Summary
The current knowledge on border disease in goats is reviewed. The entity is caused by pestivirus. Such infection occurs naturally in goats, particularly in cattle, but also in pigs and captive and free-ranging ruminants. The viral agent, epidemiology, clinicopathological lesions, pathogenesis, diagnosis and control are discussed.

Introduction
Border disease (BD) was first described and reported as a clinicopathological entity in sheep in Great Britain in 1959 [1]. The condition was endemic in the border counties between England and Wales, which explains the name border disease. Synonyms are "hairy shaker disease" and "fuzzy-lamb syndrome", as some BD lambs show characteristic signs of body tremors and/or hairiness. This syndrome in sheep is induced by pestivirus and can be defined as a congenital, teratogenic infection [2-4]. In cattle, pestivirus-induced disease was first described in 1946 in the USA [5]. In this species, pestivirus infections can result in a variety of clinical and pathological conditions. However, the most common infection in both species develops without any signs [6]. The causal virus was first isolated and identified in 1954 as a pestivirus in cattle [7]. The occurrence of pestivirus infections in cattle and sheep is distributed world-wide, particularly in cattle, with a prevalence rate of neutralizing antibodies as high as 50 to 90 percent in several countries.

Pestivirus infections in pigs, causing classical swine fever or the synonymous hog cholera, were reported as early as the 1930's in the USA (cited by Liess [8]). The pestivirus responsible for swine fever infects only porcine species. In latter years, from the sixties onwards, natural infections with ruminant pestiviruses have been detected in several other animal species such as goats, captive and free-ranging ruminants and also in pigs. Experimental infections in these species have been studied to some extent.

The Viral Agent
The genus Pestivirus is allocated in the family Flaviviridae [9-11]. Pestiviruses include ruminant strains which are closely related, and also the swine fever virus in pigs which is related to the ruminant strains to a lesser extent [12-14]. Isolates from different ruminants are able to infect a wide range of different cells in culture. Isolates can infect spontaneously across the ruminant species barriers, and are also able to infect pigs [15-17], while porcine CSF-strains seem to be species restricted [18]. Pestivirus in goats are isolated only on a few occasions [19-22] and there are only a few reports describing isolates from not-domestic ruminants [23,24]. Pestiviruses isolated from cattle, sheep and pigs are from a single goat strain have been genetically characterised to some extent [22,25]. Such isolates demonstrate great antigenic diversity, which is found both within and between ovine and bovine isolates. However, this finding cannot be defined in conventional terms of species. Pestiviruses from ruminants have been suggested to taxonomically comprise one single virus species [4,14,26]. Examinations by radio-immunoprecipitation of homologous polypeptides from ovine and bovine pestiviruses, [27] and analysis using monoclonal antibodies [28], have confirmed their structural relation. Panels of monoclonal antibodies against pestiviruses have been used to differentiate and characterize different pestivirus isolates [29,30]. In spite of this close relationship, ruminant pestiviruses are increasingly considered to comprise distinct entities [15].
In cell culture, ruminant pestiviruses appear as two biotypes, cytopathogenic or non-cytopathogenic. Fetal infection, and the ensuing persistent infection (pi) in the progeny, are suggested to be a feature of the...
non-cytopathogenic virus only. The cytopathogenic type may also be recovered from cases of the bovine clinicopathological mucosal disease [31,32]. Both biotypes have been isolated in bovines, while ovine strains appear almost exclusively to be non-cytopathogenic [33-35].

