Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Faculty of Veterinary Medicine
and Animal Science
Department of Clinical Sciences

Evaluation of the Economic Impact and Description of a BRSV-outbreak in a Dairy Herd

Cecilia Lefverman

Uppsala
2018

Degree Project 30 credits within the Veterinary Medicine Programme

ISSN 1652-8697
Examensarbete 2018:54

Evaluation of the Economic Impact and Description of a BRSV-outbreak in a Dairy Herd

Utvärdering av de ekonomiska konsekvenserna och beskrivning av ett BRSV-utbrott i en mjölkkobesättning

Cecilia Lefverman

Supervisor: *Jean-Francois Valarcher, Department of Clinical Sciences*

Assistant Supervisors:
Karin Alvåsen, Department of Clinical Sciences
Sara Hägglund, Department of Clinical Sciences
Julia Österberg, The Swedish Livestock Research Center, SLU

Examiner: *Nils Fall, Department of Clinical Sciences*

Degree Project in Veterinary Medicine

Credits*: 30*
Level*: Second cycle, A2E*
Course code*: EX0830*

Place of publication*: Uppsala*
Year of publication*: 2018*
Number of part of series*: Examensarbete 2018:54*
ISSN*: 1652-8697*
Online publication*: https://stud.epsilon.slu.se*

Keywords*: BRSV, economic impact, dairy herd, respiratory disease*
Nyckelord*: BRSV, kostnad, mjölkkobesättning, luftvägssjukdom*

Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Faculty of Veterinary Medicine and Animal Science
Department of Clinical Sciences

SUMMARY

Bovine respiratory syncytial virus (BRSV) is globally one of the most important causes of respiratory disease in beef and dairy cattle of all ages and results in considerable costs for cattle farmers and significant suffering for the affected animals. The BRSV-infection can be subclinical to severe, and even fatal. There is no effective treatment and no commercially available vaccine that induces satisfying duration of protection, though promising vaccine candidates are under development. In addition to treatment costs and animal loss BRSV is associated to reduced production, such as reduced growth, reduced milk yield and fertility disorders. The virus can be transmitted directly and indirectly by respiratory secretion. Spread between and within herds is often rapid. The contagious nature of the virus together with its severe impact on animal welfare and economy necessitate effective preventive measures.

To develop cost-efficient prevention strategies against BRSV evaluation of the economic impact caused by the virus is necessary. This study aimed to estimate the economic impact of BRSV by analyzing the short-term costs associated to a BRSV-outbreak in a Swedish dairy herd. The parameters investigated were veterinary care, drug treatment, diagnostic tests, milk production, death and extra labor. The sum of the estimated budget items was 71,464 SEK, which rounded corresponded to 130 SEK per animal housed in the farm during the outbreak, or 270 SEK per cow. Out of the investigated costs milk loss (23,234 SEK, 32,5%), death (21,000 SEK, 29,4%) and extra personnel (17,112 SEK, 23,9%) were the three major budget items (61,346 SEK, 85,8%). Veterinary cost (2656 SEK, 3,7%), medicine costs (5399 SEK, 7,6%) and costs for diagnostic tests (2063 SEK, 2,9 %) were comparably small costs (10,118 SEK, 14,2%). Due to the possible long-term consequences such as reduced growth and reproduction disorders not being included, the estimated sum of 71,464 SEK is most likely an underestimation of the true cost for the farm.

The estimated cost in this study is an example of the short-term economic impact of a BRSV-outbreak. By seemingly small changes of an outbreak's characteristics the economic impact can change greatly. The investigated outbreak in the present study was for example characterized by relatively low mortality, 0,37%. In literature outbreaks of up to 20 % mortality are described. The clinical illness in the present herd was also relatively low, which was explained mainly by high inter-herd biosecurity and overall good cattle management and air quality resulting in minimized viral exposure and consequently less severely affected animals. The economic estimations and the epidemiologic observations presented in this study are in agreement with other papers emphasizing the economic impact and animal suffering of BRSV. Further, the epidemiologic observations presented in this study indicates that decreased feed consumption and decreased milk yield can be used as early warning signs of an upcoming BRSV-outbreak. In conclusion more research is needed to gain broader and more in-depth knowledge about the economic impact of BRSV, both for different kinds of herds and in terms of long-term economic consequences.

SAMMANFATTNING

Bovint respiratoriskt syncytialt virus (BRSV) är globalt en av de viktigaste orsakerna till luftvägssjukdom hos nötkreatur av alla åldrar och resulterar i stora kostnader för nötbönder och avsevärt lidande för de drabbade djuren. En BRSV-infektion kan vara subklinisk till allvarlig, och har i vissa fall dödlig utgång. Det finns ingen effektiv behandling och kommersiellt tillgängliga vaccin skyddar inte optimalt. Lovande vaccinkandidater är dock under utveckling. Utöver vårdkostnader och djurförluster leder BRSV till försämrad produktion, så som i form av minskad tillväxt, sänkt mjölkproduktion och reproduktionsstörningar. Viruset kan smitta direkt eller indirekt via sekret från luftvägarna. Spridning mellan och inom besättningar sker ofta snabbt. På grund av virusets smittsamma natur i kombination med dess negativa påverkan på djurvälfärd och bondens ekonomi är behovet av effektiva förebyggande åtgärder stort.

För att möjliggöra framtagandet av kostnadseffektiva preventionsstrategier är det nödvändigt att kvantifiera kostnaderna associerade till BRSV. Den här studien syftar till att bidra med information om BRSVs påverkan på lantbrukets ekonomi genom att analysera de kortsiktiga ekonomiska effekterna av ett BRSV-utbrott i en svensk mjölkkobesättning. Parametrarna som undersöktes i den här studien var veterinärvård, läkemedelskostnader, diagnostiska tester, mjölkproduktion, dödsfall och extra arbete. Totalsumman för dessa utgifter uppgick till 71 464 kronor, vilket avrundat motsvarade 130 kronor per djur i besättningen. De tre största utgiftsposterna var mjölkförlust (23 234 kronor, 32,5 %), dödsfall (21 000 kronor, 29,4 %) och extra personal (17 112 kronor, 23,9 %). Veterinärvård (2656 kronor, 3,7 %), läkemedels-kostnader (5399 kronor, 7,6 %) och kostnader för diagnostik (2063 kronor, 2,9 %) var förhållandevis små utgifter (10 118 kronor, 14,2 %). På grund av att potentiella långtidseffekter så som minskad tillväxt och reproduktionsstörningar inte inkluderades är det troligt att kostnadsberäkningen i studien är en underskattning av gårdens verkliga totalkostnad av utbrottet.

Den framtagna totalkostnadsuppgiften i den här studien är ett exempel på vad ett BRSV-utbrott kan kosta. Med till synes små förändringar i ett utbrotts karaktär kan de korrelerande ekonomiska följderna förändras stort. Utbrottet i den här studien karaktäriserades exempelvis av en förhållandevis låg mortalitet, 0,37 %. I litteraturen finns utbrott med upp till 20 % mortalitet beskrivna. Vidare var den kliniska sjukdomsgraden i det undersökta utbrottet förhållandevis låg, vilket framförallt förklarades med gårdens strikta hygienrutiner och överlag goda djurhållning och luftkvalitet, som antogs resultera i en under omständigheterna låg virusexponering och motståndskraftiga djur, och därigenom mindre allvarligt påverkade djur. De ekonomiska estimeringarna och de epidemiologiska observationerna i den här studien stödjer de i litteraturen tidigare angivna observationerna för BRSVs negativa konsekvenser gällande ekonomi och djurvälfärd. Vidare indikerar de epidemiologiska observationerna i den här studien att nedsatt aptit och sänkt mjölkproduktion kan användas som tidiga varningstecken för ett nära förestående BRSV-utbrott. Fortsatt forskning är nödvändig för att bredda och fördjupa kunskapen om BRSVs ekonomiska konsekvenser, både för olika besättningstyper och gällande långtidskonsekvenser.

CONTENT

ABBREVIATIONS

ALRI	acute lower respiratory infections
BCoV	bovine coronavirus
BPIV3	bovine parainfluenza virus type 3
BRD	bovine respiratory disease
BRSV	bovine respiratory syncytial virus
BVDV	bovine viral diarrhea virus
ELISA	enzyme-linked immunosorbent assay
HRSV	human respiratory syncytial virus
IDAMY	individual daily average milk yield
Ig	immunoglobulin
MDA	maternally derived antibodies
RT-PCR	reverse transcription polymerase chain reaction
RT-qPCR	quantitative reverse transcription polymerase chain reaction

INTRODUCTION

The actualities for many cattle farmers today with high production costs and low production income lead to a difficult economic situation where the need for optimal management and healthy animals is high. An important factor for animal production characterized by profitability and high animal welfare is prevention of infectious diseases. To calculate the cost-efficiency of prevention for a disease it is necessary to know the economic impact associated to the disease.

This study aimed to provide information about the economic impact of BRSV, based on a BRSV-outbreak in a Swedish dairy herd. In the literature there is sparse information about the actual costs related to BRSV-infection. The losses included in this study were milk loss, death, extra labor and treatment costs. Along with these economic estimations the epidemiologic aspects of the outbreak, such as morbidity and transmission within the herd were described. Long-term effects such as growth reduction and fertility disorders are still under investigation and were not included in this thesis.

LITERATURE REVIEW

Bovine Respiratory Syncytial Virus

Bovine respiratory syncytial virus (BRSV) is one of the most important causes of respiratory disease in beef and dairy cattle (Stott *et al.,* 1980; Verhoeff and van Nieuwstadt, 1984). This virus is a member of the genus *Orthopneumovirus,* belonging to the family *Pneumoviridae* (Rima *et al.,* 2017). The viron is enveloped and the genome is negative-sense unsegmented RNA. BRSV was first isolated in 1970 in Switzerland (Paccaud and Jacquier, 1970) and is globally widespread and endemic in many areas (Elvander, 1996; Sarmiento-Silva *et al.,* 2012). The virus can be pathogenic to both calves and adult cattle, but affects calves more severely in areas where adult cattle are immune (Larsen *et al.,* 1999). The infection can be subclinical to severe, and even fatal (Sarmiento-Silva *et al.,* 2012; Stott *et al.,* 1980; Verhoeff and Van Nieuwstadt, 1984). A symptomatic infection leads to clinical signs associated with respiratory disease, and may involve both upper and lower respiratory tract (Castleman *et al.,* 1985). Treatment is mainly symptomatic and effective treatment alternatives are missing (Viuff *et al.,* 2002). A BRSV-infection can cause severe suffering for the affected animal and is of great importance in terms of animal welfare (Hägglund *et al.,* 2007). This virus is generally considered to result in considerable economic consequences for cattle farmers worldwide (Brodersen, 2010). BRSV is genetically, pathogenetically and epidemiologically similar to human respiratory syncytial virus (HRSV), making it possible for actors within veterinary and human medicine to exchange useful knowledge in their fight against RSV-associated disease (van der Poel *et al.,* 1994).

Human respiratory syncytial virus

HRSV is, in similarity to BRSV, host-specific (Valarcher and Taylor, 2007) and is under normal circumstances not pathogenic to any other host than its natural host (Thomas *et al.,* 1984). HRSV is globally the most common and most important pathogen identified in young children with acute lower respiratory infections (ALRI) (Nair *et al.,* 2010; Wright *et al.,* 2000). ALRI is one of the major causes of mortality in children younger than 5 years (Liu *et al.,* 2016). In similarity to BRSV, there is a great need of preventive medicine against HRSV. Today there are more than 60 HRSV vaccine candidates in clinical development (Shi *et al.,* 2017). BRSV vaccines, of varying efficacy, have been available since the late 1970's (Ellis, 2017).

