# Current Knowledge of the BVD Syndrome of Cattle: Agent, Immune Response, Course and Spread, Control

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## Introduction

Bovine Virus Diarrhea/Mucosal Disease (BVD/MD or BVD) has been recognized both clinically and pathologically as one of the viral diseases affecting the digestive system of young cattle since 1946/53 in the U.S.A. (53,57) and since 1959 in the Federal Republic of Germany (30,62,68,69,70, 72). Since that time numerous experimental investigations and practical observations have shown that the causative agent of BVD can also affect or be carried by newborn calves and non-immune adult animals, and can infect embryos and fetuses in utero (9,10a,14a,21,22,29,32,37,40,44,54,56,61,63, 71). The disease picture seen in such cases deviates more or less strongly from the one seen in classical BVD. Therefore the practitioner presented with one of these cases does not always think of a causal relation with the BVD virus. Investigators have chosen the term "BVD-Syndrome" for the clinical and subclinical effects resulting from this agent. Further effects of this agent, which have possibly yet to be proven or discovered, can be included within this term.

The following presentation attempts to give a summary overview of the wealth of facts and assumptions which are available in the literature on the BVD syndrome. Some of the author's own opinions will be added. The first of these concerns itself with the often heard opinion that the nature of bovine virus diarrhea has changed completely in recent years. In light of the biological laws which viruses and the diseases they cause "obey", such a "fundamental change" hardly seems conceivable. The author is convinced that we are more often deceived by the rapidly accumulating knowledge of the life cycle and pathogenicity of the BVD virus as well as the response of cattle to this agent, and by the diagnosis of BVD-virus-caused disease or injury being made far more frequently than before because of the improved, more routinely applied methods of investigation (see table 1). We see a situation, which was always present, as "new" or "changed", because before it was not "apparent" to the degree it is now. Additionally, changes in cattle management and in the movement of animals may likewise have played a certain role.

### *Agent*

The BVD virus (of the genus Pestivirus in the family Togaviridae) is an enveloped RNA virus antigenically related to the hog cholera virus, with worldwide distribution and high infectivity. It can invade only susceptible (non-immune) individuals, and primarily their lymphoreticular tissues including the circulating lymphocytes ("mononuclear phagocyte system") (6,22,29,37,44,50,58,59,61,67). There are several biotypes and variants which differ from one another in their antigenic properties, as well as cell-culture-pathogenic and non-pathogenic field stains of the BVD virus. Their disease producing efficacy in cattle seems to be fairly uniform (or dependent upon other factors). There is also a series of attenuated field strains of the BVD virus (22, 29,31,47,58,60,67).

The BVD virus is found not only in domestic cattle, but also in sheep, goats and wild ruminants—for whom it is also pathogenic (9,29,73)—as well as in swine (17,18). The virus is also shed by these species (17,29). Still, cattle are regarded as the main carrier, including both clinically ill animals and those more or less healthy appearing virus carriers and shedders which are to be discussed more fully (9,13,22,25, 29,37,40,44,58). Spread occurs via virus-containing nasal secretions, saliva, blood, feces and/or urine (possibly also via sperm, uterine secretions, amnionic fluid, or afterbirth that contains virus; (1,2,10,40,50,59,74), by direct contact or via animate or inanimate vectors (human and animal traffic, equipment, feed; 29). As a rule the BVD virus is ingested or agent-containing droplets are inhaled; the calf in utero can be infected transplacentally (2,6,9,29,50). Oral, nasal, intratracheal, intravenous, intramuscular, and intrauterine administration have been chosen and proven as experimental routs of infection. Fetuses have been either infected via the mother, through the placentomes, or directly (intraamnionally, intramuscularly, or intraperi-toneally) (1,2,4,5,11,37,50,59,74,75). The artificial inoculation of BVD virus also produces manifest disease only in susceptible individuals (thus only seldomly except in appropriately selected experimental animals; see "Immune Events"). Regardless of the site of inoculation it results in viremic multiplication and spread of the agent within the host and then to injury of the sensitive organs. In postnatal life this includes primarily the mucosae of the digestive system (9,29,30,53,57,62), but includes lungs, skin, central nervous system, eyes and thymus during certain phases of intrau-

terin development of (5,6,11,15,28,29,32,71). Detection of BVD virus is done mainly with immunofluorescence techniques (9,29,36,59,60).

TABLE 1. Overview of the clinical, gross post mortem, and virologic findings from 44 patients admitted to the Hannover Cattle Clinic in 1982 with symptoms corresponding to BVD* or simply with diarrhea (Average Age: 13 months [2 days to 6 years]). Notice the increasing percentage of BVD-positive results in this order.

| Clinical findings* | Gross Post Mortem Findings** | Virologic Findings*** |
|---|---|---|
| 7 × +: | 5 × +: | 4× + |
| | | 1 × n.e. |
| | 1 × −: | 1 × − |
| | 1 × n.e.: | 1 × + |
| 27 × ?: | 15 × +: | 11 × + |
| | | 4 × − |
| | 2 × −: | 1 × − |
| | | 1 × n.e. |
| | 10 × n.e.: | 3 × + |
| | | 5 × − |
| | | 2 × n.e. |
| 10 × −: | 1 × +: | 1 × + |
| | 4 × −: | 1 × + |
| | | 3 × − |
| | 5 × n.e.: | 2 × + |
| | | 3 × − |
| 15.9% + | 47.8% + | 52.2% + |
| 61.4% ? | 15.9% − | 38.8% − |
| 22.7% − | 36.3% n.e. | 9.0% n.e. |

Explanation of symbols:

* = diarrhea, erosions in the mouth and/or interdigital space
** = erosive - inflamed lesions in the gastro-intestinal tract, especially the mouth, pharynx, and/or esophagus
*** = identification of the BVD virus in biopsy samples of nasal or oral mucosae or in post mortem samples of pharyngeal lymph nodes
\+ = positive finding
− = negative finding
? = suspicious finding
n.e. = not examined

Footnote: Thanks to Ms. B. Lehmann (candidate for degree of Dr. med. vet.)