Epidemiology
Spontaneous BD in goats with BD-like signs has been reported in only one case, in addition to some outbreaks of reproductive failure [19-21,36] and weak-born kids [22]. The BD case was a new-born kid presenting central nervous system (CNS) signs [37]. Pestivirus has been isolated from only a few naturally infected goats. The virus has also been recovered from a few aborted fetuses, from three stillborn and two weak-born kids in other outbreaks and from three kids with pathological lesions suggesting other illnesses [19-22,36,38]. Pestiviruses have not been recovered from healthy goats. However, goats have been successfully infected with bovine, ovine or porcine pestiviruses under experimental conditions [16,39-43].
The routes by which goats are infected with ruminant pestiviruses are not known. As in sheep and cattle, the infection in goats is likely to occur through several routes, although the oronasal route is probably the most common in natural dissemination [4,44]. Parenteral transmission of pestiviruses poses a serious risk given the methods for treatment administration used in the field. Virused can easily spread when needles are not changed between injection of a pi animal and susceptible ones. The pi animal may be healthy or show no characteristic signs of disease, and may or may not be of the same species. This is particularly relevant with mass vaccination, a common practice in goats. Modified, non-inactivated vaccines represent a particular risk and have been reported as responsible for several field outbreaks. Pestiviruses may also spread by ear-tagging, castration and oral infusion, and even through rectal examination using gloves contaminated with feces from a pi animal [45].
Serological surveys in many countries in all continents, have demonstrated widespread natural infection of pestiviruses in goats [46]. The first report was from Senegal in 1971 [47]. Investigations of neutralising antibodies against cytopathogenic bovine strains have shown considerable variation between herds and geographical location (local and regional), ranging from zero up to 50 per cent. The overall prevalence rate found for populations in large areas is mostly found between 2 and 25 per cent. These findings are comparable to similar surveys in sheep, but results are low compared to those in cattle. There is no evidence that breed or gender influences susceptibility. There is much variation in neutralizing antibody titres, levels reaching up to 1:4000 [48]. An antibody titre is influenced by the antigenic homology between the test and the field virus.
Experimental infections of mature goats induced an immunological response with demonstrable neutralizing antibodies within 2 - 5 weeks of infection. Neutralizing antibodies remained detectable for 4 years in all animals still alive [48]. These results are in accordance with those reported in cattle and sheep. Parenteral inoculation with bovine or ovine strains of new-born kids demonstrated a similar immunological response. Kids showed impaired growth rate, but no other signs [49].
Acutely infected goats do not usually transmit pestiviruses to other animals, as occurs in cattle and sheep. However, susceptible goats have been easily infected during cohabitation with pi animals [19,48]. Experiments in pregnant goats showed that the infection can spread transplacentally to the fetus. Infected progeny was delivered, and kids were highly contagious to other goats with which they were in contact and to susceptible animals of other species [49]. The survival rate of the infected conceptus has been found to vary but is mostly very low under experimental conditions when infected early in gestation [39,50,51]. In natural infections, few pi kids are liveborn following maternal infection. It seems therefore, fairly reasonable to suggest that pi sheep and particularly cattle, are the main reservoir of pestiviruses that infect goats.
Experimental pestivirus infections have not been studied extensively this species. Parenteral infections have induced no signs apart from reproductive failure, which is reported to occur frequently when infection occurs before 60 days of pregnancy. Ultrasound examination has shown that most abortions occur a few days after fetal death [51], which is different from findings in sheep [52,53]. One study found that severely infected lambs were still alive until a few days before parturition [51].
Following the use of an orf vaccine contaminated with a pestivirus of unknown origin resulted in an extensive outbreak of BD in 276 pregnant goats [48]. The incidence of goats showing reproductive failure was 82 per cent overall, with herd incidence rates ranging from 79 to 96 per cent. Failure was manifested by barrenness, abortion and birth of dead or weak kids. None of the young showed characteristic signs of BD. Non-cytopathogenic pestiviruses were demonstrated in weak and apparently healthy new-born kids.
Clinicopathological Lesions

Few reports describe clinicopathological lesions in naturally or experimentally infected goats. The descriptions agree with those reported in sheep and cattle. After natural post-natal infection with pestivirus, reproductive failure and affected progeny are the only reported features. In experiments, new-born kids parenterally infected with bovine or ovine pestiviruses showed no signs of disease or gross lesions, but had a lower mean growth rate [49]. Significant histological changes were restricted largely to hypercellular foci and mild perivascular cell infiltration in the white matter of CNS.