Epidemiology

BRSV is globally widespread and herd seroprevalence can in geographic regions be as high as 100% (Elvander, 1996; Ohlson *et al.,* 2010). Individual seroprevalence increases by age (Van der Poel *et al.,* 1994). In temperate climates there is a seasonal periodicity with the highest outbreak incidence during the winter season. Both calves and adult cattle are susceptible for BRSV-associated disease (Larsen *et al.,* 1999). Morbidity varies greatly, from subclinical outbreaks to outbreaks where most animals fall ill (Elvander, 1996; Jacobsson *et al.,* 1989; Kimman *et al.,* 1988). Mortality is usually low but up to 20% has been reported (Valarcher and Taylor, 2007). The virus can be transmitted directly from animal to animal, through aerosol within a building or indirectly through contaminated humans or equipment (Mars *et al.,* 1999; Ohlson *et al.,* 2010). It is not known how the virus survives between outbreaks (Larsen *et al.,* 2000). RSV is a labile virus, but a study on HRSV has shown that HRSV can survive six hours

in room temperature (Hall *et al.*, 1980). BRSV is considered to have high genetic stability, but yet different field isolates have genetic diversity (Deplanche *et al.*, 2007; Valarcher *et al.*, 2000). Through mutations new BRSV populations with genetic variability that might have biological implications evolve (Valarcher *et al.*, 2000). Up to 11% nucleotide sequence variation in certain analyzed genes was found when sequencing virus isolates from outbreaks from different years within the same closed herd (Larsen *et al.*, 2000).

Clinical signs

After the incubation period of 2-5 days (Valarcher and Taylor, 2007) the course of infection can be subclinical to severe, and even lethal (Sarmiento-Silva *et al.*, 2012; Stott *et al.*, 1980; Verhoeff and Van Nieuwstadt, 1984). Common clinical signs are serous nasal discharge, malaise, anorexia, fever (up to 42°C), tachypnea, dyspnea, abnormal breathing sounds and coughing (Baker *et al.*, 1986; Elvander, 1996; Paccaud and Jacquier, 1970; Smith *et al.*, 1975). The duration of clinical signs varies depending on the course of infection, in literature an average of three to ten days is described (Paccaud and Jacquier, 1970).

Pathogenesis and lesions

The pathogenesis of BRSV-infection is complex (Sarmiento-Silva *et al.*, 2012), and so far not completely elucidated. Studies have shown that the pathogenesis is closely related to the host response to the BRSV-infection (Gershwin, 2007). It has further been demonstrated that pathological changes correspond well to clinical signs, both in natural and experimental infections (Kimman *et al.*, 1989; Viuff *et al.*, 2002).

After a couple to a few of days following transmission, BRSV is observed in a variety of ciliated and non-ciliated epithelial cells from upper to lower respiratory tract, as well as intraluminally ((Bryson *et al.*, 1991); (Castleman *et al.*, 1985); (Viuff *et al.*, 2002)). Depending on how fast the infection is limited by the immune system the virus can be detected during approximately one week (Kimman *et al.*, 1989; Viuff *et al.*, 2002). Significant infection in cells beneath respiratory epithelial cells has not been observed, but pathological changes such as oedema and cellular infiltration, are present in the interstitial tissue (Viuff *et al.*, 2002). After replication in the cytoplasm viral particles bud directly through the apical membrane, initially without obvious cytopathology (Ellis, 2017). Within a couple of days after onset of viral replication characteristic microscopic and macroscopic changes occur (Castleman *et al.*, 1985; Viuff *et al.*, 2002). Infected ciliated cells lose their cilia, epithelial syncytial cells appear and progressively the epithelium becomes irregular, necrotic and hyperplastic.

It has been indicated that infected cells die by apoptotic mechanisms, whereafter most of the apoptotic cells are phagocytised by neighbouring epithelial cells and macrophages (Viuff *et al.*, 2002). Apoptosis of the infected epithelial cells is believed to be one of the major means of limiting the infection. The major mechanism of intraluminal viral clearance is thought to be phagocytosis by neutrophils. The cell loss occurs in upper and lower respiratory tract, and in pulmonary parenchyma, with loss of type I and type II pneumocytes.

In trachea, bronchi and bronchioles there is mucopurulent exudate and beneath the respiratory epithelium there is interstitial oedema (Viuff *et al.*, 2002). The lumen of bronchi, bronchioles,

and alveoli might be obstructed or filled with cellular debris, mainly consisting of neutrophils and epithelial cells. Affected lung areas are often red, depressed and firm (Bryson *et al.,* 1991; Castleman *et al.,* 1985). In severe cases bronchiolitis obliterans and emphysema might develop (Bryson *et al.,* 1991; Castleman *et al.,* 1985; Viuff *et al.,* 2002). Consolidation is commonly observed (Viuff *et al.,* 2002). In severe cases total consolidation of cranial, middle, accessory, and part of the caudal lobes has been observed at the peak of clinical signs, 6-8 days after experimental inoculation. The consolidation can remain weeks after acute phase of disease.

In a recent study where proteome analysis of bronchoalveolar lavage from experimentally BRSV-infected calves were performed at the peak of clinical signs, the following cell processes were indicated: neutrophil activation and chemotaxis, epithelial cell response, lymphocyte and natural killer cell activation and chemotaxis, macrophage activation, systemic acute-phase response, cell necrosis and/or apoptosis, and gluconeogenesis (Hägglund *et al.,* 2017). The most characteristic findings were neutrophil activation and a reduction in identified antioxidant enzymes, in the experimentally infected non-vaccinated calves compared to vaccinated calves or non-infected control calves. The level of neutrophil activation and the low levels of antioxidant proteins correlated to the severity of disease. Neutrophils in excessive numbers are believed to have negative effects (Geerdink *et al.,* 2015) and antioxidant enzymes are needed for detoxification of reactive oxygen species (Hägglund *et al.,* 2017), which are released by neutrophils.

In case of an uncomplicated primary BRSV-infection, in an otherwise healthy animal, the main part of the BRSV-associated lesions are often relatively well repaired two weeks after infection (Bryson *et al.,* 1991; Viuff *et al.,* 2002). Examples of more long-lasting tissue changes are bronchiolitis obliterans, collapsed alveoli, hyperplastic bronchial-associated lymphoid tissue, and increased number of neutrophils in the bronchioles, alveolar macrophages in the alveoli and $CD4^+$ and $CD8^+$ T cells in the tissue.

Immunity

Seroconversion occurs as a result of BRSV-infection in seronegative animals. Seroconversion has been observed as early as three days after experimental infection in calves (Castleman *et al.,* 1985). Antibodies may remain detectable in bulk milk for years without reinfection (Beaudeau *et al.,* 2010), but the degree of protection and the duration of immunity is not known. Reinfection in seropositive animals result in an increase in antibody titer, but clinical signs are less common than in primary infections (van der Poel *et al.,* 1994).

In an experimental infection of BRSV-seronegative (colostrum-deprived) calves BRSV-specific IgM and IgA was detected from eight to ten days after infection in serum, nasal and lacrimal secretions and faeces (Kimman *et al.,* 1987). BRSV-specific IgG1 could be detected in sera from day 13 to 17 after infection. In the same study seropositive (colostrum-fed) calves had largely or totally suppressed antibody responses. When the calves were reinfected a strong immune response characterized by IgA developed already six days after infection. The immune response during the reinfection was the strongest in the group of colostrum-deprived calves.

BRSV-specific maternally derived antibodies (MDA) are partially protective against BRSV-associated disease (Kimman *et al.,* 1988). An inverse correlation has been observed between the level of BRSV-specific MDA and the incidence and severity of disease. The mean half-life of MDA in non-vaccinated calves is seven weeks (Fulton *et al.,* 2004). MDA can remain in the circulation for up to six months, duration depending on the amount consumed and absorbed and the rate of decay.

Diagnostic methods

There is a variety of possible tests to diagnose BRSV infection. In acute stage of infection, after virus shedding has begun, direct tests aiming to detect virus can be used. In later stages indirect tests, aiming to detect virus-specific antibodies, can be carried out. Direct tests include virus isolation, fluorescent antibody staining, antigen enzyme-linked immunosorbent assay (antigen-ELISA), reverse transcription polymerase chain reaction test (RT-PCR) and quantitative reverse transcription PCR (RT-qPCR) (Brodersen, 2010). Indirect tests include serum neutralization tests, and indirect and capture ELISAs (Hägglund, 2005).

Virus isolation in cell culture is a laborious and time-consuming method that can take over a month to complete (Wellemans, 1990). Another negative aspect with this method is that it requires viable virus, and BRSV is very labile (Smith *et al.,* 1975). In virus isolation a presumably virus containing specimen is inoculated onto a cell culture. After inoculation of the cell culture cythopathogenic effects, such as lysis of cells and syncytia, are searched for (Wellemans, 1990). The isolation is finally confirmed with immune based antigen detection. A benefit with virus isolation over other methods is that a positive test result guarantees that the animal was infectious at the time of sampling (Hägglund, 2005).

In fluorescent antibody staining fluorescent BRSV-specific antibodies are used to visualize BRSV-specific antigens in the specimen (Hägglund, 2005). Fluorescent antibody staining is faster than virus isolation, but is still not satisfactory under veterinary diagnostic laboratory conditions due to lack of sensitivity and specificity (Osorio *et al.,* 1989). The low sensitivity and specificity can, among other factors, be due to autolysis, difficulty in visualizing the positive-staining cell types, and quenching of fluorescent signal (Brodersen, 2010). Another negative aspect with fluorescent antibody staining it that the window of detection is limited to only a few days in the acute phase of the disease (Hägglund, 2005).

The principle of antigen-ELISA is that BRSV-specific antigens from the specimen attach to the walls of microtiter wells coated with BRSV-specific monoclonal antibodies, whereafter BRSV-specific enzyme-linked antibodies and finally an enzyme substrate is added, resulting in a color change if BRSV-specific antigens are present (Hägglund, 2005; Uttenthal *et al.,* 1996). There are different ways to preform antigen-ELISAs, all with varying degree of complexity, sensitivity and specificity (Quinting *et al.,* 2007). In one study antigen-ELISA showed a sensitivity of 60% and specificity of 100% compared to the reference test RT-PCR. In similarity to fluorescent antibody staining antigen-ELISA is an optional diagnostic test only for a few days in the acute phase of the disease (Hägglund, 2005).

RT-PCR is a highly sensitive and specific diagnostic approach that in optimal cases qualitatively can detect BRSV genome up to two weeks after the first clinical signs (Larsen *et al.*, 1999; Valarcher *et al.*, 1999). The high sensitivity of PCR is due to the minimal amount of virus-specific nucleic acid needed (Larsen *et al.,* 1999). In RT-PCR reverse transcriptase generates complementary DNA from specific BRSV-genome sequences. Which genome sequences that will be amplified is determined by which nucleotide primers that has been added. The synthesis is regulated by thermocycling. After repetitive thermocycles the amplicons can be detected through visualization in gel electrophoresis (Hägglund, 2005).

RT-qPCR is similar to RT-PCR but requires only one round of amplification and the detection of the amplicons can be carried out directly in the test tube by the means of fluorescent molecules (Hägglund, 2005). The strength of the fluorescence signal is proportional to the amount of BRSV in the sample and the rounds of amplification. RT-qPCR has the advantage over RT-PCR that it is faster and has a lower risk of sample contamination.

In serum neutralization test mixtures of serum sample and BRSV suspension are inoculated onto cell cultures (Murphy *et al.*, 1999). By inoculating the cell cultures with serum-virus mixtures of different serum concentrations, and then after incubation observe which concentration protects the cell culture from viral infection, the amount of BRSV-neutralizing antibody in the serum sample can be estimated.

In indirect ELISA the presumably antibody containing sample is put in microtiter wells coated with BRSV-specific antigen (Elvander *et al.,* 1995). After incubation and wash enzyme-conjugated anti-bovine immunoglobulin antibodies are added. Incubation and wash is repeated and then substrate is added as the final component. After a few minutes of reaction the color development is stopped and the optical density is measured. If the optical density is above a certain threshold the test is considered positive.

In capture ELISA the microtiter wells are instead coated with isotype-specific monoclonal antibodies (Uttenthal *et al.,* 2000). The following ingredients are serum sample, BRSV-antigen, enzyme conjugated BRSV-specific antibodies and substrate. Through this method antibodies of a specific isotype can be measured.

Treatment

There is no antiviral treatment for BRSV infection, instead treatment is symptomatic (Viuff *et al.,* 2002). Anti-inflammatory drugs are commonly used in attempts to mitigate clinical symptoms, increase appetite and decrease inflammatory lung damage (Francoz *et al.,* 2012). NSAID-treatment has shown to decrease rectal temperature but proofs of beneficial effects for other ancillary drugs are weak. Antibiotic treatment of bacterial co-infection is sometimes used, but needs due to the policy of restrictive use to be restricted to severe cases.

