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BHV1 INFECTIONS: RELEVANCE AND SPREAD IN EUROPE

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Abstract—Infections caused by BHV1 are very common in Europe, but the disease pattern is quite different: the diseases of the genital tract are most common, those of the respiratory tract vary in intensity and prevalence. Digestive disorders connected with BHV1 are in general only observed in calves and mainly in Belgium. Virus strains causing abortion or encephalitis are only present in a few countries. The same is true for BHV1 induced mastitis. Dermatitis and lesions in the interdigital space seem to be a rare event.

BHV1 infections are frequently complicated by bacterial secondary infections, but there is evidence that BHV1 infections can occur simultaneously with bovine virus diarrhoea (BVD) and/or parainfluenza-3 (PI 3) virus.

The biggest problem associated with BHV1 infection is the ability of the agent to become latent following a primary infection. The genome of the virus probably remains during the life of the animal in the ganglia of the region where the primary infection occurred. No vaccination can overcome this latent stage.

By prophylactic vaccination it is possible to prevent an outbreak of clinical disease but it is impossible to prevent infection followed by the establishment of latency.

Eradication programmes in Austria, Denmark and Switzerland have removed most of the seropositive cattle from the bovine populations. Currently a sanitary programme is also being conducted in Germany.

Key words: BHV1, various diseases, latency, vaccination, attenuated and inactivated vaccine, sanitation and eradication programmes.

BHV1 INFECTIONS: IMPORTANCE ET DIVERGENCE EN EUROPE

Résumé—Les infections avec le virus herpes bovin type 1 sont très fréquentes, mais les formes de la maladie sont très variées. Les atteintes des organes génitaux sont les plus fréquentes, celles des organes respiratoires varient en intensité et fréquence. En général des indigestions sont seulement observées chez les veaux et le plus souvent en Belgique. Les avortements et les encéphalites sont observées dans quelques pays, de même que les mammites. Les dermatites et les lésions des espaces interdigités semblent être très rares.

Les infections par BHV1 sont souvent compliquées par des infections bactériennes secondaires mais il est aussi bien connu que l'infections avec le virus de la diarrhée bovine (BVD) et/ou le parainfluenza-virus (PI 3) sont concomitantes.

Le problème le plus important c'est la possibilité par le virus de devenir latent après la première infection. Le génome du virus reste rassemblablement pendant la vie de l'animal dans les ganglions de la région de la primo infection. La vaccination ne peut venir à bout de cette situation. La vaccination peut empêcher l'apparition des signes cliniques de la maladie, mais il est impossible d'empêcher l'infection suivi d'un développement de la latence.

Les programmes d'éradication en Autriche, Danemark et Suisse ont réduit le nombre des animaux séropositifs de la population bovine. Un programme sanitaire est aussi mis en place en Allemagne.

Mots-clés: BHV-1, maladies variées, latence, vaccination, vaccins atténués et inactivés, programmes sanitaires et éradicatifs.

INTRODUCTION

Diseases caused by bovine herpesvirus type 1 (BHV1)—a member of the Herpesviridae family, subfamily Alphaherpesvirinae—have caused great concern in many countries when it became known that this virus, originally believed to cause only infection in the genital tract, had increased its capacity to cause disease in almost all organ systems. The virus is spread worldwide but the disease pattern varies from continent to continent and from country to country. It can be assumed that more trouble will arise after 1992 when the borders of the EC countries are removed.

THE INDIVIDUAL DISEASES [1, 2]

Infectious pustular vulvovaginitis (IPV)

This disease, originally called coital exanthema, has been known in Europe for more than 150 years. It affects cattle of all ages and as the original name suggests was, in general, transmitted by an infected bull serving females. But it could be shown that horizontal spread is also possible. The characteristics of the disease are: high body temperature, lesions in the vulvar and vaginal mucosa resembling plaques, i.e. areas where the epithelial cells have been destroyed by the replication of the virus, and vaginal discharge for 8–14 days. Humoral, cell-mediated and local immunity follow.