*Immune Events*

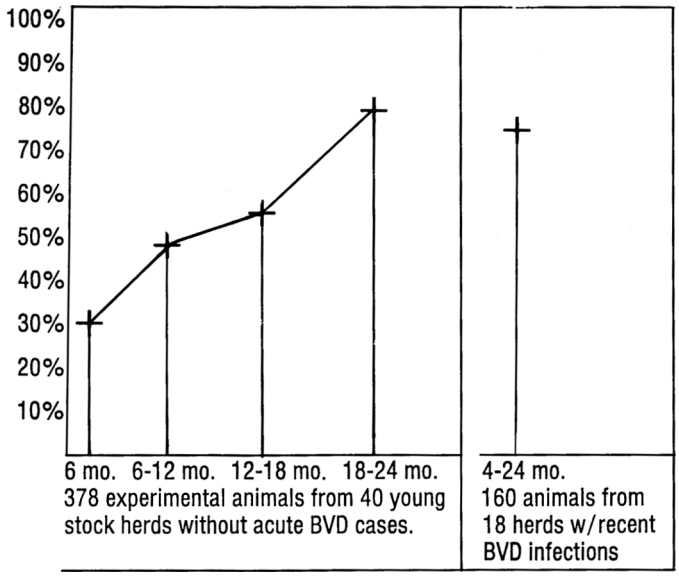
The presence of virus neutralizing antibodies in the serum (SNA) is generally considered as evidence, but less as a measure, of the resistance of the individual animal to the BVD virus (9, 10a, 14a, 29, 37, 39, 58, 60, 61, 64). A distinction is made between passive maternal antibodies, which have been acquired by timely intake of antibody-containing colostrum, and actively developed antibodies, which have been produced by the animal itself in the course of a BVD virus infection. The former is contained in the colostrum of cows which have undergone and survived a BVD infection and whose serum therefore has SNA against this agent. These maternal antibodies are detectable in the serum of their colostrum-fed calves for at least 3, usually for 6 to 9, and occasionally for up to even 18 months, after which they return to concentrations no longer serologically measurable (3,9,26,29,39,58). During this time such animals are considered to be protected against a BVD virus-caused disease, and upon possible contact with the agent develop their own active SNA in the course of a clinically asymtomatic or mildly symptomatic period (= "silent protection"; 9, 26, 29, 37, 39, 58). This type of active antibody production is apparently still often possible when the titer of maternal SNA has already declined to levels unmeasurable by laboratory means (9,11,13,29,39,64,74). Actively acquired SNA usually remains with the affected animal for life, with a minor and slow decrease in the titer (26,60). Re-newed contact with the BVD virus leads to a marked increase in titer when the initial SNA titer is low ("Booster Effect"), but usually does not appreciably influence an already high titer (9,44,74).

The ubiquitous spread of BVD virus and the occurrence of silent (latently affected) or chronically ill carriers and shedders create a situation where the percentage of cattle whose serum contains actively acquired BVD-SNA becomes greater with increasing age and reaches 70 to 90% in adult animals (9,27,29,37,61). The age distribution, presented in Figure 1, of BVD-SNA positive animals from "normal" herds (61) shows that the immunization caused by the BVD field virus in the form of a "silent protection" often still shows up (instead of illness) when no serologically demonstrable titer of maternal SNA was present at the time of exposure.

At irregular time intervals the affected herd experiences increasing and decreasing numbers of such "reactors". This depends on the extent of the incoming animal turnover in the individual herds (entrance and exit of BVD-SNA positive and negative animals, including calves being born there) as well as the presence or absence of BVD virus shedders (26,29,37, 61). In these situations there can be occasional new outbreaks of clinically manifest bovine virus diarrhea (or other forms of the BVD syndrome; see "Course and Spread"), with stress factors possibly playing a role. In general, however, further cases of disease are unlikely during the first years after a BVD disease outbreak in milking herds which predominately raise their own replacements (9, 69, 70).

Up to 80% of young animals standing in contact with affected ones in a new BVD outbreak show BVD-SNA at the time of diagnosis. Silent immunization has already reached the majority of the members of the group at this time (9, 29, 44, 61; figure 1). This indicates that the infection causing the disease had started earlier (44, 59), since the first SNA appears from 9 to 11 days following experimental, immunizing BVD virus infection, while the viremia lasts about 2 weeks (50, 59).

Figure 1. Portrayal by age group of the frequency of BVD-SNA positive findings in calves and youngstock (according to *Schaal et al,* 1972).




The overwhelming majority of the herdmates which did not become BVD-SNA positive despite the same exposure (about 20 to 30%) are, in fact, capable of such a reaction (seroconversion), as experimental controls show (9, 39, 40). Included in this group there are some few animals (29, 37, 61; an estimated 1 to 5%) which are, and remain, BVD-viremic (9, 37, 40, 61). It is usually not clear in retrospect whether these have become infected in the course of the BVD outbreak, or whether they were the source of it themselves—as shedders within the herd already (44). Cattle both BVD-SNA negative and at the same time BVD viremic (probably due to immune tolerance; (13,37,54) are apparently unable to develop their own active SNA against the BVD virus (9,24,37,40,44). Sooner or later they become ill (after 1 to 18 months; 37), usually with chronic BVD (29,37,61; see "Course and Spread"), and for no immediately apparent reason (possibly due to stress; 9, 29). There are exceptional cases which seem to remain fully healthy for life while both BVD-SNA negative and BVD viremic (13). Animals which remain "immune tolerant" and BVD-viremic for shorter or longer periods are perpetuating shedders of the BVD agent within the bovine population in the sense of a "slow virus infection". They can be found only by means of serologic surveys with follow-up virologic testing of the blood of the cattle thus found SNA negative (37,40), and present special problems when vaccinating with attenuated BVD virus (38,40,41,42; see "Control").

BVD-SNA positive heifers and cows are also protected from a diseae-producing BVD infection during pregnancy. The fetuses developing within them are likewise protected. However, since the maternal antibodies cannot cross the placenta these calves remain BVD-SNA negative until birth and only receive the antibodies with the colostrum (54).

From about 180 to 200 days of gestation the fetus in utero is capable of confronting BVD virus, which can cross the placental barrier (in contrast to the maternal antibodies), and developing its own SNA against it in the possible case of infection of the mother (an event possible only with BVD-SNA negative heifers and cows; 15, 54). Such calves will thus be born with a demonstrable BVD-SNA titer before receiving colostrum and are therefore actively immunized and BVD virus free (4,10,11,32,50,54).