Prevention

To prevent transmission of BRSV between herds infectious control measures such as no purchase of infected animals and profound hygiene routines for people visiting different herds are important (Ohlson, 2014; van der Poel *et al.,* 1994). It is also important with high herd

health, good management and good housing to keep the animals as resistant to infection as possible (van der Poel *et al.*, 1994).

The today commercially available vaccines against BRSV only give partial protection against BRSV-infection and due to short duration of efficacy they require repeated boosting (Blodörn, 2015). A new generation of vaccine candidates are under development. The goal of the new generation of BRSV vaccines is a vaccine with complete protection against clinical illness, prevention of virus replication to stop transmission, long lasting immunity after only one shot and an immunologic response differentiable from the response acquired from natural infection so that infected and non-infected animals can be differentiated.

Economic consequences

Bovine respiratory disease (BRD) results in considerable costs for farmers worldwide and BRSV is a major contributor to BRD (Brodersen, 2010; van der Fels-Klerx *et al.*, 2001). To the author's knowledge there are no papers in the literature quantifying the total cost of BRSV-infection on herd level in a dairy herd. Factors identified as likely to be affected by pneumonia in dairy cattle are mortality, culling, treatment costs, veterinary costs, extra labor, reduced milk production, growth reduction and fertility disorders (van der Fels-Klerx *et al.*, 2001). Klem *et al.* (2015) demonstrated that BRSV-infection was correlated to reduced weight gain and feed conversion, both in subclinically infected and severely affected in bull calves (Klem *et al.*, 2015). These negative effects on production were observed to last for several months. In another study abortion was observed in dairy cows with BRSV-associated clinical illness (Jacobsson *et al.*, 1989). In the same study 72% decrease in daily bulk milk production was reported for two days during the most acute phase of a BRSV-associated outbreak and decrease in milk production was reported to last for two months. When comparing average individual milk yield in cows of non-infected and BRSV-infected herds during a seven-month period a significant reduction of 0,9 kg/day was observed for cows in infected herds (Beaudeau *et al.*, 2010).

MATERIAL AND METHODS

Farm description, animal housing and management

The farm description below is a compilation of the farm database, interviews with farm personnel, observations made during farm visits and the farm information booklet of 2016 (Lövsta, 2016), a booklet published annually by the farm.

Lövsta dairy farm is a modern research farm with high biosecurity, high herd health level and highly automatized milking and feeding systems. The farm moved to new facilities in 2011 and the herd size was at the same time increased through purchase of animals from four other farms. From 2011 no new animals were bought, instead own recruitment has been practiced. By the time of the outbreak the total number of animals on the farm was about 545, about 60 % of the breed Swedish Red-and-White and 40 % Swedish Holstein. Between the move to the new facilities in 2011 and the BRSV-outbreak in January 2016 there were no observed outbreaks of respiratory disease in the herd. Like other cattle farms in Sweden Lövsta is free from bovine viral diarrhea virus (BVDV). Sweden was declared free from BVDV in 2014 (Statens veterinärmedicinska anstalt, 2018). During the time of the outbreak there were several BRSV-

outbreaks diagnosed in the area of Uppsala. It was never found out how BRSV was transmitted to the farm.

The high biosecurity on the farm is created by the practice of own recruitment, different stable sections for different animal categories and profound hygiene routines for human beings and equipment. Everyone who enters the stable enters through a changing room, to change into clean clothes and foot wear provided by the farm. The changing room is followed by several hygiene checkpoints, where wellingtons and hands can be washed and disinfected. The hygiene checkpoints are located throughout the stable, between the different areas of the stable. The personnel are divided into smaller workgroups, each responsible for different animal categories, to avoid transmission of infectious agents within the herd. Each stable area has its own set of tools, and equipment that is moved between different areas is cleaned between times of use.

Overview of the farm building

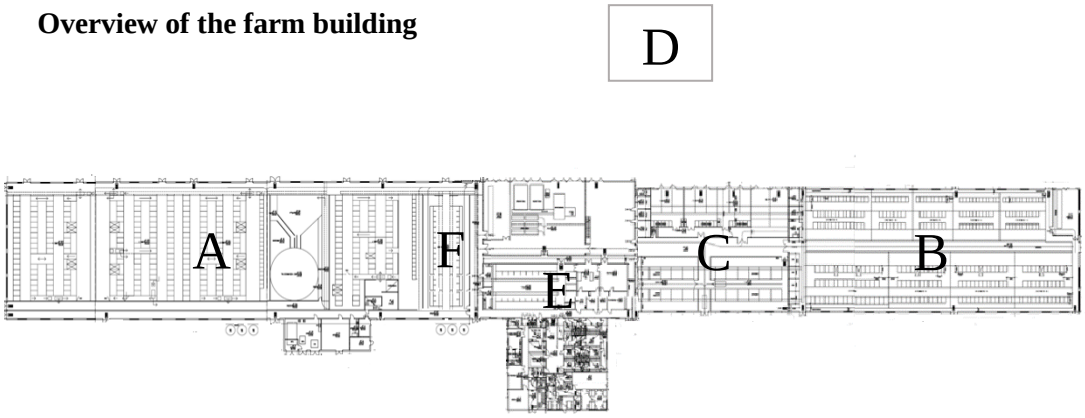

Figure 1. *A, lactating cows; B, recruit animals over six months of age and dry cows; C, calves age two to six months, calving and sick ward; D, calf hutches, calves under two months of age; E, changing rooms, personnel facilities, education room, storage rooms and feed mixing; F, extra section for animal housing, not in use during the outbreak.*

The stable has different sections for different areas of use and different animal categories (Fig. X.X). Section A is where the lactating cows are being housed. It is a heated free-stall with passive ventilation. By the time of the outbreak there were about 230 lactating cows, divided into four groups, separated by fences. Group one is being milked in an automatic milking system (DeLaval VMS^{TM}) and group two, three and four are being milked in a milking rotary parlour (DeLaval AMR^{TM}). Cows in group one and two are fed roughage in weight cells, making it possible to record, and if desired limit, roughage consumption on individual level. Cows in group three and four have free access to roughage, and their consumption can not be recorded on individual level. The concentrates are fed through automatic concentrate feeders and the maximum daily distribution is regulated for each individual animal.

Stable section B is in similarity to section A a heated free-stall with passive ventilation and fenced areas for housing of different animal groups. The animal groups in section B consist of recruitment animals over six months of age and dry cows. The groups of younger animals are segregated by age. All animals in section B have free access to roughage. Concentrate is distributed manually.

Stable section C consists of several smaller rooms, with controlled and separate heating and ventilation for each room. There is a room for calving heifers and cows (maximum 18 adult animals), a room for sick animals (16 pens), and four rooms for calves two to six months of age. The animals in section C are fed roughage manually, concentrate manually or through feeders, and when needed milk through milk feeders. The lactating cows in section C are milked separately, and not through the milking systems in section A.

On the farmyard there is a roofed area, section D, where the youngest calves are being housed in calf hutches. The calves normally live individually in one calf hutch per calf. The calves live in the calf hutches from the day they are born until the age of two months. They are fed colostrum from their respective mother the three first days of life, and thereafter good quality whole milk produced on the farm. During the outbreak the number of calves varied between 26 and 36.

Section E consists of changing rooms, hygiene checkpoints, offices, a canteen, education rooms, storage rooms and a room for feed mixing. Section F is a room for animal housing that was not in use during the time of the outbreak.

The farm recording system and database

The data recorded at the farm consists to a smaller part of handwritten records on paper and to the greater part of either manually digitalized records or data recorded through automatic recording systems. The database system for the farm is called Basreg and is created by the Swedish University of Agricultural Science for research purpose. It is under constant development and stores big amounts of various kinds of production data, gathered both manually by the personnel and automatically by the feeding and milking systems. Examples of collected data used in this thesis are individual milk yield and feed intake, calving records, treatment records and records of individual animal movement between stable sections. The recording systems vary for different kinds of data and for the same kind of data, and sometimes there is no recording at all. The varying degree of recording makes it difficult to create complete overall pictures both on herd and individual level, and to find explanations for abnormal records.

Outbreak description

Information to define the extent and the clinical details of the outbreak was gathered from veterinarian medical charts, health records of individual animals, email correspondence between personnel and researchers connected to the farm, and interviews with personnel, farm veterinarians, and researchers working at the farm by the time of the outbreak. To estimate the cost of the deaths Swedish official numbers from 2015 was used, 10500 SEK for a cow in production (Oskarsson and Engelbrekts, 2015).

Cost estimation method

The economic effect of the BRSV-outbreak in the herd was explored by means of partial budgeting. In partial budgeting only factors of potential economic relevance and that are expected to be changed by the event are analyzed for estimation. The budget items that were expected to be changed by the BRSV-outbreak were veterinary expenses, medicine costs, cost

for laboratory investigations, additional personnel, death, loss in milk yield, decreased feed consumption, decreased growth and decreased fertility. Due to complicated feeding system and feed recording system on the farm the feed consumption was only possible to estimate partially and in terms of weight, and not in terms of economic effect. Investigations on growth and fertility are ongoing, but will be outside the scope of this thesis. Excel was the software used for calculations. If nothing else is stated prices of the outbreak period, January 2016, were used. The currency rate in January 2016 for one SEK was 0,11 EUR or 0,12 USD (XE, 2018).

Veterinary and medical costs

The cost for the field veterinarian was calculated by going through veterinarian bills from the time period of the outbreak and identify the bills that were directly associated to the BRSV-outbreak. The prizes given in the bills were then summarized. In the calculations tax free prices were used, because all farmers in Sweden are permitted tax deduction by law.

To estimate the total cost of the administrated medicines the outbreak associated BRSV-treatments were first identified in the farm's treatment records. Secondly the total volume for each administrated medicine was calculated, based on the information given in the treatment record. Thereafter the total medicine volumes were converted to a corresponding number of doses or bottles, depending on the information in the veterinarian bills. Lastly the number of doses or bottles for each medicine was multiplied with the respective prices given in the veterinarian bills. For medicines sold in bottles the cost estimation was based upon the price for an entire bottle, even if an entire bottle was not used during the outbreak.

To estimate the cost of syringes and cannulas the number of syringes and cannulas used during the outbreak was calculated, based on the information about numbers of medicine administrations and the volume of each dose given in the treatment record. The doses administrated by the field veterinarians were not included, because the field veterinarians did not charge specifically for syringes and cannulas. The corresponding number of syringe and cannula packages were then calculated. Lastly the number of packages were multiplied with the respective prices of January 2016. The estimation was based upon the price per whole package even if an entire package was not used during the outbreak.

Laboratory investigations and costs

To find out what laboratory investigations were carried out, and their respective results, medical charts of the farm veterinarian and investigation and laboratory records of the farm connected researchers were compiled. There were three different kinds of diagnostic tests performed, nasal swabs for RT-qPCR, nasal swabs for virus isolation in cell culture and serum samples for indirect-ELISA for detection and qualitative measuring of BRSV-specific IgG1 antibodies. Three RT-qPCR samples were collected by the farm veterinarian for routine diagnostic purpose, and payed by the farm. The other tests were performed within independent research projects and therefore not payed by the farm.

Estimation method for cost of extra work hours

The number of hours during which the farm hired extra personnel to meet up the extra work load caused by the outbreak were estimated by, together with the stable foreman, going through

the work schedule of the month in which the outbreak occurred. The cost for the farm for these additional hours were then estimated based on the farm's regular wage, fees and general payroll tax for the intended period. The information about the wage, fees and general payroll tax was given by an economist employed by Swedish University of Agricultural Sciences, to which the farm belongs.

Estimation of milk production and losses

To estimate the daily milk production on herd level bulk milk reports from the purchasing dairy company was analyzed. The bulk milk was analyzed in terms of amount of sold milk, the milk quality parameters fat, protein and somatic cell count, and selling price. Due to a selling pattern of every other day, or when highly uneven amounts between consecutive days was detected, the bulk milk data was recalculated to mean values of two-day-intervals. To estimate the changes of milk production due to the outbreak at a herd level, reference values were calculated. Reference values for the amount of bulk milk were calculated by using the data given in the reports from the dairy company. The data was used to calculate an imaginary line between the first day of visually observed milk loss to when the milk production was expected to be close to normalized again, 1st to 23d of January. The end point dates for the analyzed time period of presumably decreased milk production were chosen based on the values in the bulk milk report, individual production data and clinical records. The amount of decreased milk production was estimated by calculating the difference between the expected amount of bulk milk and the actual amount of bulk milk.