Infectious balanoposthitis (IBP)

This disease in the genital tract of the bull occurs in general after a bull serves an infected female, but it has also been shown that the virus can be spread within insemination centres by various routes. The infection is in general limited to the preputial mucosa and the distal portion of the urethra. The semen is therefore considered to be free of virus but it becomes contaminated during ejaculation. Two facts render bulls especially dangerous. The bulls continue to serve following infection until the lesions become very painful which is 1–3 days p.i. The semen is by then contaminated with high amounts of infectious virus.

The course of the disease is in general somewhat longer than in the female. But after 4 weeks the bulls' mucosa is again sufficiently healed to resume service unless a vaccination programme is started. Immunity is the same as in the female.

Infectious bovine rhinotracheitis (IBR)

Most attention has been drawn to this disease. The original cases were diagnosed in the western U.S.A., where feedlot conditions enabled the virus to increase its virulence for the respiratory tract by numerous rapid passages. The disease is characterized by a sudden onset of high fever, loss of appetite and milk production, followed by a rapid loss of weight, especially in fattening cattle. The nasal discharge, first serous, becomes mucoid and later mucopurulent; the saliva frothy. If the animals are not treated to prevent secondary infection, a high percentage will succumb to pneumonia and die. After proper treatment recovery is fast; humoral, cell-mediated and local immunity are induced.

Conjunctivitis

Conjunctivitis is usually associated with IBR but has been reported to occur separately or even in combination with genital tract infection [1, 3]. If *Moraxella bovis* infection occurs simultaneously a severe keratoconjunctivitis is the result.

Table 1. Occurrence* of the various diseases/infections caused by BHV1 in cattle in Europe

Country	IPV/IBP or serological evidence	IBR and/or conjunctivitis	Abortions	Encephalitis	Mastitis	Other	Other hosts
Albania	+	+	?	?	?	?	?
Austria†	+	-	+	-	-	-	-
Belgium	+	+	-	+	-	+	-
Bulgaria	+	+	+	-	-	-	-
CSFR	+	+	+	-	-	-	-
Denmark†	+	+	-	-	-	-	-
Finland	-	-	-	-	-	-	+
France	+	+	?	+	+	-	-
Germany	+	+	+	+	-	+	-
Greece	+	+	?	-	-	-	-
Hungary	+	+	+	+	-	-	-
Iceland	-	-	-	-	-	-	-
Ireland	+	+	-	-	-	-	-
Italy	+	+	+	-	-	-	-
Luxembourg	+	?	?	-	-	-	-
Norway	+	-	-	-	-	-	+
Poland	+	+	-	-	-	-	-
Portugal	+	?	?	-	-	-	-
Romania	+	+	+	-	-	-	-
Soviet Union	+	+	?	?	?	?	?
Spain	+	+	?	-	-	-	-
Sweden	+	-	-	-	-	-	-
Switzerland†	+	+	+	-	-	-	-
The Netherlands	+	+	-	-	-	-	-
United Kingdom	+	+	+	-	-	-	+
Yugoslavia	+	+	?	-	-	-	-

*Based on a review [2] and personal experience.

†Almost seronegative following an eradication programme.

Encephalitis

BHV1 related encephalitis is of interest mainly in overseas countries, but BHV1 has also been isolated from cases of encephalitis in Germany and Hungary. The onset is also very rapid and affected cattle—in general only calves—die within a few days.

Abortion

The first cases of abortion occurred in the U.S.A. following the use of a vaccine which was not properly attenuated. Since then cases have also occurred in a few European countries (Table 1), most likely after the importation of the virus. It is interesting to note that it is not necessary for adult pregnant cattle to demonstrate any distinct clinical symptoms prior to the abortion which usually occurs during the last trimester of pregnancy.