**Should the transplacental BVD infection occur in the fetus or embryo (of a dam at first BVD-SNA negative, and then seroconverted in the course of a usually subclinical event) before 170 to 180 days of gestation, then the virus is confronting a more or less immunologically incompetent calf. This leads, depending on the timing of the occurrence, to resorption, abortion, retention of a mummified fetus, certain developmental defects, or to development of a living but BVD viremic and BVD-SNA negative calf (11, 13, 15, 27, 28, 44a; details see "Course and Spread"). Such calves either show signs of neonatal BVD at birth or shortly after (12,13,24,35), or they survive a variable length of time (weeks to years) in more or less healthy appearing condition. These latter form the main reservoir of BVD carriers and shedders, which remain asymptomatic for some time (immune tolerant) but usually later become affected with chronic BVD (13,15,29,37,40,41,44). Up to now, however, even timed infections of BVD-SNA negative pregnant animals have been unsuccessful in reproducing this BVD immune tolerant condition in their calves (3, 10, 15, 54).**

*Immunosuppression.* Considering the immune tolerance described, the BVD virus is apparently capable of an immunosuppressive effect. This seems to be confirmed by the predilection of the agent for invading and damaging the lymphoreticular tissue including the thymus (6, 22, 44, 50, 63), the inhibition of various lymphocyte functions shown in vitro and in vivo (22, 24, 51, 63, 67), and the outbreaks of clinically manifest BVD seen occasionally following BVD vaccination (3, 12, 16, 20, 23, 29, 34, 43, 58, 63). It is also reflected by the fact that in the course of other diseases appearing in a herd, but especially in "crowding" diseases, the BVD-virus is also often found, without the animals involved ("already") showing the clinical or pathologic-anatomic manifestations of bovine virus diarrhea (22, 29, 44, 56, 58, 63, 70a). This is particularly the case for "enzootic bronchopneumonia" (Pasteurellosis), "calf scours", infectious keratoconjunctivitis, and possibly also for dermatophilosis and interdigital necrosis, which, however, also present a sign of BVD (9, 22, 29, 56, 58, 63, 70a). It should be particularly emphasized that BVD virus in cattle has no independent disease-producing effects in the respiratory system. In enzootic bronchopneumonias, it performs at most a supporting, defense system weakening function for the actual viral agents. Here, in the opinion of those reporting this, a situation is postulated for those individuals with silent protection, as well as for the immune tolerant BVD virus carriers and shedders just mentioned, like the one

often thought of in "crowding".

The attempt to produce signs of BVD from the immune tolerant condition with the administration of prednisolone was unsuccessful (59). On the other hand vaccination of BVD-SNA negative animals with an attenuated strain of BVD virus during continued administration of dexamethasone led to clinical disease (7) and experimental infection with a field strain of the virus caused more pronounced disease signs in animals under these same conditions than in untreated control animals (64).

Trial results speak against the opinion, which is based partly on experiments, but more on "practical observations", that the BVD virus produces a generalized immunosuppression (meaning not only a BVD specific immune tolerance). According to these results the immunological insufficiency (connected with a low serum IgG2 level) of BVD-diseased or clinically healthy cattle shedding the BVD virus is limited to their inability to mount a SNA titer against the field strain BVD virus, while their immune capabilities against other strains of BVD virus and other agents (parainfluenza-3, parvo- and rotaviruses) are unaffected (67).

From the preceding statements on the immune events connected with the BVD syndrome, which are significant to the understanding of its course and spread, several conclusions may be drawn:

1. In view of the world-wide distribution of the BVD virus, we can no longer speak of "strongly" or "weakly" contaminated areas: the risk of exposure to BVD virus is real in any area as well as under all forms of management; the rate of occurrence of cases of the BVD syndrome, however, seems to differ from area to area. The risk of disease from the BVD-virus in the individual herd undergoes gradual fluctuations that are "dictated" by the periodicity of immunity.

2. For animals supplied with colostral antibodies against the BVD virus the later decrease of the titer of these passive virus neutralizing antibodies into the serologically unmeasurable range certainly does not always mean the loss of protection against the agent.

3. The presence of BVD neutralizing antibody in the serum of cattle over 9 months of age, including adults, indicates an active confrontation with the virus, but leaves the question of when this event—usually in the form of a subclinical immunization—occurred.

4. Animals that become clinically ill with BVD are viremic and have no BVD virus neutralizing antibodies.

5. Both in practice and in research special attention should be given to the immune-tolerant virus shedders, which are significant in the spread of the BVD syndrome, and to the circumstances under which such a tolerance develops. This is especially the case for experimental investigations into the infectious process (29, 39, 40, 42; see also "Control").

## Course and Spread

Before discussing the clinical pictures of the different forms of the BVD syndrome it should be stressed that cases of manifest disease are much less common than the number of animals becoming immune with subclinical BVD (see frequency column in table 2). The former relate to the latter like the tip of an iceberg to the mass of ice remaining below the level of the water (see figure 2).

1. *Intrauterine exposure of the embryo or fetus to the BVD virus:* This event, which is possible only in BVD-SNA negative, and thus usually young, dams, and which has been observed until now mostly in experiments, leads to the following fetal reactions depending on the stage of pregnancy:

—Infection between days 50 and 100 of gestation: Abortion (10 days to 3 months after infection of the mother) or retention of a mummified fetus (9,11,32,44a).

—Infection between days (90) 100 (120) and 150 (165) of intrauterine life: Damage to the organs in active cell division at this time, namely:

- —lungs (necrosis, hypoplasia or aplasia; 11,22,63);
- —skin (partial hypotrichosis; 11,22,29);
- —eyes (microphthalmus, lens cloudiness, incomplete iris pigmentation, retinal dysplasia, optic neuritis with impairment of vision; 9,29,63);
- —thymus (thymus hypoplasia with underdevelopment, possibly also decreased function in defense of the affected calf against infectious agents; 5,15,63);
- —central nervous system (hydrocephalus internus or hydrancephaly, cerebellar hypoplasia, dysmyelinization and/or hypoplasia of the spinal cord with ataxia/incoordination/dysmetria, dystasia or astasia/recumbency, tremors, opisthotonus or torticollis; 5, 9, 11,15,29,71).

Infection with BVD virus at this stage therefore displays certain more or less pathognomonic teratogenic effects and no longer leads to the death of the fetus in a considerable percentage of the cases (9,10,11,32,71).

—The time between days 150 and 190 of gestation (i.e. after the BVD- teratogenic and before the immunocompetent phase of intrauterine development of the calf; but possibly earlier; 41, 42, 71) seems to be the one during which a BVD-virus infection leads to an agent-specific immune tolerance (see "Immune Events"). As mentioned, this has not yet been successfully reproduced experimentally (11,54).

