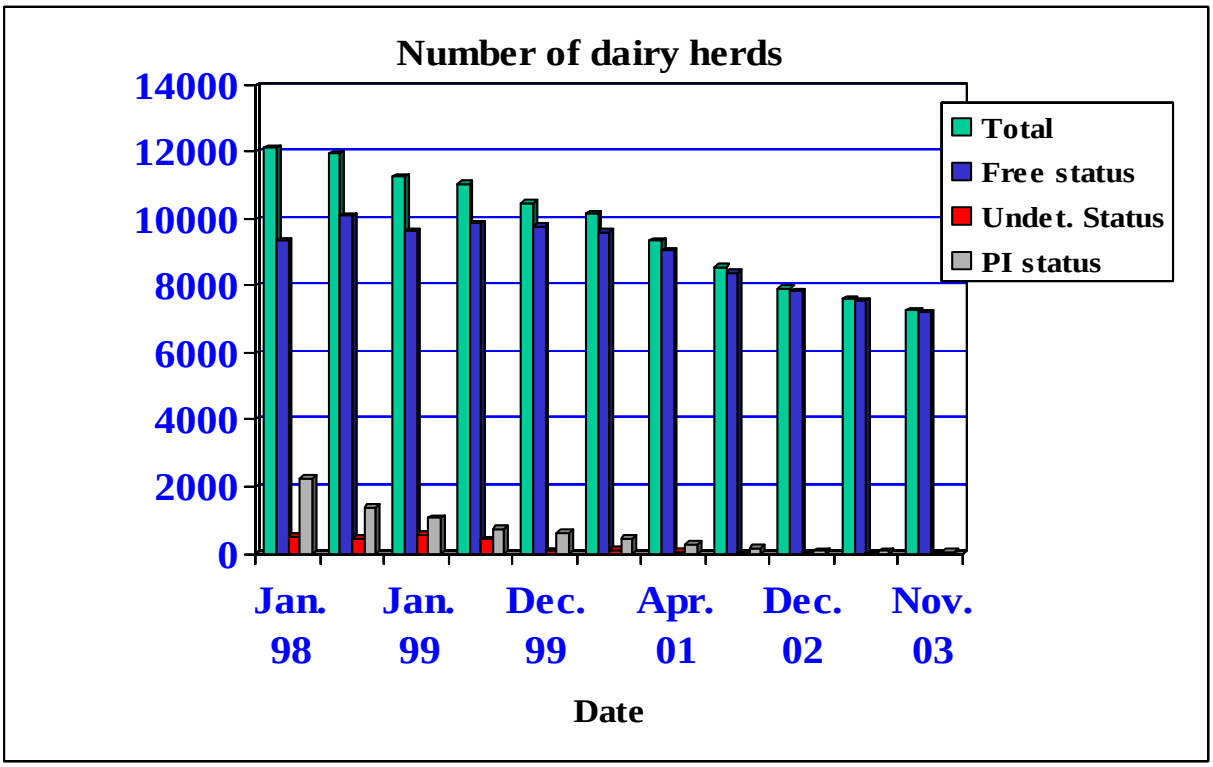
Question	Norway	Finland	The Netherlands	Denmark	Austria	Sweden
Scheme progress						
Use a graph to describe the development since the start of the scheme in terms of:						
*** % of herds in the scheme (if applicable)**	*All herds are in the scheme*		± 12%	n.a.	55% (roughly 80 % of the animals) (end 2003)	Graph
*** % certified free and in other statuses (if applicable)**	In graph		± 9%	Graph (only dairy)	22% (roughly 50 % of the animals)	Graph
*** Prevalence (describe prevalence measure used)**		According to dairy herd screening results only ~ 0,15% seropositive in bulk milk, beef suckler herds? (most accurate estimate from year 1994)	There was a BMT on antibodies in 1996 indicating ± 85% of the herds were positive for BVD.	Prevalence of infected herds (with PI animals) has bee reduced from appr. 50% to less than 1 %)		Graph. Prevalence of infection estimated as no. of herds under investigation in Dec. each year/total population in Dec that year.
*** Incidence (describe incidence measure used)**		No new cases found in 2003 among dairy herds that were bulk milk seronegative in 2002, beef suckler herds? (estimate of the seroprevalence, when the screening samples for year 2003 have been tested)	± 10% of our certified free herds have a positive spot test annually, in 50% of those herds a PI is discovered.			Graph. Incidence of new infections estimated as no. of herds with positive virus isolation after being certified free/no. herds at risk (=free herds)
If you have any other way of describing the development of the scheme, please describe how!					Since the beginning of BVDV eradication the number of certified herds rises continuously in cattle herds of organised cattle breeders . The number of PI animals decreases every year. First tests in herds of non organised cattle breeders started in December 2002. Out of 4822 herds 3589 herds were tested with an undetectable or low level of antibodies in bulk tank milk. 427 herds had a test negative milk sample from 5-10 young cows.	