Enteritis

It is most remarkable that digestive tract disease caused more concern in Belgium than in any other European country in the early 1970s. There it caused a frequently fatal diarrhoea in calves [4], whereas it has been shown to induce only mild diarrhoea cases in adult cattle, where the virus replicates in the caudal portion of the colon and rectum where the pH of the gut content is again close to 7.0 [5].

Mastitis

BHV1 has been shown, in France and overseas, to cause a catarrhal type of mastitis when the virus reaches the mammary gland. It may, however, be that it is frequently

overlooked, because the incidence of mastitis decreased for example in a herd after vaccination [6].

Dermatitis and lesions in the interdigital space

The reports describe isolated cases. It can be assumed that these manifestations are connected with some other disorders.

Mixed viral infections

Recently attention has been drawn to the question how frequently BHV1 is shown to be associated with other virus infections [7, 8].

In the first report BHV1 was isolated together with BVDV in two of 162 fatal cases in calves, in another two cases bovine coronavirus was involved and in one of each of one case parainfluenza-3, resp. parainfluenza-3 and BVD virus were found. In the second report BHV1 was associated with BVD virus infection in 3.6% of cases.

Occurrence of BHV1 infection in other hosts

There are numerous reports available from Africa and America, but in Europe there are only a few sporadic reports from Norway, Finland and Scotland [2].

In Table 1 the data concerning Europe are summarized.

Diagnosis

Confirmation of virus and/or antigen is possible by conventional methods such as cell culture, immunofluorescence, immunoperoxidase assay and ELISA. For the proof of the presence of the viral genome *in situ* hybridization and the PCR technique are suitable.

Antibodies are detectable by numerous serological methods such as serum neutralization, plaque reduction immunodiffusion, and passive haemagglutination tests. ELISA, counter-immunoelectrophoresis and micro complement fixation [2] are also used.

Lately an intradermal test has been introduced whereby it is for example possible to differentiate between a passively and an actively acquired immunity [9–11].

Immunity

Following an infection a local, humoral and cell-mediated immunity is induced. Methods are available to measure the actual content of the various immunoglobulins in milk and blood serum. This is of practical value in controlling the proper administration of colostrum. It has been shown that the titer of humoral antibodies in the newborn may exceed that of the dam, if a sufficient quantity of colostrum—a minimum of 1000 ml during the first 12 h—is given [12]. After a mixed infection with parainfluenza-3 virus the antibody response is delayed and significantly lower than after single infection [13].

Latency

Following infection, latency is established in the ganglia of the respective organ system where the primary infection occurred. After stress situations such as transportation, dystocias in heifers or cases of mucosal disease or immunosuppression by corticosteroid application virus is shed from the respective tract. In trials where the infection was produced by intravenous inoculation the results were different from those where the infection occurred via the natural entrances [14, 15]. The recrudescence may be influenced by the composition of the immunosuppressive corticosteroid [16]. In a recent experiment

it could clearly be demonstrated that 10 heifers inoculated intranasally only shed virus from the respiratory tract when immunosuppressed [17].

An early publication [2, 18] frequently resulted in the wrong conclusion. There it was shown (Fig. 1) that following local infection the period of virus excretion was shortened when the animals were reinfected and a certain correlation existed then between the humoral antibody titer and the days virus was excreted. The wrong interpretation claimed that a correlation existed between humoral antibodies no matter how they were obtained and the ability to shed virus.

Therefore a number of experiments were conducted to prove that there is no correlation between a humoral antibody titer and the readiness to shed virus and also the duration of virus shedding following immunosuppression. Group 1 consisted of 17 animals which were latently infected following the intranasal inoculation of BHV1 field or vaccine strain and then immunosuppressed. The results are demonstrated in Fig. 2. The animal which shed virus longest (14 days) had a fairly high titer of humoral antibodies. The same is true for 16 cattle which were first infected with field virus by the intranasal route and then twice vaccinated at 4 week intervals with inactivated BHV1 vaccine licensed in Germany. After immunosuppression, virus could be recovered for a period of 2–12 days in the presence of high humoral antibody titers (Fig. 3). In the third group 33 animals were twice vaccinated with inactivated BHV1 vaccines at 4 week intervals and then challenged with BHV1 field virus. Three months later immunosuppression was carried out. The results are presented in Fig. 4. It is remarkable that some animals excreted virus for a short period of time but the majority for longer periods of time as did the animals of groups 1 and 2.