Congenital pestivirus-induced signs and lesions have been reported in several caprine cases. Spontaneous significant BD has so far been reported in one kid only, in addition to some cases of still- and weak-born kids and aborted fetuses. The BD kid, that had similar signs to those characteristic of ovine BD, had severe body tremors from birth onwards and was able to rise and walk only with difficulty [37]. The kid was of normal size and shape, showed normal teat seeking activity and suckled vigorously when assisted. No abnormality in the birth coat was seen. The tremors later worsened and the kid was euthanized four days after birth. No gross lesions were revealed at the post-mortem examination. Histopathological changes were confined to the brain and spinal cord and included decreased affinity for myelin stains, hypergliosis and vasculitis. Lesions were especially pronounced in the white matter of the cerebrum and the cerebellum. In three aborted kids infected with pestiviruses, two kids had arthrogryposis and one had a cleft palate [20]. Two weak-born kids in different flocks showed enteric signs and died during the first week of life, demonstrating post-mortem hypomyelination in the brain and lymphoid depletion in the thymus [22]. In another outbreak of abortions, histopathological brain lesions suggestive of BD were not further described [36]. Pestivirus was also isolated from the lung of a kid with pneumonia [38]. Most of these clinicopathological findings agree with those found in experimental pestivirus infections in goats, and also with findings in experimental and natural ovine cases.

Experiments in pregnant goats have demonstrated that the caprine conceptus is highly susceptible to pestivirus infection [39,42,50,51]. One study demonstrated severe necrotizing carunculitis which developed between 10 and 30 days after inoculation, and which could well account for the high rate of abortion. The effect of the virus on the caprine fetus seems to be similar to the effect on the ovine and bovine fetus. However, when infected early in gestation, goats have shown a particularly high fetal mortality. Reports from such experiments described reproductive failure in a large proportion of animals, including early fetal death with possible absorption, abortion, birth of dead or weak-born kids, malformations, and also apparently normal offspring that were persistently infected. Some infected goats had fetal fluid production with no conceptus in late gestation. This finding is not uncommon in goats [54]. Small and markedly decomposed fetuses and placental remains with up to 4.2 litres of turbid fetal fluid in the uterus were found in some animals. Normal alertness and viability were reported in some affected kids, with varying degrees of the characteristic body tremors or ataxia, which became more intense upon handling. These signs were comparable to those in typical BD lambs and the single reported spontaneous BD kid. Hairiness and microscopical changes in hair follicles have not been described in goats [55]. Twins from the same pair have been found to be affected differently, such as one being stillborn or weak-born with severe lesions and the other being normal. Principal histological changes in the CNS comprised cerebral white matter necroses, cerebellar dysplasia, hypercellular areas in the white matter, and lymphocytic perivascular infiltrations. Several kids had lesions of more than one type. Dysplastic changes of the cerebellar cortex have been observed in aborted fetuses, in weak-born kids and in viable kids. These changes included disorganization of all cortical layers. Hypercellular areas in the white matter exhibited a decreased affinity for myelin stains. Mostly non-cytopathogenic pestiviruses were isolated from clinically and/or pathologically affected kids, however, cytopathogenic viruses have also been isolated from experimentally infected fetuses [42]. Viruses were found in two healthy pi kids at slaughter at two months and two years of age, respectively [51]. All pi kids infected with pestiviruses were negative for neutralizing antibodies at birth, while some other transplacentally infected kids were positive before uptake of colostrum.