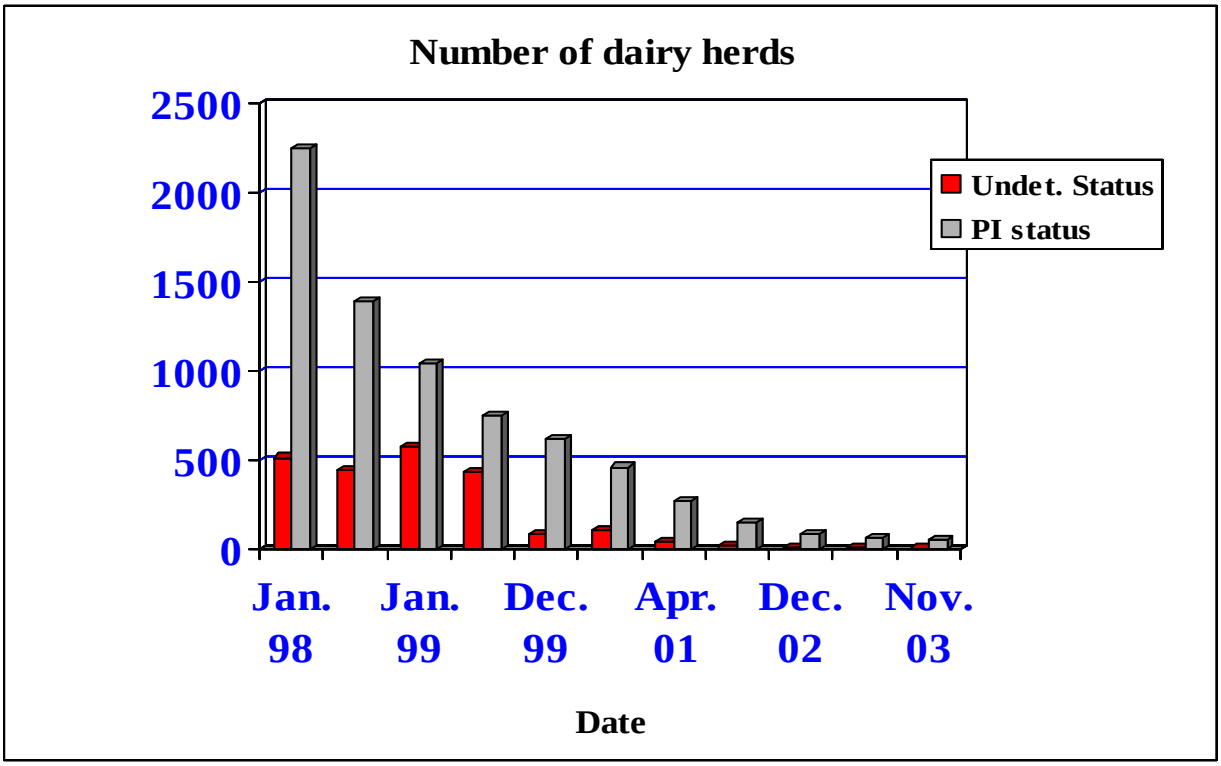


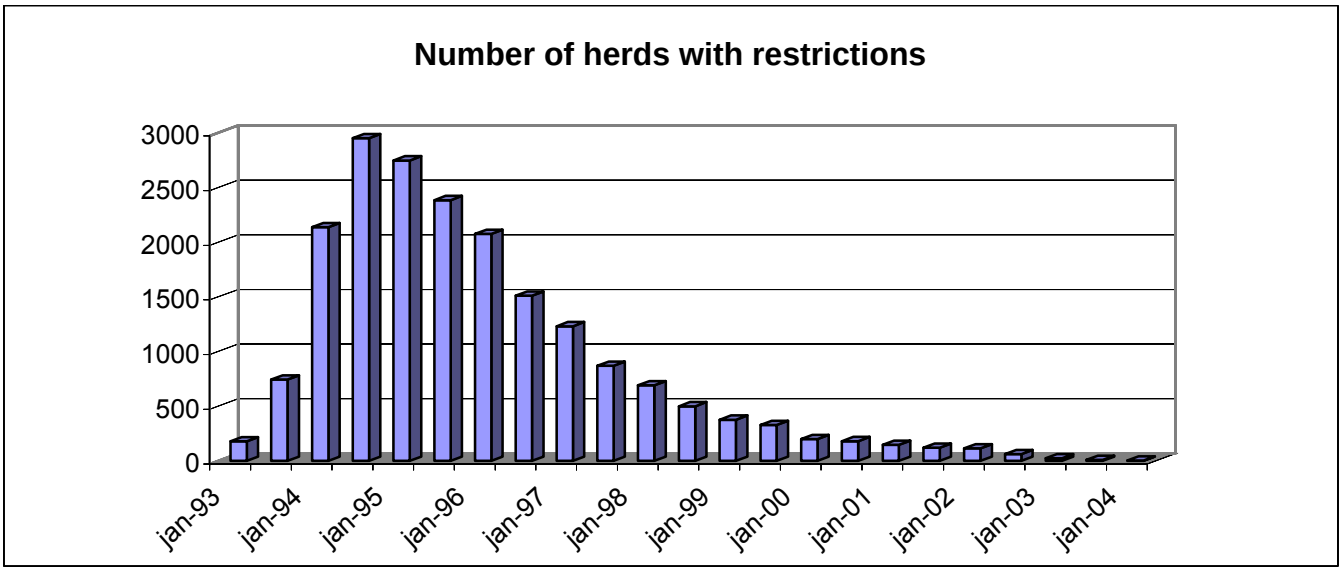
This was the routine used during so called regionalised eradication campaigns (more intense projects where all herds in an area are investigated during one housing season with the goal not to have any PIs on pasture the summer after. It was performed on the Isle of Gotland and in the Kalmar area (south-east Sweden). These were areas with an initial high prevalence of BVDV. Today (2004), they are among those with the best situation.