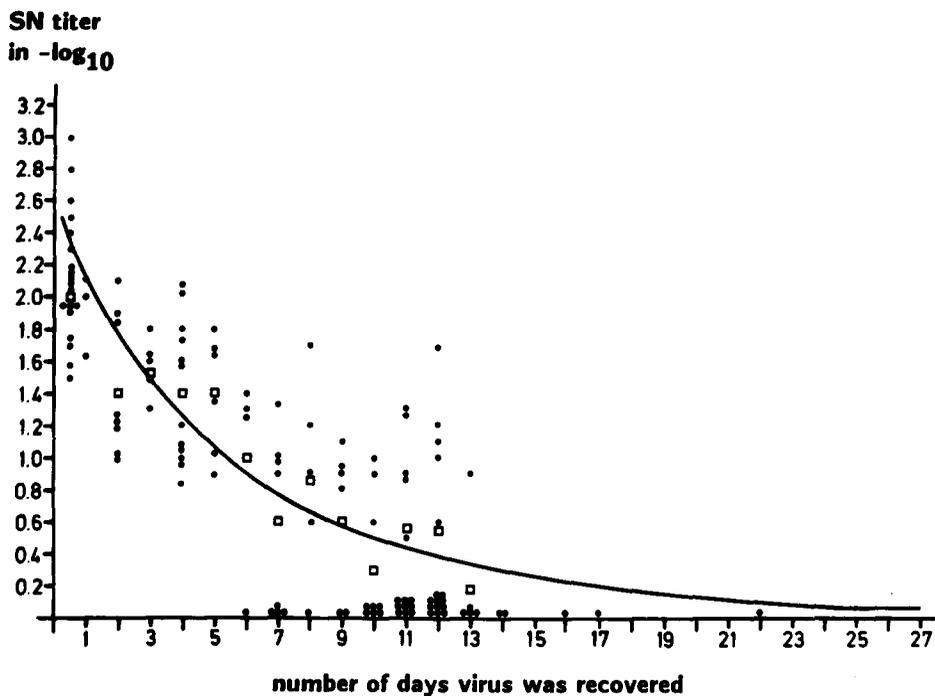


Fig. 1. Correlation between humoral antibody titers obtained after local inoculation of BHV1 and the days virus was excreted after local reinfection. (□) Average titer at days; (●) individual titers.

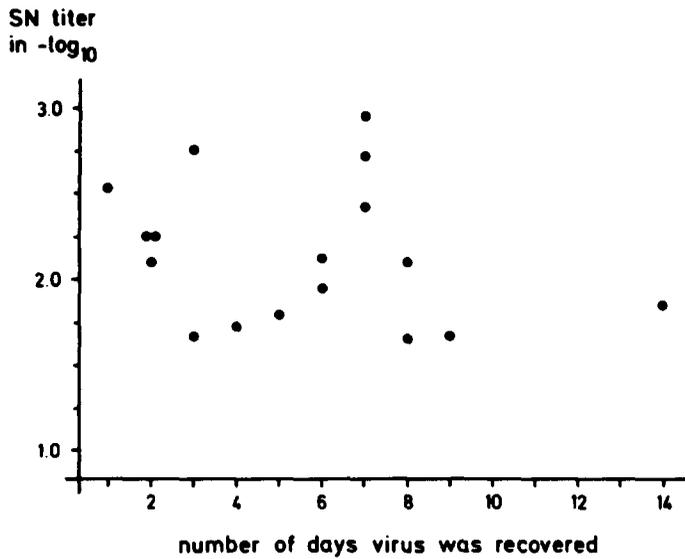


Fig. 2. Humoral antibody titers and number of days virus was recovered from the respiratory tract of 17 cattle after the injection of corticosteroids. The animals had previously been inoculated with field virus or an attenuated BHV1 vaccine.