—Should the infection with the BVD agent occur after day (168) 180 to 200 of pregnancy, the calf has become immune competent in the meantime and, as a rule, will remain healthy. Usually it will have gotten over the 20 to 56 day viremia and developed its own BVD-SNA by the time of birth (10, 11, 27, 28, 29, 63). Such an infection can from time to time produce a BVD-caused neonatal diarrhea (see section 2; 33).

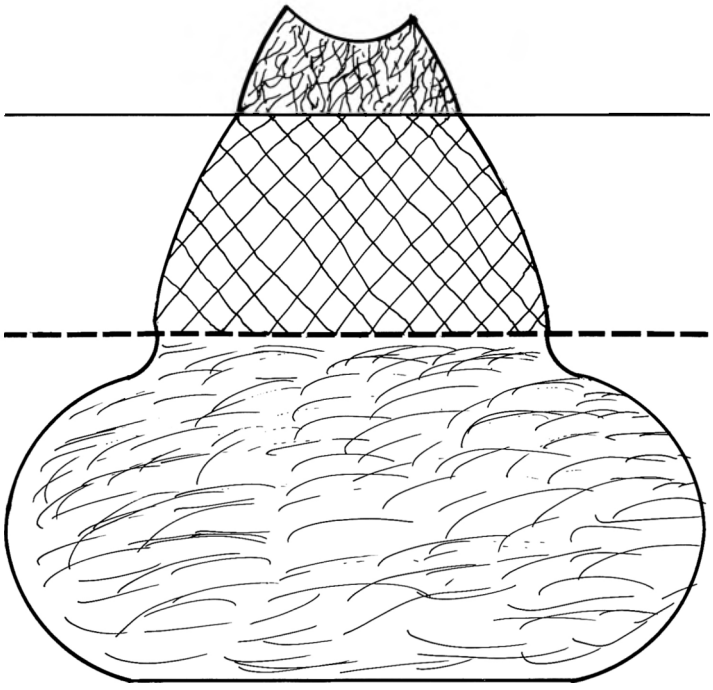
The frequency of intrauterine fetal damages due to BVD

TABLE 2: Overview of the most important characteristic of the different forms of the BVD syndrome of cattle (summarized from the literature and the author's observations).

| Form of BVD Syndrome | Commonly affected animal or age group | Estimated Frequency | Clinical Picture | Diseases to consider in differential diagnosis | Deciding diagnostic criterion |
|---|---|---|---|---|---|
| 1. Intrauterine exposure of the embryo or fetus to the BVD virus: | Days of 50-100 of pregnancy<br>Days 100-150 of pregnancy<br>(Days 150-190 of pregnancy?)<br>>190 days of pregnancy | 2 - 7.5% of bovine abortions or 1 - 6% of exposed pregnancies | Resorption, mummification or abortion | Other causes of abortion | Virus identification in the dam and/or fetus |
| | | | Defects of lungs, skin, eyes, CNS, thymus, and/or stunted growth | Defects due to other causes | Presence of defects suspicious of BVD virus infection |
| | | | Immunotolerance which develops into BVD virus related disease in utero or postnatally | o/o | Virus identification in the fetus, no BVD/SNA present |
| | | | Asymptomatic overcoming of the viremia accompanied by seroconversion | Other neonatal diseases | Calf BVD-SNA positive before colustrum |
| 2. Intrauterine or postnatally occurring BVD infections which manifest in the neonatal phase or shortly thereafter. | 0 - 3 months | Individual cases, occasional outbreaks involving up to 25% of the herd | Weakness, oculo-cerebellar syndrome congenital defects, peracute deaths without prior symptoms-ranging to typical (acute) cases of mucosal disease with mucosal lesions | Feeding errors, E. coli scours and sepsis, Rota-and corona virus enteritis, salmonellosis, cryptosporidiosis, purulent and diptheroid stomatites, (enzootic bronchopneu monias), heritable zinc malabsorption. | Evidence of viremia, no BVD-SNA present post mortem findings more or less characteristic for mucosal disease. |
| 3. Subclinical immunization against the BVD virus. | All ages, but especially 6-24 months of age (occurs less frequently with increasing age) | 70-90% of all exposed cattle | 'Silent Protection' (exceptionally also mild cases of diarrhea which recover) | none | Seroconversion: development of BVD-SNA in serum (following transient viremia) and in colostrum. |
| 4. Classic, acute mucosal disease | 6 - 18 months | 1-5% of the herd (in exceptions up to 25% related to immune periodicity). | Illness with diarrhea and typical mucosal lesions, leading to death within several days | All diseases of the 'Mucosal Disease Complex', stomatitis papulosa, malignant catarrhal fever, foot & mouth disease, salmonellosis, arsenic poisoning, coccidiosis. | Virus isolation in biopsy or post mortem tissue samples (blood, mucosae or lympatic tissue); post mortem findings; no BVD-SNA present. |
| 5. Immune tolerance - terminally, chronically occurring virus diarrhea | 6 months - 3 years (but also older & younger) | 1-2 (5)% of the herd | Diarrhea, slowly progressive over weeks to months, or recurrent and exacerbating, leading to death; with unremarkable mucosal lesions. | Paratuberculosis, Salmonellosis, gastro-intestinal parasitism by Trichos rongyloides, renal amyloidosis. | In the clinically inapparent stage, only evidence of viremia; following this, as under 4; no BVD-SNA present |
| 6. Genital Males | Permanently viremic, BVD-immunotolerant bulls | unknown | Inapparent, according to present knowledge | o/o | Sperm with BVD virus; bulls BVD viremic; no BVD-SNA present |
| Females: Infection during heat period | (Probably only BVD-SNA negative heifers and cows) | unknown | Inapparent experimentally (74); in practice allegedly lesions similar to those of IPV (45). | Other fertility problems | (Histologically demonstratable changes of the uterine duct and uterus); seroconversion with temporal relation to matching or insemination. |
| Females: Infection during pregnancy | BVD-SNA negative heifers and cows | see row 1 above | Asymptomatic or transient diarrhea | Other causes of abortion and congenital defects. | Seroconversion in the course of pregnancy |

Footnote: Explanation of symbol — o/o = not applicable

Figure 2. 'Iceberg' model of the BVD syndrome.



Illness with an easily recognizable clinical course and which are simple to identify etiologically, following postnatal infection (mucosal disease), or in the terminal phase of immunotolerance acquired in utero (virus diarrhea).

Abortions, congenital defects, neonatal losses and fertility problems with a clinically non-specific course and which are often etiologivally difficult to clarify.