Pathogenesis

Epidemiological investigations and clinicopathological findings indicate that the pathogenesis of the pestivirus syndrome in goats is comparable to that in sheep and cattle. Infection of healthy immunologically-competent and susceptible animals with pestiviruses is mostly short-lived and only occasionally results in disease at all. In pregnant females, pestiviruses spread through the circulation to different tissues and organs including the uterus, where it crosses the placenta and reaches the conceptus. Transplacental pestivirus infection may induce severe and fatal lesions in the fetus. Some offsprings that survive the infection, become by a specific and still partly unknown pathogenesis, persistent producers and excreters of the virus.
Ovine and bovine blastocysts (16 and 30 days respectively) are refractory to infection by pestiviruses. This is the period before the embryo implants in the uterus [56,57]. Indications of a similar refractory period to pestiviruses have been reported in goats [51]. During the preimplantation period, the embryo may be protected from the virus by the intact zona pellucida and the lack of intimate contact with the uterine mucosa [53,58].

The outcome of a fetal infection with pestivirus depends particularly on the gestational age at which infection occurs. The fetus can first respond immunologically to the virus after it gains immunological competence. In goats immunological competence seems to occur 20 days later than in sheep corresponding to about 80 to 100 days of gestation [39,51]. After this stage of development, the virus is likely to be controlled and subsequently eliminated by a specific immune response of the fetus. At an early gestational age, prior to immunological competence, the immune system will not be able to respond in an effectively mature manner and the virus is able to persist. Early infected individuals that survive beyond the phase of immune competence development, will develop a specific immune tolerance to pestiviruses. The immune apparatus in such animals will consequently never respond against this particular agent [59]. This type of immune tolerance persists throughout life and is a prerequisite for persistence of the infection [3]. Experiments in pregnant goats indicate that infection with pestiviruses before the time of immune competence, results in a fetal death rate of up to 100 per cent. This would result in a very low prevalence of pi goats.

Fetuses infected transplacentally with pestiviruses prior to immunological competence, will likely die due to the uncontrolled virus infection. That seems to be particularly true in goats. Resorption of the embryo may follow an early death, inducing regression of the corpus luteum and return to estrus in the dam. It has been reported that in goats as in sheep, one infected fetus may die and be resorbed or mummified, while a twin-progeny or litter mates survive and may be born normal. As in sheep and cattle, the factors which influence the outcome of intrauterine infections, ranging from early fetal death to the birth of apparently normal but pi offspring, have not been fully elucidated [46,60]. Pestiviruses and associated virus antigens have been demonstrated in several organs of pi goats, same as in pi sheep and cattle [3,35], indicating a generalised infection. In BD lambs, the infection is considered to be a likely cause of thyroid hormone deficiency [61-63], which may influence several processes and cause retardation in the development of several tissues [57,64]. These clinical findings has not been investigated in the goat. In the CNS of BD lambs, the virus is stated to affect cell differentiation, which in turn affects the process of myelination of the axons resulting in myelin dysgenesis, including myelin deficiency, abnormal chemical composition, and probably degeneration. This dysmyelination is reported to strongly influence the characteristic tremors in BD lambs [2], while congenital tremors in piglets induced by swine fever virus are reported to be associated with cerebellar hypo-/dysplasia [18]. The pathogenesis of such changes in goats infected with pestiviruses is not known.

Maternal pestivirus antibodies received via colostrum in pi animals wane during the weeks following birth, as is the case in all domestic ruminants and pigs. Such antibodies will persist considerably longer in non-pi offsprings, the actual period of time being correlated to the amount of antibodies received [65]. These passively acquired antibodies (in sheep and goats) do not seem to influence the persistence of the virus.

Cytopathogenic pestiviruses were recovered from the gut of sheep that developed a syndrome similar to mucosal disease in cattle [66]. A tentative pathogenesis of this disease includes super-infection with a cytopathogenetic strain which is homologous to the primary persistent non-cytopathogenic virus [32,66]. Mucosal disease-like cases in goats have not been reported.