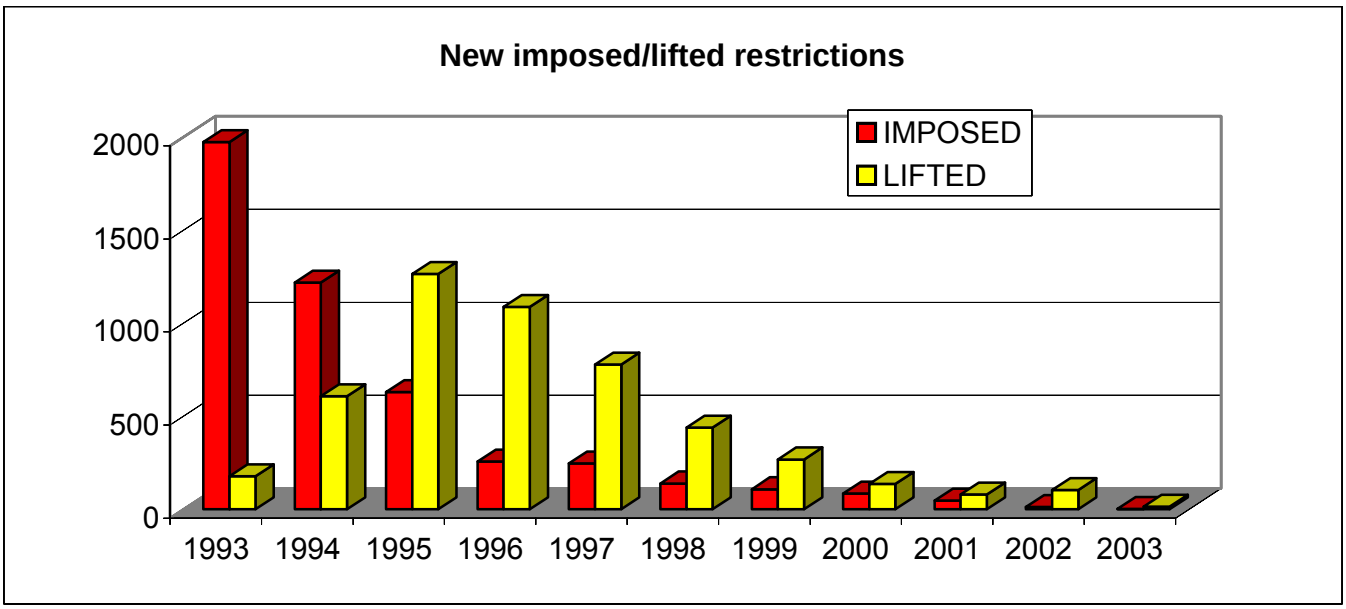

NORWEGIAN BVD CONTROL PROGRAMME
Step 1:
BULK MILK TEST FOR ANTIBODIES
C10
C11
C12
C13
Step II
TEST FOR ANTIBODIES IN MILK FROM PRIMIPAROUS COWS
NEGATIVE
POSITIVE
STEP III: Beef cattle
TEST FOR ANTIBODIES IN POOLED BLOOD FROM YOUNG ANIMALS (8 – 12 MONTHS)
NEGATIVE
POSITIVE
BVD/MD IS A NOTIFIABLE DISEASE GROUP B
THESE HERDS GET RESTRICTIONS
Step IV:
INDIVIDUALS TESTED FOR ANTIBODIES/ANTIGEN FOR DETECTION OF PI-ANIMALS