Clinically inapparent beginning phase of immunotolerance acquired in utero, subclinical course of silent protection, possibly also the immunosuppressive side effects of the BVD virus in the pathogenesis of other diseases (predominately those related to "crowding").

virus is reported as 7.5% of 1033 (22) or 3 of 20 (56) aborted bovine fetuses, as 2% of 101 abortions (32), as 1% of all pregnancies (28), or as one of every 16 fetuses being endangered (15).

Determination of whether the abortion or congenital defect of a fetus or calf is the result of a BVD virus infection relies on the identification of the agent in the calf (15, 28, 29), if it is not too heavily contaminated by bacteria. When this produces negative results, a test for BVD-SNA should be conducted on the serum of the fetus or—before feeding of the colostrum—on the serum of the calf (15, 28, 29), which must be positive. Findings from the dams of calves infected in utero with BVD virus will be referred to in section 6.

2. *Intrauterine or postnatally occurring BVD infections that manifest in the neonatal phase or shortly thereafter:*

The BVD virus diseases of newborn calves and calves up to about three months of age, and summarized here for practical reasons, do not present a single, uniform clinical picture. Instead, one or the other of the following manifestations of the BVD syndrome appears, some developing and "preprogramming" in utero, others beginning postnatally:

—too early, dead, deformed (oculo-cerebellar syndrome) or weak calves (see section 1) with or without recognizable lesions of the digestive tract mucous membranes as seen in mucosal disease (see section 4).

—apparently healthy calves, born at term, that receive no, or insufficient, colostrum-derived BVD-SNA protection. Within the first week of life these become ill and die, some peracutely (as with septicemia), others with typical (i.e. with mucosal lesions and acute) mucosal disease (see section 4) (33).

—calves born approximately at term, that appear either normal at first or are stunted (considered to be too small), and which show the clinically inapparent immune tolerance described earlier. These succumb at this young age to the constant "infection pressure" of the BVD virus connected with this condition, with a more insidious form of the disease without very remarkable mucosal erosions (similar to the clinical picture described in section 5).

—possibly also calves with generalized immune weakness consequent to latent BVD virus infection (e.g. in the course of silent protection). These fall victim to another perinatally dangerous disease agent that determines the disease picture, and where the BVD virus is viewed only as the "mediating" associated agent. This etiopathogenic hypothesis, "construed" on the basis of practice experience (56), is still in need of experimental evidence and shows how important further investigation is of possible immunosuppressive effects of BVD virus not associated with BVD.

The frequency of losses due to BVD virus during the first three months of life is given as 7 of 51 calves born dead or weak (14%) and 202 of 824 (24.5%) dying within this time period with signs of the "abomaso-enteritis-pneumonia-complex". In 80% of these cases the BVD virus apparently played its pathogenic role in conjunction with other agents (Salmonella, E. coli, Pasteurella, Klebsiella, Clostridia, etc.), thus in the form of a "multifactorial" disease (56). Due to their economic significance the perinatal forms of the BVD syndrome deserve closer attention (conducting tests

for the agent in routine post mortem diagnosis).

3. *Subclinical immunization against the BVD virus:*

The active protection of the overwhelming majority of all BVD-virus-exposed young cattle, following the drop of their maternal BVD-SNA titer, as a rule is clinically inapparent ("silent"). It is accomplished by transient diarrhea (possibly also by virus shedding) only as an exception (11,29,33). This inevitably leads to an age dependant selection of BVD virus susceptible animals in the sense that disease manifestations are rare in cattle over two years old. It has not been clarified whether the subclinical immunization against the BVD virus can be connected with a temporary immune deficiency (generalized immunosup-pression) in certain circumstances (e.g. "crowding" or other stress loads).

The occurrence of BVD immunity can be shown with the associated "seroconversion". To this end "paired serum samples" (blood samples without anticoagulant) must be drawn from the same animal at the time of the assumed infection (recognizable by the BVD disease of herdmates) and three weeks thereafter. This is considered proven if the BVD-SNA titer of the first sample is 0, while that of the second is positive, or if simultaneous testing of the sera of several animals shows a (general) rise of titer (29).

4. *Classic, acute mucosal disease:*

The clinical picture of mucosal disease (9, 29, 53, 57, 58, 61, 62, 68, 69, 70, 72) is the best known form of the BVD syndrome to veterinarians and farmers due to its relative frequency and its conspicuous nature and for a long time it has "hidden" other diseases of BVD virus origin. Mucosal disease affects young, non-BVD-immunized cattle. It primarily affects animals from 4 to 18 months of age because of the age related "selection" of the immune process described (see above). Depending on the state of resistance of the affected herd at the time, 1 to 5% of this age group (in exceptions up to 25% under especially unfavorable conditions) will become ill, usually one after another rather than all simultaneously. According to the BVD registration statistics of the Federal Republic and Lower Saxony—which does not differentiate between acute and chronic cases (see section 5)—an average of 2.5 animals fall ill per BVD outbreak (see table 3).

TABLE 3. Overview of cattle herds reported as newly infected with BVD from 1978 to 1982 in Lower Saxony and the Federal Republic of Germany; an average of 2.5 animals per herd became ill and died out of this group.

| **Lower Saxony** (Statistics from the Animal Disease Reimbursement Office) | | **Federal Republic of Germany** (Statistics according to the registration ordinance/animal disease laws) | |
|---|---|---|---|
| 78/79: | 352 | 78/79: | 1935 |
| 79/80: | 581 | 79/80: | 2343 |
| 80: | 805 | 80/81: | 2521 |
| 81: | 817 | 81/82: | 2521 |
| 82: | 969 | 82 (9 Monate): | 968 |

After an incubation time of 4 to 6 days in experimental cases, but usually 1 to 3 weeks in practice (following introduction of a new disease carrier), patients show the following disease signs: temporary fever; profuse, watery diarrhea, sometimes containing blood or fibrin clots or accompanied by tenesmus; characteristic inflamed-reddened and erosive lesions of the mucosa of the nares, muzzle, mouth including the tongue, as well as the interdigi-tal space (sometimes including the coronary band). Other signs include anorexia, salivation, ocular discharge, and mucous, later crusting, nasal discharge, as well as a hesitating, stiff to outright lame gait, and occasionally corneal opacity. The mucosal lesions which give this form of the BVD syndrome its name become ulcerative to diphtheroid, depending on the duration of the illness and possible involvement of secondary bacterial invaders in the individual case. Clinically apparent cases lead routinely to death, usually in 5 to 7 days, from rapidly progressive dehydration (sunken eyes, lethargy and weakness). Attempts at therapy are hopeless and thus inappropriate.