Reference values for the milk quality parameters were calculated by calculating mean values for a ten-day period one month before the outbreak, 1st to 10th of December 2015. The milk quality values during the outbreak were then compared with the reference values. To estimate the value of the decreased milk production the actual income was compared with the expected income. The expected income was based on the expected amount of milk, the reference milk quality and the price setting of the outbreak period.

To estimate the daily number of cows in lactation data from the automatic milking systems, farm records on individual animals and reports from the stable foreman was used. To estimate the individual daily average milk yield (IDAMY) the bulk milk amount was divided with the number of cows that had been milked in the automatic milking systems on the corresponding day. On the farm only milk from the automatic milking systems is being sold, and no milk produced by cows housed in the sick ward or the calving room is transferred to the milk tank.

For individual milk curves data provided by the automatic milking systems were used. To identify any distinctive decrease in milk yield in a milk curve the curve was eyed visually and compared with itself. If the identified decrease corresponded to BRSV-associated clinical records, and no other explanation to the decreased milk yield was to be found in available records, the decrease was suspected to be due to the BRSV-infection. To as accurate as possible estimate the extent and duration of the decrease in milk production in an individual milking curve the physiological daily decrease was taken into account. The average physiological daily decrease in milk yield for a Swedish cow is 0,05-0,09 kg/day (Nygren, 2010).

Data for the number of calvings per day was collected from the farm database Basreg. Based on animal-ID and individual records the number of heifers and older cows was determined.

Estimation of feed consumption

In addition to interviewing the personnel and going through health records and protocols of farm meetings, feeding data was collected from the farm database Basreg. Data was collected based on date and animal-ID or feeder. The daily total consumption for the chosen animals was calculated by in Excel adding the individual records. The individual daily average was then calculated by dividing the total consumption for each day by the corresponding number of recorded animals for each day. To estimate how much the feed consumption changed during the outbreak a reference consumption level was calculated. The reference was calculated for the same reference period as used for the milk quality reference period, 2015-12-01 to 2015-12-10, one month before the outbreak. Due to different feeding systems and varying degree of feed recording in the different parts of the farm feed consumption was only possible to estimate qualitatively for the cows in section A. For the calves housed in the hutches paper copies of their daily health records were used to investigate for any BRSV-associated changes in feed consumption.

RESULTS

Outbreak description

The clinical phase of the outbreak was recorded to begin on the 3rd of January 2016. On the first day only one clinical case of respiratory disease was detected, but already on the second day there were over 20 animals recorded with clinical signs. The first observed clinical case was a three-year-old cow housed in milking group 1. The cow had no known health problems but had ten days earlier entered second lactation. The cow was observed to have fever and heavy breathing and was moved to the sick ward and treated with the non-steroidal anti-inflammatory drug meloxicam 20 mg/ml (0,5 mg/kg) for one day and the antibiotic benzylpenicillin 300mg/ml (20 mg/kg) for five days, both drugs administrated according to the manufacturers' recommendations. The first animals to fall ill were the lactating cows housed in section A. Progressively more animals fell ill and within a week the outbreak had spread to all stable sections in the main building. Within two weeks clinical signs were recorded also among the calves in the hutches, in section D. On herd level clinical signs of BRSV were observed during at least three weeks.

The farm veterinarian was called out to the farm on the second day of the outbreak, on the 4th of January. The farm veterinarian suspected BRSV as a causative agent and collected samples for laboratory diagnosis, see paragraph *Laboratory investigations*. Together with the personnel the farm veterinarian set up guidelines for sick care, prevention of disease spread and early detection of new cases. Depending on the severity of clinical signs sick animals were given medical treatment, and if space in the sick ward, moved to the sick ward. For cows in milking group 1 and 2 that were too depressed to walk to the feeders hay was distributed in front of the cubicles. Some calves were given additional milk and three hutch calves were moved inside for protection of the cold weather, about -20 °C (Fig. 2). To minimize spread within the herd the personnel aimed to be as strict as possible in their division of work areas and the hygiene

routines. For example one stable worker was set to work solely in the sick ward and the personnel who worked with the calves changed clothes and gloves when moving between the calves in section C and the hutch calves. To as quickly as possible detect new clinical cases all calves and all cows in section A were monitored at least twice daily and when motivated rectal temperature was checked. This procedure lasted for at least two and a half weeks. The last case of detected fever was on the 19th of January, 16 days after the first observed clinical case. The recruit animals and dry cows in section B were also monitored but without any systematic recording of their health.

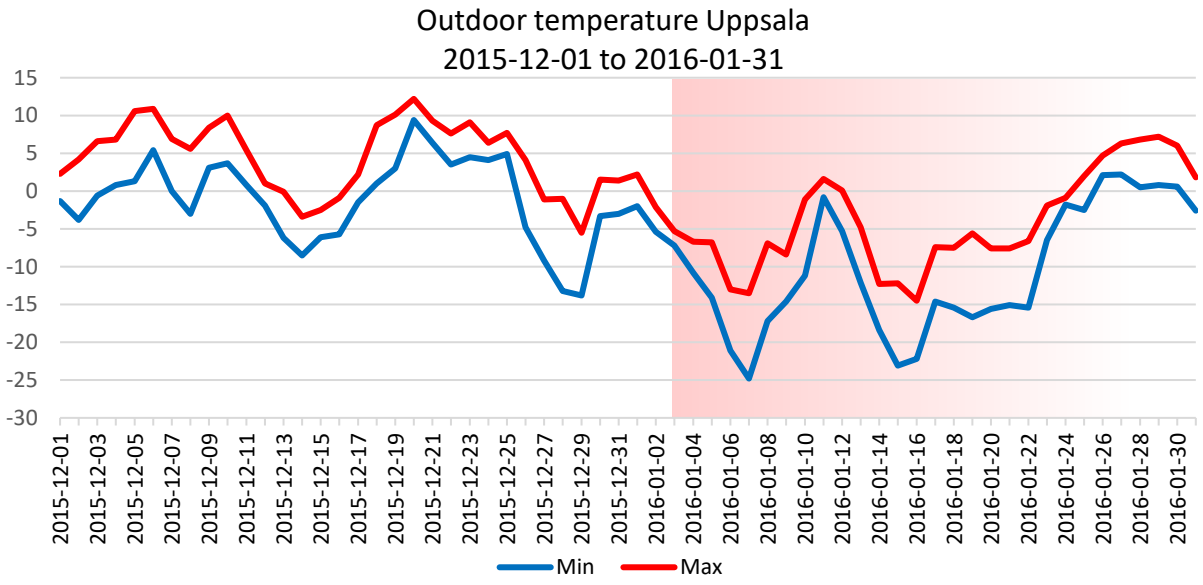

Figure 2. *Outdoor temperature in Uppsala December 1st 2015 to January 31st 2016. The semi-transparent area represents the clinical phase of the outbreak, recorded to have started on January 3rd 2016.*

Due to incomplete health records the herd morbidity was not possible to determine with certainty, but compilation of the health records of the cows in section A showed that BRSV-associated illness was suspected in about half of the cows. The animal categories that were recorded with highest morbidity and most severe clinical illness were the lactating cows in section A, the peripartum animals in the calving room and the two to six months old calves in section C. The seemingly least affected animal group was the calves in the hutches. They appeared to be subclinically to mildly affected by the virus, with mild respiratory signs and only a few cases of detected fever. However, the low outer temperature (Fig. 2) seemed to prevent the calves from rising their body temperature since several calves were shivering.

The degree of clinical signs varied among the animals in the herd, from subclinical to severe, and even death. The most common clinical signs were serous to mucopurulent nasal discharge, tachypnea and decreased general condition. Other common clinical signs were fever (up to 41,1°C), coughing, dyspnea, abdominal breathing, inappetence and serosal lacrimal discharge. Some animals developed severe dyspnea, anorexia and apathy.

The mortality was relatively low, with two cases of death, 0,37%. The first death occurred on the 7th of January. The cow that died was a three-year-old otherwise healthy cow, that begun to

show respiratory illness and fever one day after she was dried off. Despite attempts to mitigate the cow's illness through medical therapy with the nonsteroidal anti-inflammatory drug ketoprofen 150 mg/ml for one day and the antibiotic benzylpenicillin 300 mg/ml the following day the severity of the disease increased. The cow was found dead on the third day of clinical illness. The second case of death occurred on the 8th of January, to a five-year-old cow, seven weeks postpartum. The cow was considered to have had a poor health since long time, and was euthanized when apathetic on the fifth day of clinical illness after two days of fruitless treatment with the nonsteroidal anti-inflammatory drug ketoprofen 150 mg/ml. The total cost of the two deaths was estimated to 21000 SEK.

Veterinary care and medicine treatment costs

The farm veterinarian was called out to the farm because of BRSV-associated morbidity two times during the outbreak, on the 2nd and 6th day of the outbreak respectively, 4th and 8th of January. The cost of these two veterinary services was 2 656 SEK, veterinary medicine administration excluded. In addition to these two veterinarian visits other veterinarians, such as the research coordinator on the farm and cattle researchers connected to the farm, were consulted several times, but free of charge.

The total cost of medicines, syringes and cannulas were 5399 SEK. Medical treatments were carried out to decrease suffering and facilitate recovery. There was a total of 28 animals treated, all cows, representing 5,1% of the average number of animals in the herd and 10,7% of the average number of cows. With the exception of a cow that fell ill one day after she was dried off and moved from stable section A to stable section B, all animals that were treated with drugs were either peripartum animals in the calving room or lactating cows in section A. No calves or recruitment animals were medically treated. Treatment decision criteria were high fever, moderately to severe breathing difficulties and/or moderately to severely decreased general condition. A treatment decision could be carried out either by the field veterinarian or personnel at the farm. Characteristics of the treated animals, other than that they all were cows, were that 18 out of the 28 cows, 64%, were within two months post-partum (15 cows) or dry cows (3 cows). Six of the treated animals that gave birth during or shortly before the outbreak were heifers. Eight of the 28 treated cows, 29%, were born in other farms and purchased by Lövsta in 2011, when the new farm was built and the herd was enlarged. The age range of the treated animals was two years and two months to six years and seven months, with an average three years and eight months. The first treatment in the herd was carried out on the first day of observed respiratory signs, the 3rd of January. Treatments were then carried out during 14 consecutive days. A total of 82 doses were given. The average number of treatment days per cow was 2,7 days, with a variation of 1 to 8 days. Median number of treatment days was 2 per treated animal. All medicines were administrated according to manufacturers' recommend-dations, concerning both dose and route. All treated cows were given anti-inflammatory treatment. 27 cows received non-steroidal anti-inflammatory, ketoprofen 150 mg/ml (3 mg/kg, once daily, one to three days) and/or meloxicam 20 mg/ml (0,5 mg/kg, once daily, one to two days). Two cows received glucocorticoid treatment, dexamethasone 1 mg/ml or 2 mg/ml, respectively. Five cows were given antibiotic treatment, benzylpenicillin 300 mg/ml (20 mg/kg, once daily, up to five days). The treatments resulted in a total of 70,5 days of milk withdrawal. The outcome of the treatments was recovery in 26 cows and death in two cows.

Laboratory investigations

The first set of diagnostic samples were collected by the farm veterinarian on the second day of the clinical phase of the outbreak, the 4th of January. Three nasal swabs for PCR diagnosis were taken from three cows with fever (39,4-40,0°C), tachypnea, increased breathing sounds, anorexia and decreased milk yield. The nasal swabs were analyzed by Swedish National Veterinary Institute, SVA, who analyzed the samples through RT-qPCR. The total cost for these three tests was 2063 SEK. All three samples were positive.