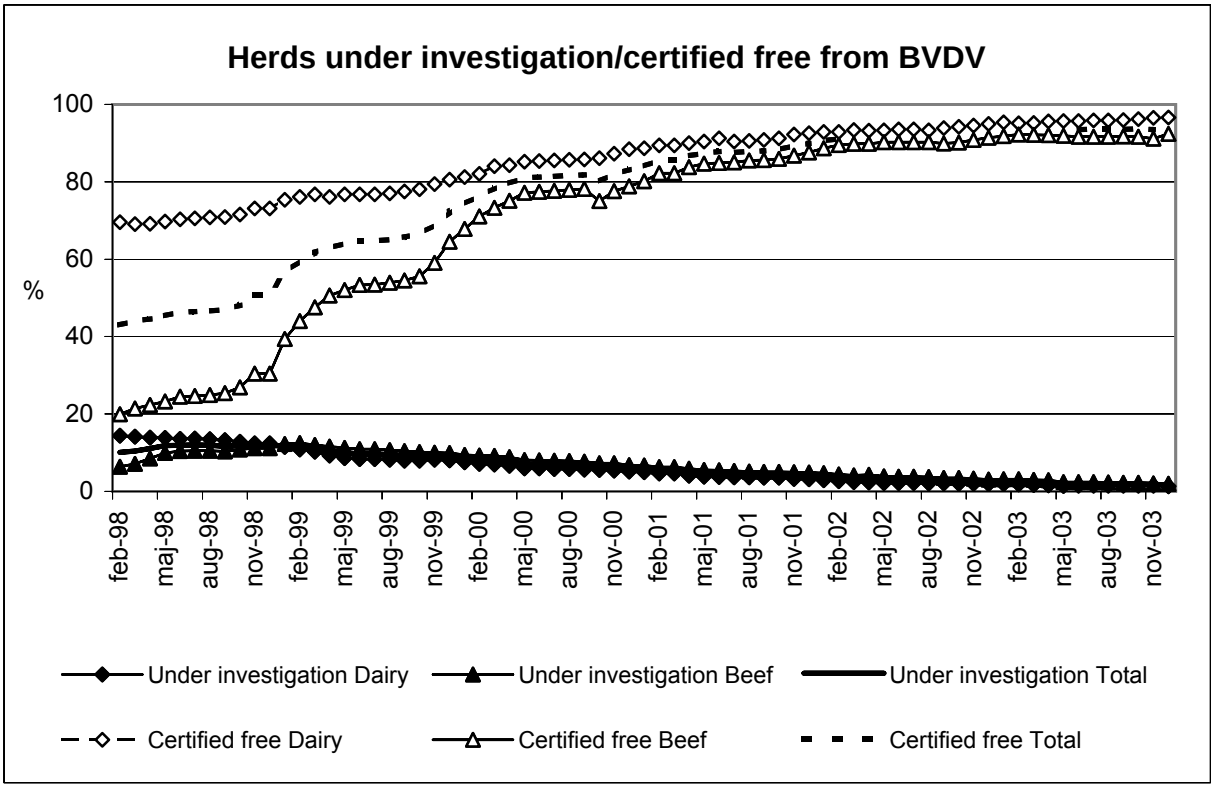

BVD- Untersuchungs- und Sanierungsverfahren
1. Tankmilch-untersuchung
kein aktuelles BVD-Geschehen
7 Monate
Tankmilch-untersuchung
Verdacht eines aktuellen BVD-Geschehens
Milchuntersuchung von mindestens 5 Jungkühen
kein aktuelles BVD-Geschehen
7 Monate
Milchuntersuchung von mind. 5 Jungkühen + Tankmilch
Verdacht eines aktuellen BVD-Geschehens
Blutuntersuchung von 8–10 Jungtieren (6–24 Monate)
kein aktuelles BVD-Geschehen
7 Monate
Blutuntersuchung von mind. 5 Jungtieren über 15 Monaten + Tankmilch
Verdacht eines aktuellen BVD-Geschehens
Bestandsuntersuchung nach Virusstreuern ab 4 Wochen
kein Virusstreuer gefunden
1 Jahr lang ab Bestandsuntersuchung alle nachgeborenen Kälber (vor Biestmilchaufnahme oder ab 4 Wochen) + Blutuntersuchung von 5 Jungtieren (6–9 Monate)
Virusstreuer gefunden
Schlachtung
14
kein aktuelles BVD-Geschehen
7 Monate
Tankmilch untersuchung
kein aktuelles BVD-Geschehen
kein aktuelles BVD-Geschehen
7 Monate
Milchuntersuchung von mind. 5 Jungkühen + Tankmilch
kein aktuelles BVD-Geschehen
NUR bei Zukauf oder Weide mit nicht untersuchten Tieren 1 Jahr vor 1. Tankmilch
kein aktuelles BVD-Geschehen
7 Monate
Blutuntersuchung von mind. 5 Jungtieren über 15 Monaten + Tankmilch
kein aktuelles BVD-Geschehen
Bescheinigung der Freiheit von einem aktuellen BVD-Geschehen
15