Recognition of mucosal disease in a fully developed clinical case is possible with adequate certainty even on the still living animal. It is critical to consider this possibility in all cases of young cattle with foul-smelling diarrhea, and to conscientiously inspect the mucosae and the interdigital spaces at the first examination and any later visits. Following the "outbreak" of the problem the patient's herdmates should be similarly inspected: in positive cases the subsequent development of diarrhea would be sufficient reason to cull the animal immediately. As confirmation of the presumptive diagnosis "mucosal disease" it is advisable to attempt BVD virus identification on a biopsy sample of affected oral or nasal mucosa (tissue from a punch biopsy with a sharp, large bore cannula, or a sample removed with a fine scissors and forceps and sent in physiological saline with 20% glycerine; 19), or on a blood sample (specifically the leukocyte fraction; requires an anti-coagulant, preferably heparin) (29, 59, 60)*. Please refer to the relevant literature (9, 29, 53, 57, 58, 62) for the gross post mortem findings, of which erosions and necroses along the length of the esophagus are especially pathognomonic. The pharyngeal lymph nodes and other non-decomposed lymphoreticular tissues are sources for post mortem virus identification (9, 29, 59, 60).

It is worth noting that the clinical picture of mucosal disease will rarely develop to its full extent even in calves raised colostrum deprived.

5. *Immune tolerance—terminal, chronic virus diarrhea.*

This form of the disease (9,21,22,29,37,40,41,70), which develops because of the unusual effects of the BVD

**Footnote: A more or less large number of the herdmates will show BVD-SNA seroconversion in connection with such an outbreak, but in practice it is usually too late or too tedious to conduct this (indirect) test.*

syndrome on the immune system (see above), is distinguishable from mucosal disease not by any fundamental differences, but due to its development in time (see section 4). It develops in animals of different ages, but primarily in those from one half to three years of age. It involves mostly single cases, but other BVD-virus-susceptible animals in the herd can be infected (with the mucosal disease form). When this occurs the latter cases do not always follow, rather they often precede the appearance of the disease in the animal which continually sheds the virus before the collapse of its immune tolerance. The reasons for the turn around from a "tolerant relationship" between the BVD virus and the host animal to the development of clinical disease as virus diarrhea, are presently unknown ("crowd-ing", other stress factors, endogenous factors?).

The animal affected by this problem is apparently often a relatively small, underdeveloped or "stunted" one, which is otherwise clinically unremarkable. Upon examination, both before and after the "collapse" of its BVD immunotolerance, it shows BVD viremia and concurrent BVD-SNA negative status. The illness usually develops insidiously and leads to death over a period of weeks, or sometimes even after months of infirmity (with transient slight improvements). The symptoms of this bovine virus diarrhea are less pronounced than in typical mucosal disease. They consist of continual or recurrent, temporary bouts of watery, or occasionally only soupy diarrhea, reduced appetite, wasting, and also the accumulation of dried secretions in the medial angle of the eye and crusty scabs in the corners of the mouth. Thorough examination of the nasal and oral mucosae and the interdigital spaces at first shows either no, or only minor, inflamed erosive lesions. These (supposedly heal temporarily and) develop to the extent of the lesions common in mucosal disease only in the end stage of the illness.

Clues to the recognition of this form of BVD often, but not always, include the "advanced" age of the affected animal, history of occurrence of mucosal disease in the young animal group, discovery of at least single, minor erosions on patients with diarrhea, but especially the results of blood and serum samples taken immediately from the suspects (evidence of BVD virus and absence of BVD-SNA).*

For epidemiologic reasons it is especially important to quickly recognize these cases resulting from the break down of BVD immune tolerance in the BVD virus shedders (virus diarrhea) and to inform regulatory veterinarians and cull the animals promptly.

*6. Genital problems caused by BVD virus:*

The effects of the BVD virus on the genital apparatus of cattle still lie within the "gray zone" of the BVD syndrome "iceberg" (see figure 2). With the exception of the BVD virus related abortions, congenital defects, and neonatal problems which are somewhat clarified and discussed in section 1, the practical and economic significance of these problems still cannot be assessed. It seems worthwhile, for the future, to look into the questions related to this problem.

*Males:* Observation of a total of 10 bulls (1 bull infected naturally in utero, 9 experimental animals infected post natally and extragenitally [3 while BVD-SNA negative and 6 while BVD-SNA positive]) indicates that some danger exists of shedding of the BVD agent in the semen during states of viremia, i.e. above all in BVD-immune-tolerant, and thus permanently viremic, bulls. Sperm quality is apparently unaffected. The sexual organs of the latter 9 bulls (including BVD harboring testicles) showed neither gross nor histologic findings of disease (13, 74).

*Females:* Genital BVD infections of female cattle would be conceivable via virus contaminated urine (from contact with the tails of virus shedding neighbors; 44a) or via sperm (see above), but venereal transmission of the BVD virus has never been demonstrated.

When the question first developed of the protective value of serum BVD-SNA against appearance of intrauterine BVD infection at the time of heat (and insemination), on the basis of experimental results, and the associated danger to conception was indicated (1, 2), further experiments on a larger group of animals produced the following results: intrauterine inoculation of BVD virus 2 hours following mating did not influence the conception rate of BVD-SNA positive cows (in comparison to the non-BVD-infected control animals). The conception rate of BVD-SNA negative cows with intranasal BVD virus exposure at this time, which later seroconverted, also equalled that of the control animals. However, the conception rate of naturally bred cows with intrauterine inoculation of the same BVD virus 2 hours following, which were previously found BVD-SNA negative, was considerably lower (these also later seroconverted). The investigators concluded that BVD virus does not play a significant role as a cause of infertility, because the majority of mating-age female cattle are protected by BVD-SNA (75).

Practice experience contradicts these experimental findings, based on the appearance in a herd of a disease similar to infectious pustular vulvo-vaginitis (a blistering rash), which produces severe local itching and extends itself sometimes over 3 to 6 months, and which is attributed to the BVD virus (45). Proof of this suspected etiology has been limited until now to serologic evidence and, in the opinion of the author, still requires virologic confirmation.