For research purpose and in addition to the diagnostic tests above, nasal swabs for virus isolation in cell culture were taken from nine animals with clinical signs of BRSV-infection during the second week of the outbreak. BRSV was isolated from seven of these, based on presence of syncytia and cytopathogenic effects that are characteristic of the virus. The presence of BRSV was confirmed by RT-qPCR. BRSV was isolated from a one-month-old bull calf and six heifers of two to six months of age, but not from a seven-months-old heifer and a cow. Three of the aforementioned young heifers were also tested for the two other main bovine respiratory viruses in Sweden, bovine coronavirus (BCoV) and bovine parainfluenza virus type 3 (BPIV3). The tests were carried out by analyzing nasal swabs with RT-qPCR. No BCoV or BPIV3 was detected in any of the samples. BRSV-specific IgG1 antibodies were analyzed by indirect ELISA on paired serum samples from two one and a half month old calves and five two to six months old calves, all showing clinical signs of BRSV-infection. The first set of serum samples were collected simultaneously as the nasal swabs for the virus isolation. With the exception of one five months old calf, that had low levels of BRSV-specific antibodies, all calves were seronegative during the outbreak and had seroconverted within three to four months, when the second sample was obtained. The calf that was not seronegative at first sampling had the oldest mother, born in 2009. Both the virus isolation tests and the antibody tests were performed within research projects and therefore free of charge for the farm.

Cost for personnel for extra work hours

There was a substantially increased workload on the farm during roughly one month associated to the outbreak. During the first week of the outbreak no extra personnel was hired, but the regular personnel increased their work effort without demanding extra payment. During the second to fourth week of the outbreak the regular personnel was hired for extra working hours. During the second and third week they worked at least four additional hours per day, divided upon mornings and evenings. During the weekdays of the fourth week the regular personnel worked at least two additional hours per day, divided upon mornings and evenings. The total number of extra hours was 66. Multiplying each extra hour with its specific price, given by the day of the week and time of the day that it took place, the total cost was 17,112 SEK.

Estimation of milk production

On herd level a visible decrease in bulk milk amount was observed to begin on the same day as the first recorded clinical case, the 3rd of January (Fig. 3). Individual milk curves indicated that the decrease in milk production begun already two days before the first recorded clinical case, the 1st of January. Compilation of the bulk milk data and production data of individual cows suggested that the milk production was decreased for a period of at least three weeks, 1st to 23d

of January. The expected milk production during the period of presumably decreased production was estimated to 49252,5 kg. The actual amount of bulk milk during the same period was 39243,5 kg, 6,7% less than expected. The lowest production was recorded three days after the first observed clinical case, the 6th of January, with a production of 17,4% less than expected.

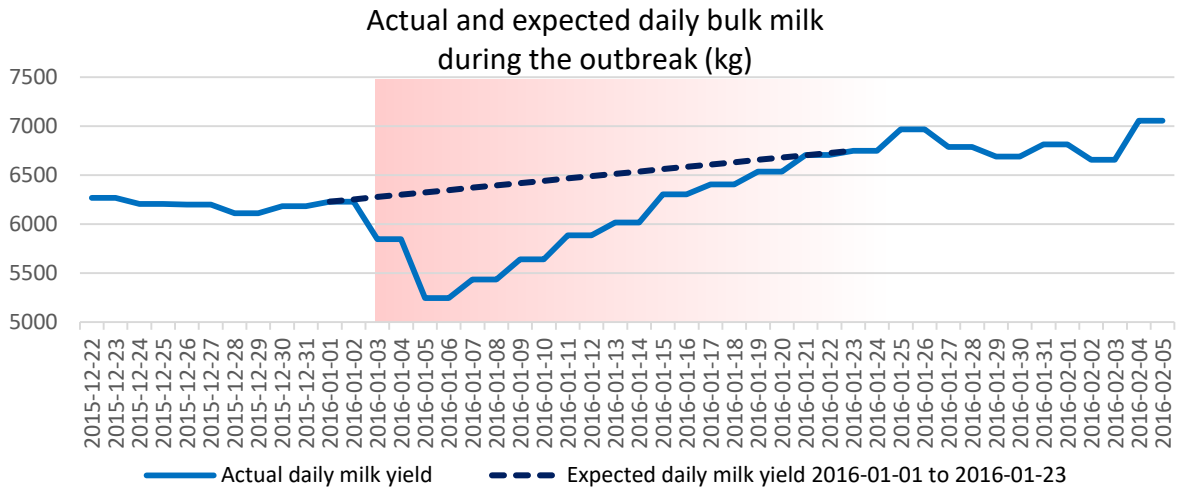

Figure 3. Actual and expected daily bulk milk during the outbreak. The semi-transparent area represents the clinical phase of the outbreak, recorded to have started on the 3rd of January 2016.

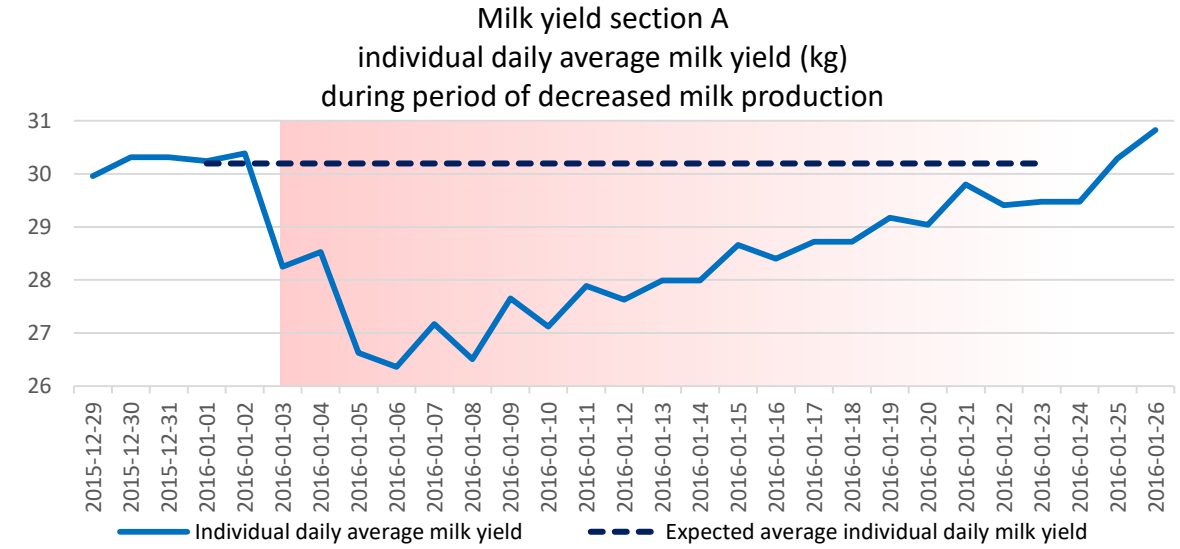

Figure 4. *Expected and actual individual daily average milk yield (IDAMY) in section A during the period of presumably decreased milk production, 2016-01-01 to 2016-01-23. The semi-transparent area represents the clinical phase of the outbreak, recorded to have started on 2016-01-03.*

The individual daily average milk yield (IDAMY), for the cows in section A, during the period of presumably decreased milk production was 28,34 kg/cow/day, 6,2% lower than the expected 30,20 kg/cow/day (Fig. 4). The lowest record of IDAMY was recorded on the same day as the day of lowest bulk milk amount, the 6th of January, 12,7% lower than expected. The most sick animals (the cows housed in the sick ward and some of the cows in the calving room) were not included in the IDAMY.

The number of cows in lactation was progressively increasing throughout the outbreak (Fig. 5). According to records made by the stable foreman the number of lactating cows increased from 219 to 239 between the 19th of December 2015 and the 22nd of January 2016, an increase of 9,3%. Due to difficulties to retrieve some data and lack of milk records of individuals housed in the sick ward and the calving room the total number of lactating cows for each day was not possible to determine with certainty. The number of cows housed in section A could on a daily basis be defined with certainty. During the period of presumed decreased milk production the number of cows in section A varied between 199 and 229. The lowest number, 199, was recorded on 6th of January, the same day as the lowest bulk milk amount was recorded.

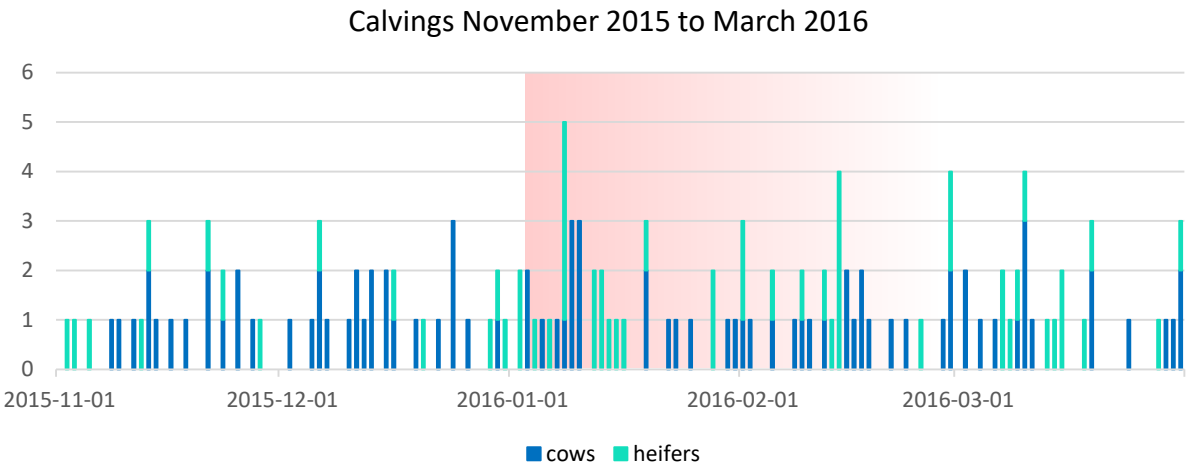

Figure 5. *Number of calvings per day in the herd from November 2015 to March 2016, divided upon heifers and cows. The semi-transparent area represents the clinical phase of the outbreak, recorded to have started on the 3rd of January 2016.*

In addition to the change in amount of bulk milk the milk quality changed during the outbreak. The fat content showed a visible increase during a period of little over a week starting on the day of the first recorded clinical case, the 3rd of January (Fig. 6). During the same period the protein content of the milk decreased (Fig. 6). The highest fat-protein-quota was recorded on the 5th-6th of January, dates corresponding with the lowest milk production. The highest fat-protein-quota was 1,44, 17,36% higher than during the reference period when the average was 1,23. Due to the Swedish price setting for milk, rewarding high fat-protein-quota, the increased fat-protein-quota was not economically negative to the farm. Compared to the reference level the somatic cell count was increased throughout the period of presumably decreased milk production. The somatic cell count average during the reference period was $126{,}5*10^3$ cells/ml. During the period of presumably decreased milk production the somatic cell count was on average $180{,}5*10^3$ cells/ml, 42,9% higher than during the reference period (Fig. 7). The missing values on the 1-2nd of January in the graph of somatic cell count are due to exclusion of abnormal values due to a measurement error ($30*10^3$ cells/ml). The increase in somatic cell count was not high enough to result in a decreased milk price. The milk loss during the period of presumably decreased production was estimated to a value of 23,234 SEK.