A fourth group of 19 animals was vaccinated intranasally with an experimental inactivated vaccine after earlier experiments had produced encouraging results in FMD vaccine studies [19]. The animals were challenged 4 weeks later with field virus and 3 months later were immunosuppressed. The results of the virus recoveries can be seen in

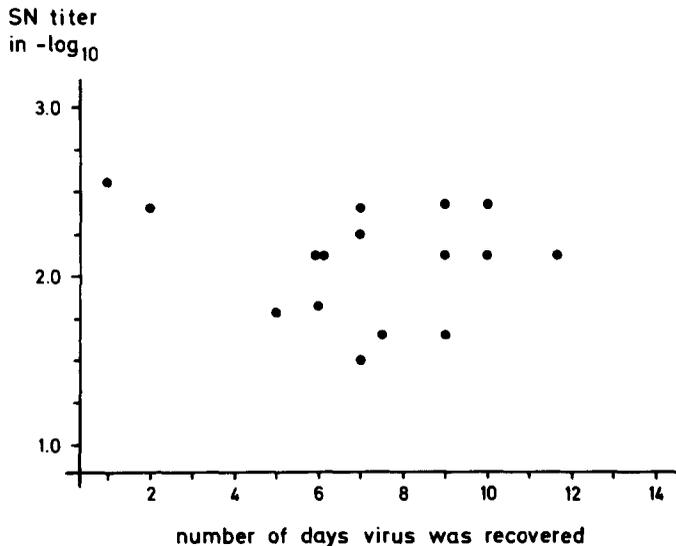


Fig. 3. Humoral antibody titers and numbers of days virus was recovered from the respiratory tract of 16 cattle after the injection of corticosteroids. The animals had first been inoculated with field BHV1 and were then twice vaccinated with inactivated BHV1 vaccines.

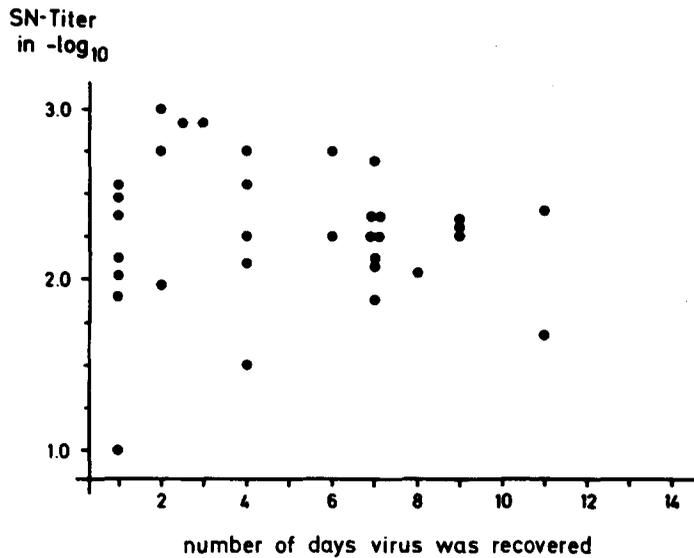


Fig. 4. Humoral antibody titers and number of days virus was recovered from the respiratory tract of 33 cattle after the injection of corticosteroids. The animals had first been twice vaccinated with inactivated BHV1 vaccine and were then challenged with field virus.

Fig. 5. There cannot be any doubt that no correlation exists between humoral antibody titers and duration of virus shedding following stress.