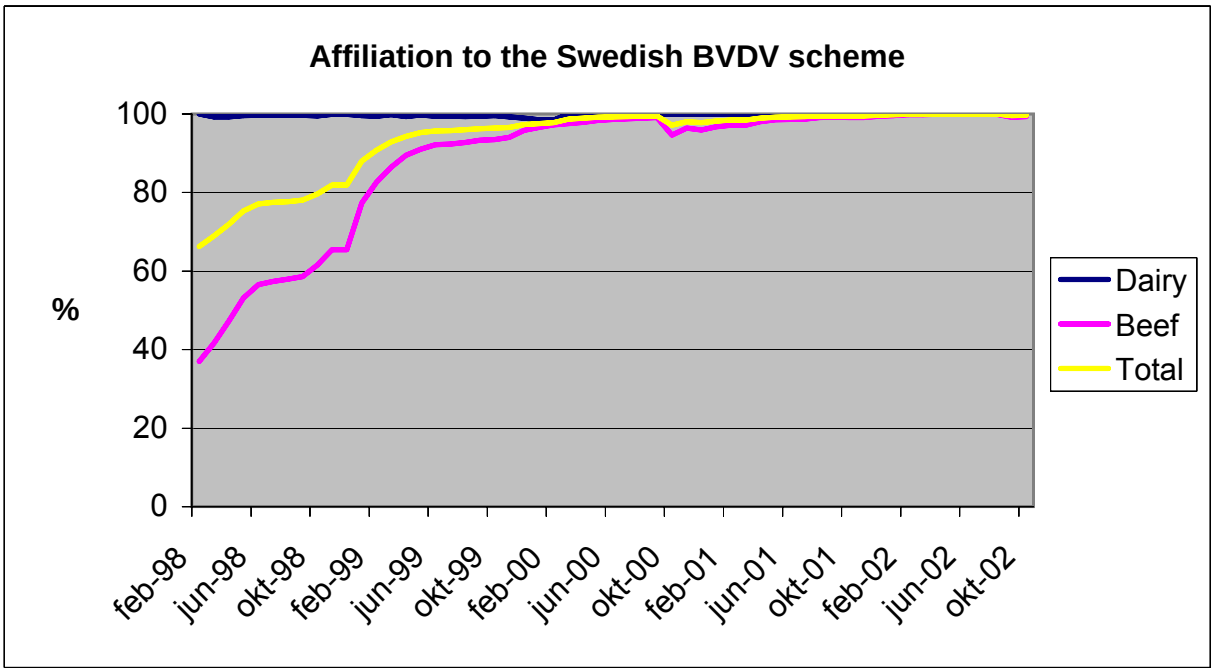

Number of dairy herds
14000
12000
10000
8000
6000
4000
2000
0
Total
Free status
Undet. Status
PI status
Jan. 98
Jan. 99
Dec. 99
Apr. 01
Dec. 02
Nov. 03
Date


Number of dairy herds
2500
2000
1500
1000
500
0
Undet. Status
PI status
Jan. 98
Jan. 99
Dec. 99
Apr. 01
Dec. 02
Nov. 03
Date


Number of herds with restrictions
3000
2500
2000
1500
1000
500
0
jan-93
jan-94
jan-95
jan-96
jan-97
jan-98
jan-99
jan-00
jan-01
jan-02
jan-03
jan-04


New imposed/lifted restrictions
IMPOSED
LIFTED
2000
1500
1000
500
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003


Herds under investigation/certified free from BVDV
100
80
60
40
20
0
%
feb-98
maj-98
aug-98
nov-98
feb-99
maj-99
aug-99
nov-99
feb-00
maj-00
aug-00
nov-00
feb-01
maj-01
aug-01
nov-01
feb-02
maj-02
aug-02
nov-02
feb-03
maj-03
aug-03
nov-03
Under investigation Dairy
Under investigation Beef
Under investigation Total
Certified free Dairy
Certified free Beef
Certified free Total


Affiliation to the Swedish BVDV scheme
100
80
60
40
20
0
%
feb-98
jun-98
okt-98
feb-99
jun-99
okt-99
feb-00
jun-00
okt-00
feb-01
jun-01
okt-01
feb-02
jun-02
okt-02
Dairy
Beef
Total