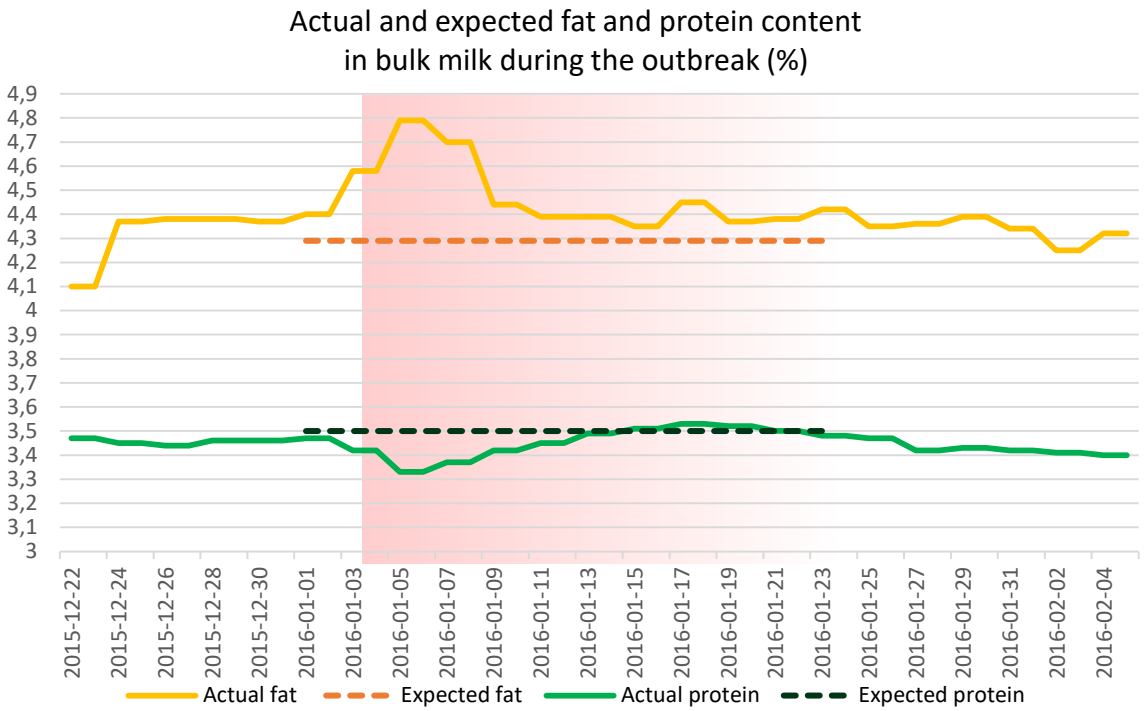

Figure 6. *Actual and expected fat and protein content (%) in bulk milk during the outbreak. The semi-transparent area represents the clinical phase of the outbreak, recorded to have started 2016-01-03.*

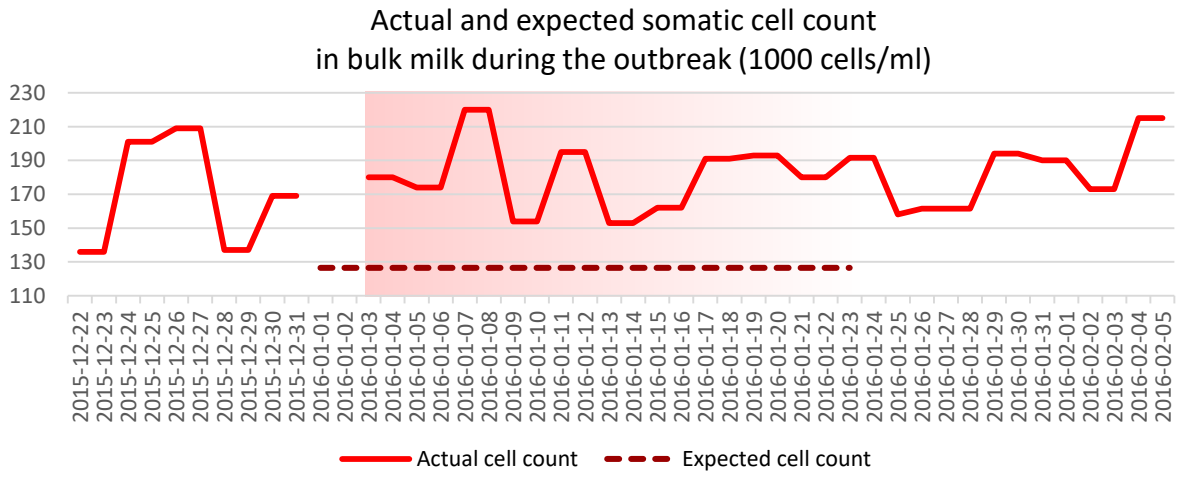

Figure 7. *Actual and expected somatic cell count in bulk milk during the outbreak (1000 cells/ml).*

Estimation of feed intake

Already before clinical signs of respiratory disease were detected the personnel on the farm noticed decreased appetite among the lactating animals in section A (Fig.10 and 12). For the estimations of feed consumption roughage and concentrate were analyzed separately. Due to varying degree of feed consumption records qualitative estimations could only be made for the animals in section A. For roughage consumption estimations could only be made for cows in milking group 1 and 2. Concentrate consumption could be estimated for all cows in section A.

On individual level roughage consumption was observed to decrease from the 1st of January, or up to three days before observed clinical signs of respiratory disease (Fig. 9). During the outbreak abnormally sunken paralumbar fossa was recorded in several animals within the milking groups. On the first day of the clinical phase of the outbreak, the 3rd of January, the average individual roughage consumption in milking group 1 and 2 reached its lowest value, 25,9% lower than during the reference period. The daily average decrease of roughage consumption within milking group 1 and 2 during the presumed period of decreased milk production was -3,62% per cow per day. The manually given roughage support feed, hay, that was distributed to facilitate feed intake in milking group 1 and 2 was estimated to roughly one kilo per cow per day during a one week-period starting on presumably the 6th of January. How much of the support feed that was eaten is not known, and therefore not included in the estimations.

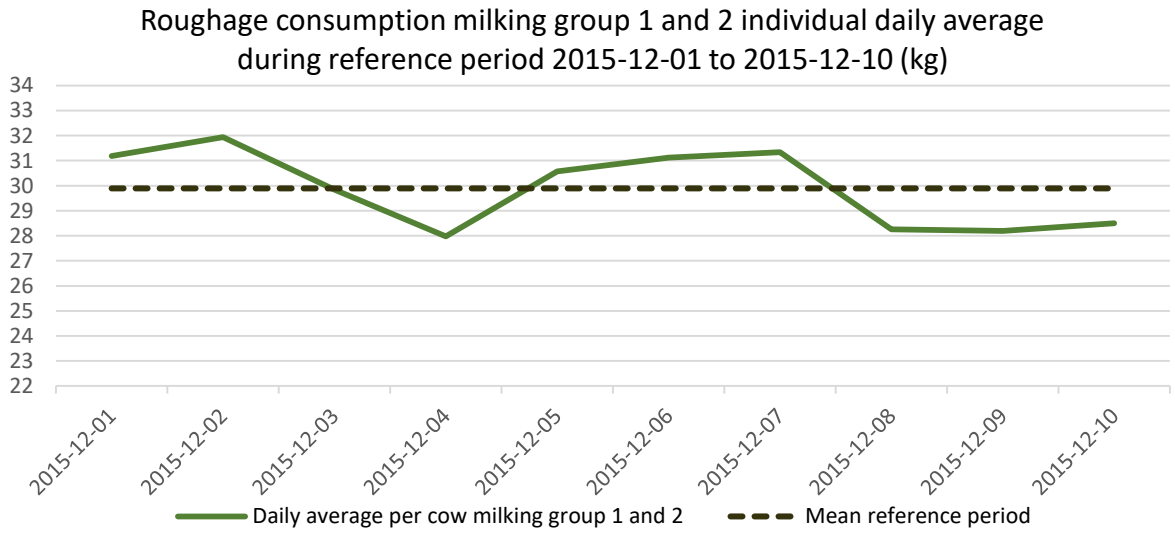

Figure 8. *Individual roughage consumption during (kg) reference period, 2015-12-01 to 2015-12-10.*

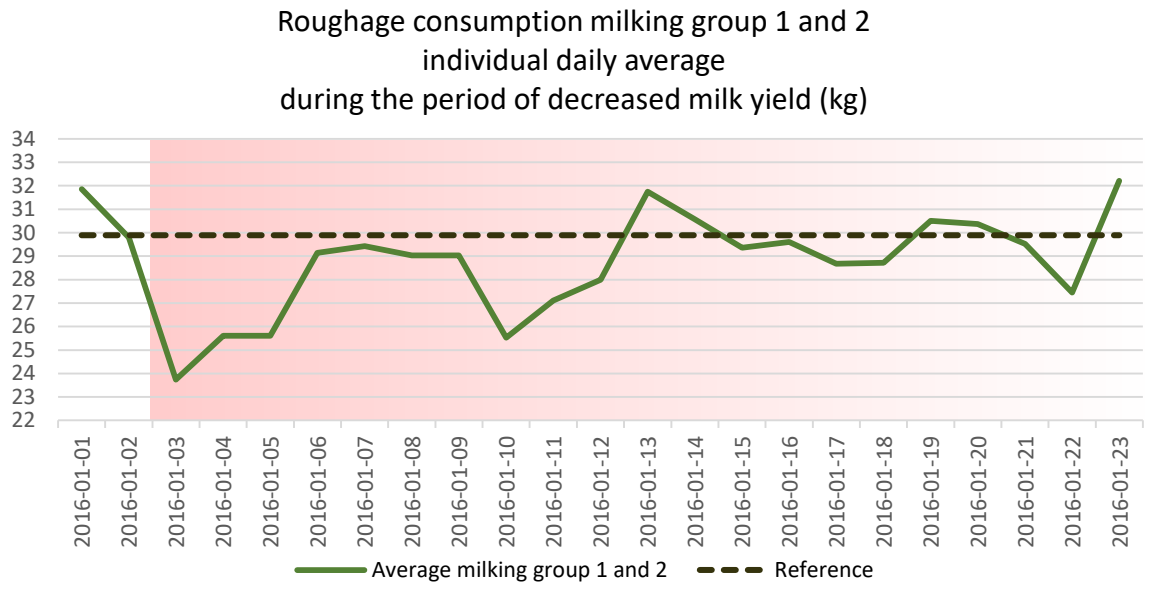

Figure 9. *Individual daily roughage consumption (kg) in milking group 1 and 2 during the period of presumably decreased milk production, 2016-01-01 to 2016-01-23.*

On the 24th of December, ten days before the first recorded clinical case, the concentrate consumption decreased in section A, both in terms of total consumption and individual average (Fig. 12). On the 2nd of January, one day before the first recorded clinical case, the consumption was observed to decrease further. It was not possible to correlate the first days of decreased concentrate consumption with clinical records of BRSV-infection on individual level. Neither could any correlation be found between the first days of decreased consumption and aggregation of drying offs (Fig. 5). The second phase of the concentration decrease could be correlated to clinical records of BRSV-infection. On individual level decreased concentrate consumption could be observed two days before recorded clinical signs, but not for all investigated individuals. The lowest individual daily average consumption was observed on the second day of the clinical phase of the outbreak, on the 4th of January. This day the individual average consumption was 4,53% lower than during the reference period. During the outbreak there was a higher proportion of animals in high production, due to early lactation, then during the reference period one month before the outbreak. Due to the composition of more high producing cows the individual daily average of concentrate consumption during the outbreak was expected to have been at least as high as the reference average (9,31 kg/cow/day), if the herd had not been affected by BRSV-infection (Fig. 10).

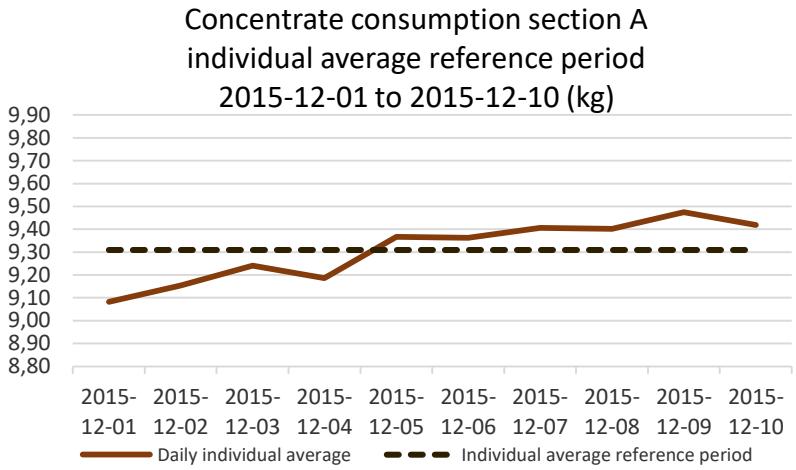

Figure 10. *Individual average concentrate consumption for cows housed in section A, milking group 1 to 4, during reference period, 2015-12-01 to 2015-12-10.*