Transplacental BVD virus infection of the fetus (see section 1) as a rule—probably—does not follow a genital infection, but a "normal" oro-nasal infection of the dam which becomes viremic for a short time. Resultant abortion apparently comes from the death of the fetus, not from damage to the placenta. The affected mother, in the course

**Footnote: A more or less large number of the herdmates will show BVD-SNA seroconversion in connection with such an outbreak, but in practice it is usually too late or too tedious to conduct this (indirect) test.*

of such an occurrence, shows no signs of disease except silent protection (experimental infections), and exception-ally a transient diarrhea (practice observations) (11, 15, 27, 28,36). Even the herd often shows no evidence of development of BVD associated illnesses (agent-spreading diarrheas) for the time in question (29). Finally the affected heifers and cows apparently conceive without problem at later matings and inseminations (45). The seroconversion connected with the BVD infection of the mother is not well suited for use as proof of BVD virus caused fetal damage because the inapparent immunization has already taken place by the time of abortion or birth of a BVD damaged calf (see section 1). Thus it would be too late to draw meaningful "paired sera" (29).

*Differentiation.* The diseases to consider in the differential diagnosis of the six various forms of the BVD syndrome are presented in table 3. Further information to help distinguish them can be obtained from the relevant publications and textbooks (8, 9, 29, 53, 57, 58, 59a, 62, 68, 69, 72).

## Control

The following will more closely examine the bases, prospects and practicabilities of the control measures aimed against the BVD syndrome (treatment, vaccination, precautionary hygiene).

*Treatment.* Mucosal disease and virus diarrhea are not influenced by medication. This is also true of the diseases of neonatal and young calves caused by the BVD virus (29, 58, 70). Even the administration of blood or serum containing BVD-SNA has no recognizable effect on the lethal course of the disease (44, 70). In this regard, one is warned against the euphoric-uncontrolled use of corticosteroids in the herd-wide appearance of "pneumo-enteritic" diseases of neonates, calves and young cattle, because the active immunization against the BVD virus can thus be disturbed (7, 64). Since experience shows that mucosal disease and virus diarrhea patients not only shed the agent, but also quickly lose carcass quality, prompt slaughter of these animals is required for both hygiene and economy. The lack of any effective therapy for the various clinical forms of the BVD syndrome is the chief reason the hopes of many farmers and veterinarians lie in active vaccination even in diseased herds.

*Vaccination.* There is both optimistic approval (7, 14, 16, 20, 22, 46, 47, 48, 49, 65) and cautious skepticism (23, 25, 29, 38, 40, 41, 70) regarding the question of necessity, efficacy and tolerance of the active vaccination against the BVD virus with attenuated, live virus strains. The former is based on the practice observation that "disease occurrence" ceases after vaccination. The latter arises from the unusual conditions of the effects of BVD on the immune system, vaccination breaks, and experiences with vaccination of BVD immune tolerant viremic animals. The following is an attempt to summarize the "pros and cons".

—The advocates of the *necessity of BVD vaccination* support their argument with the well known failure of therapeutic measures as well as the wish to get ahead of future BVD related diseases and to reduce the chance of infection (14, 20, 22). Counter to this reasoning is the equally well known fact that about three quarters of all cattle achieve solid BVD immunity without vaccination and without becoming clinically ill. Of the remaining 25% of the cattle, seen as BVD-SNA negative, the overwhelming majority seem to be protected against BVD virus infection (see the disease incidence in table 2). With herd vaccination (no preselection) all of these animals would be unnecessarily included (9,29,38,40,70). Thus there are some who consider BVD vaccination to be unprofitable or fully dispensable (55, Mussgay in ref. #61). A statistically supported cost-benefit analysis is still not possible at present, for various reasons.

—Advocates of the *efficacy of BVD vaccination* rely on the practical experience that naturally acquired BVD-SNA offers a more certain protection from clinically manifest BVD field virus infection. This is true for the antibodies developed via active BVD vaccination, appearing at the latest within 6 weeks (40) and remaining demonstrable for 6 to 18 months thereafter. However, calves still under maternal BVD-SNA protection, depending on the persistence of these antibodies, possibly could not develop a titer for 4 to 9 months.* These animals would also be unnecessarily vaccinated (29, 38).

The question arises whether all BVD-SNA negative cattle "encountered" in field conditions (i.e. despite exposure to field virus) at the time of vaccination really are capable of subsequently developing active BVD-SNA? Based on experimental trials (40, 54, 67) the answer to this is affirmative even for those animals which are viremic, that is, either in a state of BVD immunotolerance or clinically BVD ill. But the seroconversion caused by the vaccination does not lead to overcoming of the immune tolerance (toward the field virus) or the disease. More frequently such animals remain life-long BVD virus carriers and shedders (40, 67); they die sooner or later "according to the program" (see Course and Spread). An effective control of the BVD syndrome would depend directly on recognition and elimi-nation of the immune tolerant animals which spread and perpetuate the agent inapparently (40, 41).

The percentage of non-seroconverted cattle despite BVD vaccination under favorable conditions is around 2 to 5% (Lambert, ref. #65).

It is not clear to what degree cattle in a state of stress ("crowding", feed change, management change, "circulating" some disease) are capable of seroconverting "as expected" following BVD vaccination. There are proponents of "emergency vaccination" of sick, indeed even of BVD-ill, herds (20,47,48). Like many practicing veterinarians, they are convinced of the efficacy of this measure because "afterwards", as a rule, no further BVD

*Footnote: Brar et al (65) found a post-vaccinal titer rise even in the presence of maternal BVD-SNA.*

virus related diseases occur. It is emphatically countered that this type of "success" is attributable with far greater probability to the "circulating" BVD field virus which has been present in the herd for some time already, so it is only an apparent success of the BVD vaccine virus (29, 70). BVD vaccination of a herd already affected with mucosal disease or virus diarrhea therefore holds little promise (9, 22, 29, 34, 58, 66), is unnecessary (38), and may even be dangerous (29). The author views it as an "act of desperation", usually done "too late", understandable due to the circumstances, but not founded on the biology of the agent (70).

The question of the protective effect of BVD vaccination of pregnant heifers and cows can be answered based on recent investigations (40, 54), in which the vaccination took place between days 84 and 190 of pregnancy. BVD-SNA negative mothers seroconvert, while the immune status of BVD-SNA positive animals continues without significant change. The calves of the former dams are BVD-SNA positive at birth (before ingesting any colostrum—so they have already actively encountered the BVD vaccine virus in utero). Calves from the latter animals do not possess BVD-SNA at this time. (Discussion of damaging effects of the BVD-vaccine-virus on the in-utero fetus will be presented in the section on the tolerability of the BVD vaccine.)