**Diagnosis**

Very few cases of natural pestivirus-induced disease have been reported in goats, in spite of a high prevalence rate of the infection in some populations. However, in cattle and sheep, a high proportion of pi animals show uncharacteristic signs or none at all. Indeed, the range of signs is broad and often diffuse, making a diagnosis on clinical grounds difficult and highly tentative. The criteria on which suspicion of pestivirus-induced disease can be based include: reproductive failure, (particularly the history of the flock), congenital signs associated with changes in the CNS, poor growth and viability of offsprings, and late onset of mucosal disease.

Virological and serological examinations might give an ultimate diagnosis in a suspect case [44], and are obviously necessary to confirm a clinical and/or pathological diagnosis. Virological tests include detection of viral antigens by immunofluorescence [67,68] or immunoperoxidase techniques, which comprise different ELISAs [69,70], and virus isolation in susceptible cell cultures [67]. Antigen detection is performed on sections of frozen or fixed tissue, or infected cell cultures. Tissue specimens for testing for pi animals may be taken from a wide range of tissues/organs [4,71]. Nasal swabs for production of cell
smears, with subsequent preparation and detection of pestivirus by the mentioned methods has proven to be a practical approach. An ELISA for detection of pestivirus in ovine or bovine blood leucocytes has been developed [72], which would probably also be suitable for testing of samples from goats. This test has proven to be practical for the screening of large numbers of animals [72,73]. High-quality polyclonal antiserum or specific monoclonal antibodies against the pestivirus are essential for a reliable diagnosis using these assays. The use of polymerase chain reaction to detect pestiviruses in clinical specimens from cattle has been reported by several groups. This technique is extremely sensitive, and may be used also to test for pestivirus in other animal species. The test requires rigorous quality control to avoid false positive results. However, the adaptation of this technique for routine testing of clinical samples does not yet appear to be practical [44]. In situ hybridisation is another novel technique that may be used for direct detection of pestiviruses in infected cells. So far, this method has also been largely used only as a research tool, and is not adapted for routine diagnostic work [74]. Examination for antibodies can be performed by different methods, although virus neutralization tests are most sensitive and accurate for quantitative evaluation. Serological testing for pestivirus infections, like virological examination, is nowadays largely based on different modifications of the ELISA assay.

Control

Consequences for Control Program in Domestic Ruminants

Natural infections with pestiviruses in goats do not appear to be a problem, and do not usually require any systematic control. Nevertheless it might be worthwhile to prevent the introduction of pestiviruses in an animal population and reduce the risk of the ensuing disease. This is particularly relevant during early gestation in females. In this respect, it should be emphasized that pi cattle may be effective transmitters to other species, goats included. Care should also be taken not to transmit the virus iatrogenically, for example by the use of contaminated vaccines or by the use of contaminated instruments. In occasional outbreaks there may be a need to prevent new cases from occurring. In such cases, virological and serological testing should be considered to identify and dispose of pi animals.

In some countries, pestivirus vaccines are licensed for use in cattle. If critical evaluation of such vaccines provides good evidence of protection, their use in goats could be considered [75]. The failure of vaccines to protect against pestiviruses occurs because of low cross-protection between vaccine strains and local field viruses. Such problems seem particularly relevant when vaccines are to be used in populations where the virus reservoirs are not domestic ruminants.

Programs for the control of pestivirus infections and subsequent disease in cattle have been established in some countries, through the identification and disposal of pi bovines [76]. Persistently infected cattle are clearly the main virus reservoir, and are also responsible of interspecies transmissions, which seems to occur easily. However, pi animals of other species have also been shown to be possible sources of bovine infection [16,77]. Close contact is probably a prerequisite for virus transmission. Goats could be virus carriers able to spread pestiviruses back to susceptible cattle [19]. Such "backwards" transmission to cattle is considered to be very rare, but could be significant if and when bovine infections are successfully controlled. Interspecies pestivirus dissemination to susceptible cattle populations would be very harmful and costly, and must be avoided by all means.

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