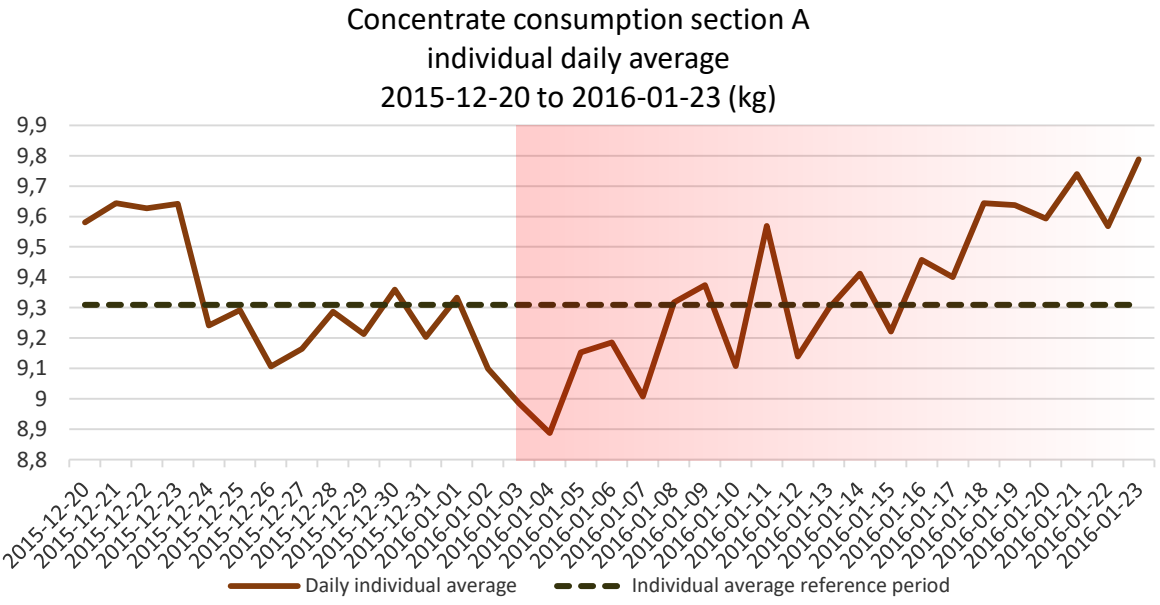

Figure 11. *Individual average concentrate consumption (kg) 2015-12-20 to 2016-01-23, compared to average consumption during reference period 2015-12-01 to 2015-12-10.*

For animals housed in the sick ward or the calving room there were no feed records. For animals in section B, due to the limited recording of feed intake, no feed-associated conclusions were possible to make. The appetite and feed consumption among the calves of two to six months of age was not possible to determine with certainty due to complicated recording system, errors in the recording system and loss of manually written health records. The hutch calves were in general recorded to maintain good appetite throughout the outbreak.

Overview of the estimated costs

The sum of the estimated budget items is 71464 SEK. Which rounded equals to 130 SEK per animal housed in the farm during the outbreak. Out of the investigated costs milk loss (23234 SEK, 32,5%), death (21000 SEK, 29,4%) and extra personnel (17112 SEK, 23,9%) were the three major budget items (61346 SEK, 85,8%) (Fig. 13). Veterinary cost (2656 SEK, 3,7%), medicine costs (5399 SEK, 7,6%) and costs for diagnostic tests (2063 SEK, 2,9%) were comparably small costs (Fig. 12).

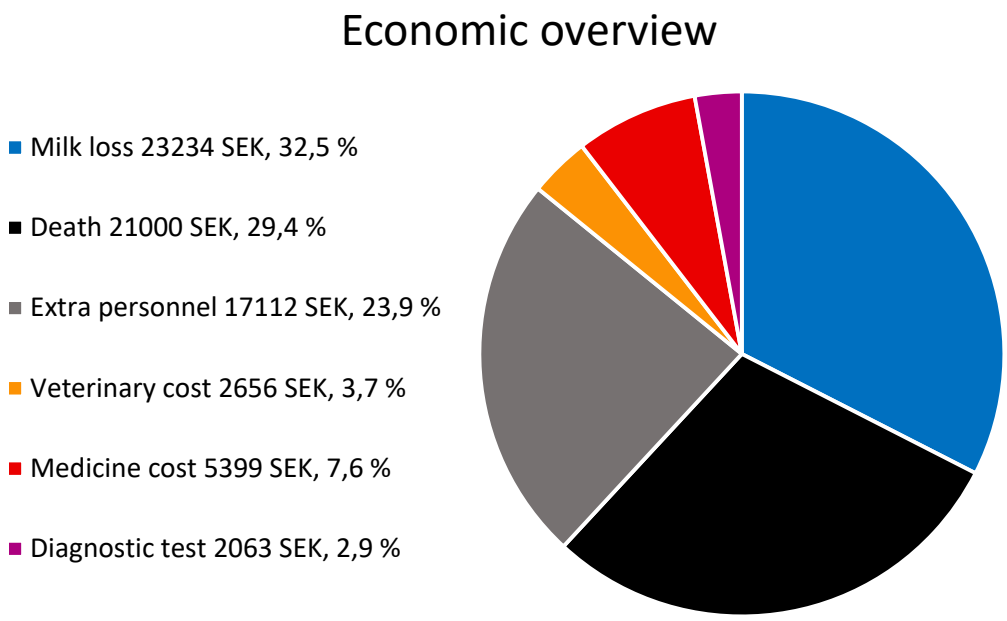

Figure 12. *Overview of the economic estimations.*

DISCUSSION

The total cost of the estimated factors of economic significance was 71,464 SEK, corresponding to about 130 SEK per animal. The main costs were due to milk loss (23,234 SEK, 32,5%), death (21,000 SEK, 29,4%) and extra labor (17,112 SEK, 23,9%). Diagnostic tests and treatment costs for veterinary service and drugs were comparably small expenses (10,118 SEK, 14,2%). However possible long-term consequences, such as reproduction disorders and reduced growth, have not been finished to be investigated and thus making the estimated cost of 71,464 SEK a likely underestimation.

Laboratory investigations carried out to determine the causative agent of the outbreak confirmed an ongoing BRSV infection and indicated the absence of other common respiratory pathogens. Based on several negative serum tests against BRSV-specific antibodies in young heifers on the farm during the last four years before the outbreak (data not shown), lack of BRSV-specific maternal antibodies in most young calves that were sampled during the outbreak and an overrepresentation of old cows in the treatment statistic, the herd immunity was assumed to have been low.

The outbreak occurred in January when the outdoor temperature reached down to -25 °C, and lasted for three to four weeks. At least two days before clinical signs of respiratory disease were detected the appetite among the animals decreased. Simultaneously or shortly later the milk production decreased. The outbreak started in the stable section of the milking cows. Within a week the outbreak had spread to the animals in the other stable sections in the main building. Within two weeks the disease had reached the calves in the outdoor hutches. The slow spread of the outbreak is believed to have been due to the stable sections being separated by walls and having separate ventilation and hygiene routines to minimize transmission between the animals. Another factor believed to have had an impact on the slowness of the spread, and also the degree of clinical signs, was the big air volume in the two major stable sections, section A and B, presumably keeping the concentration of virus particles low in the air and consequently the dose of exposure relatively low. Data suggests that there is a positive correlation between the level of exposure and the likelihood of a symptomatic infection (Kimman *et al.,* 1988). The degree of clinical signs varied. The most severely affected animal categories were the milking cows, the peripartum animals in the calving room and the two to six months old calves. Despite separate ventilation and heating in the rooms of the two to six months old calves there was a known problem of poor air quality in those rooms, possibly contributing to the high morbidity observed among the calves. The calves housed in the hutches were the seemingly least severely affected animals. The low degree of clinical illness among the hutch calves is speculated to mainly be due to probable lower infection pressure since the animals were kept outside and there was limited contact between animals. Though it should be noted that due to the cold weather the clinical signs of respiratory disease might have been undetected among the claves housed in the hutches. Calves housed in temperatures below their thermoneutral zone can be affected by cold stress and might as a consequence have a temperature dependent decreased rectal temperature hiding a pyrexia and a temperature dependent decreased respiratory rate hiding a tachypnea (Scibilia *et al.,* 1987).

The biggest loss for the farmer was due to the decrease in milk production. The milk production was reduced for at least three weeks. During these three weeks the bulk milk was decreased with 6,7%. The decrease was due to decreased individual milk yield, in addition to milk withdrawal for some of the treated cows and disposal of milk produced by the cows in the sick ward and sick cows in the calving room. The IDAMY was during the same period 6,2% lower than the expected, but since the most sick animals (housed in the sick ward and some in the calving room) were not included in the IDAMY the estimated IDAMY is expected to be an underestimation of the true IDAMY. The increased fat-protein quota is most likely a consequence of negative energy balance, as a result of the decreased appetite. The increase in somatic cell count is not necessarily only or directly due to the BRSV-infection, but also or more likely due to a higher proportion of cows being in early lactation and thereby in negative energy balance, which has been correlated to increased somatic cell count (Nyman *et al.,* 2008).

The second biggest cost for the farmer was the death of two cows. Compared to other outbreaks reported in literature, with a mortality up to 20% (Valarcher and Taylor, 2007), the mortality of this outbreak with 0,37% was comparably low. The third biggest cost for the farmer was the expenses for the extra labor. However, the estimated cost for extra labor is expected to be an underestimation, because the personnel proclaimed that their workload had been very big during the outbreak, likely causing costly secondary affects due to neglected management (Beaudeau *et al.,* 2010; Hägglund *et al.,* 2007). The veterinary cost was comparably small, but is believed to have been as low as it was because of the farm's status as a research farm providing access to veterinary service free of charge.

The observed decrease in feed consumption during the outbreak is most likely an underestimation since the most severely sick animals were not included in the estimation. The economic impact for the farmer of the decreased feed intake is debatable. The daily distribution of roughage did not decrease to the same extent as the daily intake, resulting in an increased waste of feed for the farmer. It is also likely that the sick animals had an increased maintenance energy requirement resulting in a proportionally higher feed cost in comparison to the production level. Since the concentrates were fed in automatic feeders the decreased concentrate consumption resulted in a decreased cost for the farmer in short term, but due to the at the same time decreased production the decreased cost can only partly result in a real decrease in cost.

The main challenge in illuminating this outbreak was that some aspects of the outbreak was only partly recorded, or not recorded at all. It was also difficult to retrospectively correlate existing data when information was missing. In conclusion the short-term effects of this outbreak were mainly characterized by milk loss, death and cost of extra labor. The results of this study indicate that feed consumption and milk yield can be used as early warning signs of an upcoming BRSV-outbreak, but further investigation is needed. Another aspect in the need of further investigation is the long-term effects of BRSV-infection, such as decreased growth and reproduction disorders. Decreased growth has previously been described as a consequence of BRSV-infection (Klem *et al.,* 2015) and so has abortion (Jacobsson *et al.,* 1989). In summary this study emphasizes the need of preventive measures to minimize the consequences of this virus, both in terms of animal suffering and financial burdens for the cattle farmer.

REFERENCES

Baker, J., Ames, T. & Markham, R. (1986). Seroepizootiologic study of bovine respiratory syncytial virus in a dairy herd. *American Journal of Veterinary Research,* 47**,** 240-245.

Beaudeau, F., Ohlson, A. & Emanuelson, U. (2010). Associations between bovine coronavirus and bovine respiratory syncytial virus infections and animal performance in Swedish dairy herds. *Journal of Dairy Science,* 93**,** 1523-1533.

Blodörn, K. (2015). *Development and evaluation of new generation vaccines against bovine respiratory syncytial virus.* Diss. Uppsala: Swedish University of Agricultural Sciences.

Brodersen, B. W. (2010). Bovine respiratory syncytial virus. *Veterinary Clinics of North America: Food Animal Practice,* 26**,** 323-333.

Bryson, D., Platten, M., Mcconnell, S. & Mcnulty, M. (1991). Ultrastructural features of lesions in bronchiolar epithelium in induced respiratory syncytial virus pneumonia of calves. *Veterinary Pathology,* 28**,** 293-299.

Castleman, W., Lay, J., Dubovi, E. & Slauson, D. (1985). Experimental bovine respiratory syncytial virus infection in conventional calves: light microscopic lesions, microbiology, and studies on lavaged lung cells. *American Journal of Veterinary Research,* 46**,** 547-553.

Deplanche, M., Lemaire, M., Mirandette, C., Bonnet, M., Schelcher, F. & Meyer, G. (2007). In vivo evidence for quasispecies distributions in the bovine respiratory syncytial virus genome. *Journal of General Virology,* 88**,** 1260-1265.

Ellis, J. A. (2017). How efficacious are vaccines against bovine respiratory syncytial virus in cattle? *Veterinary Microbiology,* 206**,** 59-68.

Elvander, M. (1996). Severe respiratory disease in dairy cows caused by infection with bovine respiratory syncytial virus. *Veterinary Record,* 138**,** 101-105.

Elvander, M., Edwards, S., Näslund, I. & Linde, N. (1995). Evaluation and application of an indirect ELISA for the detection of antibodies to bovine respiratory syncytial virus in milk, bulk milk, and serum. *Journal of Veterinary Diagnostic Investigation,* 7**,** 177-182.