One desirable and useful side effect occurring with BVD vaccination of pregnant cattle is the enrichment of the colostrum with maternal BVD-SNA associated with the seroconversion (or, in some cases, "boostering") (46,54).

—The *tolerabilty of the BVD vaccine* was apparently not always sufficient in the first conventional vaccines used in the USA, a problem which expressed itself in some large numbers of the vaccinates becoming ill with BVD. It was usually not clear at that time whether the infections were due to BVD field virus or the vaccine strain (7, 12, 23, 33, 43). Today this latter problem is no longer the case. The possible occurrences of postvaccinal BVD related illness seem to involve animals vaccinated in the incubation stage of a BVD field virus infection (29). The frequency of such incidences are typically estimated at about the same number (1 to 5%; 22,65) as the approximate percentage of BVD immune tolerant individuals in the cattle population.

The question of whether the BVD vaccine virus has the same teratogenic and immunosuppressive effects as the field virus seems to have an affirmative answer according to the experiments of Liess et al (40,41,42) and Trautwein et al (71). The following effects show up in some of the cases, depending on the time of the vaccination:

—birth of an immune tolerant, viremic calf (vaccination during the first two months of pregnancy);
—perinatal death of the calf (vaccination at days 60-110 of pregnancy);
—calves afflicted with congenital defects (hydrocephalus and/or cerebellar hypoplasia with opisthotonus/torticollis, ataxia/recumbency) (vaccination on days 75-120 of pregnancy);
—birth of a BVD immune, aviremic calf (vaccination on days 80-135 of pregnancy);
—abortion (vaccination at 100-130 days of pregnancy).

These observations, of importance in practice, preclude BVD vaccination during the first two thirds of pregnancy (40, 41, 42).

A further disadvantageous effect of BVD vaccination is the fact that the BVD immune tolerant animals, thus the BVD field virus shedders, seroconvert and therefore are no longer serologically recognizable (40).

The immunologic peculiarities of the BVD syndrome, as presented within this report, do not allow the author to expect any therapeutic or prophylactic benefits from paramunization (47). The concurrent use of paramunity inducers and BVD vaccine seems, to the author, contra-indicated.

After everything said about the necessity, efficacy, and tolerability of the active BVD vaccine it is not surprising that in the USA, despite yearly sales of some 10 million doses of different BVD vaccines (34), opinion on the use of this control measure remains divided (29). Still, a seemingly sensible *BVD vaccination program* will be outlined, based on the present state of knowledge and following closely the recommendations of Liess et al (40,41,42):

—Dairy operations which buy in animals: serologic examination of all heifers over 8 months of age for identification of BVD-SNA negative animals. These, as well as all animals under 8 months of age, are then subjected to a serologic blood test; individuals thus found to be BVD viremic are to be culled. All animals which remain are vaccinated when between 8 and 12 months old, and the vaccination of this age group is then repeated yearly. Pregnant animals should be vaccinated if need be, and if not viremic, in the last trimester (between days 190 and 265 of pregnancy).

—Dairy herds with their own replacements: culling of the BVD virus carriers (as above); no vaccination.

—Beef cow operations: in case BVD vaccination seems desirable, it should be done "before", not "after". That is, all animals to be introduced should be vaccinated 4 to 6 weeks prior to being brought in (while still in their original herd); it is assumed that they leave the beef herd only for slaughter and it is accepted that immune tolerant, BVD virus shedders possibly "remain in the game" and become ill sooner or later.

*Hygienic measures.* The worldwide occurrence of the BVD virus, which perpetuates itself "hiding" in the bovine population, and the resultant impossibility of eradicating the agent, force us to accept "life with the virus" with the considered use of serologic and virologic checks as well as vaccinations (see above). Vaccination, however, does not free us from the basic responsibility of hygienic animal

management, in particular:

—In dairy operations: separate, clean, warm calving areas; separate calf housing; timely feeding of colostrum; immediate isolation of individual animals which become diarrheic, followed by disinfection of the stall used by such animals; prompt slaughter of all animals affected by clinically manifest mucosal disease or virus diarrhea.

—In beef cattle herds: strict adherence to the "All in/ All out" principle, or isolation (quarantine) of newly purchased groups of animals; reduction of "crowding" stress by more gentle transport and use of the most ideal environmental and feeding conditions.

A starting point for any precautions against the BVD syndrome also includes, besides these hygienic measures, conscientious registry of all cases of BVD, as established in animal regulatory rules. This includes making the effort necessary to establish the etiology of suspicious cases (sending out the samples, looking into the results).


## Summary

This manuscript presents a practice-oriented overview of the causative agent, immune events, course and spread, and measures for controlling the BVD syndrome of cattle.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# Abstracts

*The Economics of Cattle Tick Control in Dry Tropical Australia, N. C. Sing, L. A. Y. Johnston, and G. Leatch, Aust. Vet. J. 60:37.*

The economics of strategic dipping compared to nil treatment of cattle ticks *(Boophilus microplus)* on Droughtmaster cattle was assessed using a partial budget analysis. The analysis was based on reported experimental data which showed a bodyweight gain advantage from strategic dipping of 45 kg/head for growing cattle and 35 kg/head for breeding cows. Costs of dipping were calculated using 3 acaricide costs, that is 5.9 cents, 20.9 cents, and 62.7 cents per head and allowances were made for mustering, maintenance of facilities and annual cost of asset purchase under an intensive farm management system similar to the reported experimental conditions. The net gain of benefits over costs per annum for each acaricide cost was $927, $810 and $483 per 100 breeders and their progeny. Breakeven beef prices at which it was worth dipping were found to be 61 cents, 69 cents, and 94 cents per kg dressed weight depending on the cost of acaricide used for dipping. All prices and costs are expressed in 1981 dollars of purchasing power.

*Conception Rates In Dairy Cattle Treated With Cloprostenol and Inseminated at Observed Oestrus.*

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This paper reports on published data in which treated cows were injected with cloprostenol then bred at estrus, not at a fixed time. Conception rates are compared with contemporary herd mates which were not injected. Seventeen trials in different countries were selected, covering 2422 treated cows and heifers.

When the data is pooled, the studies demonstrate an increase in conception rates following cloprostenol treatment of 7% over that for untreated cattle. This is a highly significant difference in effect (P 0.0001).

Prostaglandins have not been thought to have a fertility enhancing effect. Thus, the reasons for this improvement in conception rate is discussed.

The suggestion is made that treated animals are observed for estrous closer than untreated cows. Also, an improvement in estrous signs may come about from group behavioral and pheromonal interaction when a number of animals come into estrus together.