Francoz, D., Buczinski, S. & Apley, M. (2012). Evidence related to the use of ancillary drugs in bovine respiratory disease (anti-inflammatory and others): are they justified or not? *Veterinary Clinics: Food Animal Practice,* 28**,** 23-38.

Fulton, R.W., Briggs, R.E., Payton, M.E., Confer, A.W., Saliki, J.T., Ridpath, J.F., Burge, L.J. & Duff, G.C. (2004). Maternally derived humoral immunity to bovine viral diarrhea virus (BVDV) 1a, BVDV1b, BVDV2, bovine herpesvirus-1, parainfluenza-3 virus bovine respiratory syncytial virus, Mannheimia haemolytica and Pasteurella multocida in beef calves, antibody decline by half-life studies and effect on response to vaccination. *Vaccine,* 22**,** 643-649.

Geerdink, R.J., Pillay, J., Meyaard, L. & Bont, L. (2015). Neutrophils in respiratory syncytial virus infection: A target for asthma prevention. *Journal of Allergy and Clinical Immunology,* 136**,** 838-847.

Gershwin, L. J. (2007). Bovine respiratory syncytial virus infection: immunopathogenic mechanisms. *Animal Health Research Reviews,* 8**,** 207-213.

Hall, C. B., Douglas Jr, R.G. & Geiman, J.M. (1980). Possible transmission by fomites of respiratory syncytial virus. *Journal of Infectious Diseases,* 141**,** 98-102.

Hägglund, S. (2005). *Epidemiology, detection and prevention of respiratory virus infections in Swedish cattle.* Diss. Uppsala: Swedish University of Agricultural Sciences.

Hägglund, S., Blodörn, K., Näslund, K., Vargmar, K., Lind, S.B., Mi, J., Araínga, M., Riffault, S., Taylor, G., Pringle, J. & Valarcher, J.-F. (2017). Proteome analysis of bronchoalveolar lavage from calves infected with bovine respiratory syncytial virus—Insights in pathogenesis and perspectives for new treatments. *PloS one,* 12**,** e0186594.

Hägglund, S., Hjort, M., Graham, D., Öhagen, P., Törnquist, M. & Alenius, S. (2007). A six-year study on respiratory viral infections in a bull testing facility. *The Veterinary Journal,* 173**,** 585-593.

Jacobsson, S., Alenius, S. & Nordstrom, S. (1989). Bovint Respiratoriskt Syncytialt Virus (BRSV) som orsak till pneumoni hos kor. *Svensk Veterinärtidning,* 41**,** 641-647.

Kimman, T., Straver, P. & Zimmer, G. (1989). Pathogenesis of naturally acquired bovine respiratory syncytial virus infection in calves: morphologic and serologic findings. *American Journal of Veterinary Research,* 50**,** 684-693.

Kimman, T., Westenbrink, F., Schreuder, B. & Straver, P. (1987). Local and systemic antibody response to bovine respiratory syncytial virus infection and reinfection in calves with and without maternal antibodies. *Journal of Clinical Microbiology,* 25**,** 1097-1106.

Kimman, T., Zimmer, G., Westenbrink, F., Mars, J. & van Leeuwen, E. (1988). Epidemiological study of bovine respiratory syncytial virus infections in calves: influence of maternal antibodies on the outcome of disease. *The Veterinary Record,* 123**,** 104-109.

Klem, T. B., Kjæstad, H. P., Kummen, E., Holen, H. & Stokstad, M. (2015). Bovine respiratory syncytial virus outbreak reduced bulls' weight gain and feed conversion for eight months in a Norwegian beef herd. *Acta Veterinaria Scandinavica,* 58**,** 8.

Larsen, L. E., Tjørnehøj, K. & Viuff, B. (2000). Extensive sequence divergence among bovine respiratory syncytial viruses isolated during recurrent outbreaks in closed herds. *Journal of Clinical Microbiology,* 38**,** 4222-4227.

Larsen, L. E., Tjørnehøj, K., Viuff, B., Jensen, N. & Uttenthal, Å. (1999). Diagnosis of enzootic pneumonia in Danish cattle: reverse transcription-polymerase chain reaction assay for detection of bovine respiratory syncytial virus in naturally and experimentally infected cattle. *Journal of Veterinary Diagnostic Investigation,* 11**,** 416-422.

Liu, L., Oza, S., Hogan, D., Chu, Y., Perin, J., Zhu, J., Lawn, J. E., Cousens, S., Mathers, C. & Black, R. E. (2016). Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *The Lancet,* 388**,** 3027-3035.

Lövsta. (2016). Resources at The Swedish Livestock Research Centre [booklet].

Mars, M., Bruschke, C. & van Oirschot, J. (1999). Airborne transmission of BHV1, BRSV, and BVDV among cattle is possible under experimental conditions. *Veterinary Microbiology,* 66**,** 197-207.

Murphy, F.A., Gibbs, E.P. J., Horzinek, M.C. & Studdert, M.J. (1999). *Veterinary Virology,* Academic Press.

Nair, H., Nokes, D.J., Gessner, B.D., Dherani, M., Madhi, S.A., Singleton, R.J., O'Brien, K.L., Roca, A., Wright, P.F. & Bruce, N. (2010). Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *The Lancet,* 375**,** 1545-1555.

Nygren, R. (2010). *En analys av foderkostnader i mjölkproduktion.* Swedish University of Agricultural Siences. Agronomprogrammet (Examensarbete 590).

Nyman, A.-K., Emanuelson, U., Holtenius, K., Ingvartsen, K. L., Larsen, T. & Waller, K. P. (2008). Metabolites and immune variables associated with somatic cell counts of primiparous dairy cows. *Journal of Dairy Science,* 91**,** 2996-3009.

Ohlson, A. (2014). Kartläggning av RS-virus på svenska mjölkgårdar. *I: Växa Sverige Djurhälso- och Utfodringskonferensen.* Sweden, 2014.

Ohlson, A., Heuer, C., Lockhart, C., Tråvén, M., Emanuelson, U. & Alenius, S. (2010). Risk factors for seropositivity to bovine coronavirus and bovine respiratory syncytial virus in dairy herds. *Veterinary Record,* 167**,** 201-207.

Oskarsson, M. & Engelbrekts, E. (2015). Kostnader for hälsostörningar hos mjölkkor [report]. Växa Sverige. http://djurvalfard.svenskmjolk.se/HTML/Ber%C3%A4kningar%20i%20H%C3%A4lsopaket%20mj%C3%B6lk%20Djurh%C3%A4lsokostnader.pdf.

Osorio, F.A., Anderson, G.A., Sanders, J. & Grotelueschen, D. (1989). Detection of bovine respiratory syncytial virus using a heterologous antigen-capture enzyme immunoassay. *Journal of Veterinary Diagnostic Investigation,* 1**,** 210-214.

Paccaud, M. & Jacquier, C. (1970). A respiratory syncytial virus of bovine origin. *Archiv für die gesamte Virusforschung,* 30**,** 327-342.

Quinting, B., Robert, B., Letellier, C., Boxus, M., Kerkhofs, P., Schynts, F. & Collard, A. (2007). Development of a 1-step enzyme-linked immunosorbent assay for the rapid diagnosis of bovine respiratory syncytial virus in postmortem specimens. *Journal of Veterinary Diagnostic Investigation,* 19**,** 238-243.

Rima, B., Collins, P., Easton, A., Fouchier, R., Kurath, G., Lamb, R.A., Lee, B., Maisner, A., Rota, P. & Wang, L. (2017). ICTV Virus taxonomy profile: Pneumoviridae. *Journal of General Virology,* 98**,** 2912-2913.

Sarmiento-Silva, R.E., Nakamura-Lopez, Y. & Vaughan, G. (2012). Epidemiology, molecular epidemiology and evolution of bovine respiratory syncytial virus. *Viruses,* 4**,** 3452-3467.

Scibilia, L., Muller, L., Kensinger, R., Sweeney, T. & Shellenberger, P. (1987). Effect of environmental temperature and dietary fat on growth and physiological responses of newborn calves. *Journal of Dairy Science,* 70**,** 1426-1433.

Shi, T., McAllister, D.A., O'Brien, K.L., Simoes, E.A., Madhi, S.A., Gessner, B.D., Polack, F.P., Balsells, E., Acacio, S. & Aguayo, C. (2017). Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *The Lancet,* 390**,** 946-958.

Smith, M.H., Frey, M. & Dierks, R. (1975). Isolation, characterization, and pathogenicity studies of a bovine respiratory syncytial virus. *Archives of Virology,* 47**,** 237-247.

Statens veterinärmedicinska anstalt (SVA). (2018). *Bovin virusdiarrévirus (BVDV)* [Online]. Available: http://www.sva.se/analyser-och-produkter/analyser-av-djur-och-foder/notkreatur/bovin-virusdiarrevirus-bvdv [Accessed 2018-02-05].

Stott, E., Thomas, L., Collins, A., Crouch, S., Jebbett, J., Smith, G., Luther, P. & Caswell, R. (1980). A survey of virus infections of the respiratory tract of cattle and their association with disease. *Epidemiology & Infection,* 85**,** 257-270.

Thomas, L., Stott, E., Collins, A., Crouch, S. & Jebbett, J. (1984). Infection of gnotobiotic calves with a bovine and human isolate of respiratory syncytial virus. Modification of the response by dexamethasone. *Archives of Virology,* 79**,** 67-77.

Uttenthal, A., Jensen, N. & Blom, J. (1996). Viral aetiology of enzootic pneumonia in Danish dairy herds: diagnostic tools and epidemiology. *Veterinary Record,* 139**,** 114-117.

Uttenthal, Å., Larsen, L.E., Philipsen, J.S., Tjørnehøj, K., Viuff, B., Nielsen, K.H. & Nielsen, T.K. (2000). Antibody dynamics in BRSV-infected Danish dairy herds as determined by isotype-specific immunoglobulins. *Veterinary Microbiology,* 76**,** 329-341.

Valarcher, J.-F., Bourhy, H., Gelfi, J. & Schelcher, F. (1999). Evaluation of a nested reverse transcription-PCR assay based on the nucleoprotein gene for diagnosis of spontaneous and experimental bovine respiratory syncytial virus infections. *Journal of Clinical Microbiology,* 37**,** 1858-1862.

Valarcher, J.-F., Schelcher, F. & Bourhy, H. (2000). Evolution of bovine respiratory syncytial virus. *Journal of Virology,* 74**,** 10714-10728.

Valarcher, J.-F. & Taylor, G. (2007). Bovine respiratory syncytial virus infection. *Veterinary Research,* 38**,** 153-180.

van der Fels-Klerx, H., Sørensen, J.T., Jalvingh, A. & Huirne, R. (2001). An economic model to calculate farm-specific losses due to bovine respiratory disease in dairy heifers. *Preventive Veterinary Medicine,* 51**,** 75-94.

van Der Poel, W., Brand, A., Kramps, J. & van Oirschot, J. (1994). Respiratory syncytial virus infections in human beings and in cattle. *Journal of Infection,* 29**,** 215-228.

Wellemans, G. (1990). Bovine respiratory syncytial virus. *Virus Infections of Ruminants. Elsevier, Amsterdam***,** 363-375.

Verhoeff, J. & van Nieuwstadt, A. (1984). BRS virus, PI3 virus and BHV1 infections of young stock on self-contained dairy farms: epidemiological and clinical findings. *The Veterinary Record,* 114**,** 288-293.

Viuff, B., Tjørnehøj, K., Larsen, L. E., Røntved, C. M., Uttenthal, Å., Rønsholt, L. & Alexandersen, S. (2002). Replication and clearance of respiratory syncytial virus: apoptosis is an important pathway of virus clearance after experimental infection with bovine respiratory syncytial virus. *The American Journal of Pathology,* 161**,** 2195-2207.

Wright, P.F., Cutts, F.T. & World Health Organization. (2000). *Generic protocol to examine the incidence of lower respiratory infection due to respiratory syncytial virus in children less than five years of age: field test version.* Geneva : World Health Organization. http://www.who.int/iris/handle/10665/66276

XE. (2018). *Current and Historical Rate Tables* [Online]. Available: http://www.xe.com/currencytables/?from=SEK&date=2016-01-01 [Accessed 2018-02-06].