There is, however, a correlation between the amount of virus excreted from seronegative and seropositive cattle following challenge as numerous trials have shown [20–22]. From

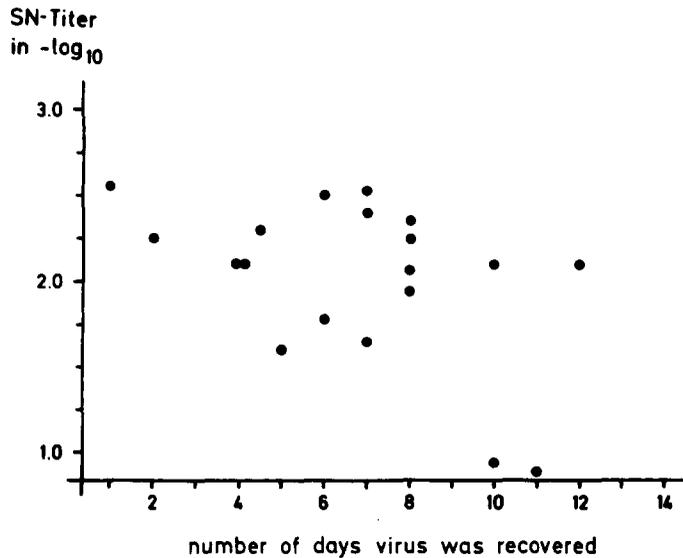


Fig. 5. Humoral antibody titers and number of days virus was recovered from the respiratory tract of 19 cattle after the injection of corticosteroids. The animals had first been vaccinated intranasally with inactivated BHV1 vaccine and were then challenged with field virus.

an epizootiological point of view this is of less importance since the infectious dose is very low [23]. In a recent experiment as yet not completed it was found that cattle vaccinated intranasally three times were most reluctant to shed virus after the application of immunosuppressive corticosteroids, even after increasing the dosage [24].

Vaccines and vaccination schedule

Numerous monovalent and multivalent BHV1 vaccines are licensed throughout the world. A summary of those licensed in the EC countries is given in Tables 2 and 3. The vaccines presently available can be grouped as follows: (a) live attenuated vaccines, (b) live ts-mutants, (c) inactivated vaccines and (d) subunit vaccines.

The live attenuated vaccines were first licensed in the U.S.A., where they were derived from IBR virus strains, whereas the ones licensed in Germany and elsewhere are from IPV strains. It is obvious that there must be some differences. The ones derived from IBR strains harbour the danger of causing abortion—at least a number of them do—when administered to pregnant cattle, whereas the ones derived from IPV strains are obviously considered safe [25].

The advantage of the attenuated strains is based on the possibility that they can be used in an emergency, i.e. when the first animals of a herd are stricken by the virus it is possible to prevent the spread to animals not yet infected. Another advantage especially useful in fattening units and feedlots is the effect caused by the production of high levels of interferon in the upper respiratory tract [26]. The protection considered to be superior to that induced by other vaccines is furthermore based on the induction of immunoglobulins class IgA [2]. Protection is achieved 2 days post vaccination.

Disadvantages are, the possible spread to non-vaccinates and the possibility of a recombination with field virus, which, however, has not occurred in 20 years since the introduction of the vaccine in Germany. It has also been postulated that a mutation to wild virus may occur, but there is also no evidence of this phenomenon occurring [27].

The live ts-mutant vaccine on the market in some EC countries was especially constructed for protection against IBR as it replicates only in the cooler portions of the respiratory tract. It appears therefore to be less apt for use as a prophylactic measure against genital disease. It has also been shown that it cannot prevent the establishment of latency by a field virus strain. Whether or not this is also true for the other live attenuated strains has not been proven satisfactorily [2].

Whereas live attenuated vaccines can be administered locally or parenterally it is not possible to administer licensed inactivated vaccines locally. It has been shown that all of the inactivated vaccines induce a fairly high level of humoral antibodies. Their disadvantage is the fact that they cannot be used as an emergency tool. Otherwise they can be

Table 2. Monovalent BHV1 vaccines licensed in the EC countries*

Type	Number of licenses in the individual countries								
	B	D	E	F	GB	I	Irl	NL	P
Inactivated	—	5†	2	2‡	—	2	—	1	2
Live†	1	1	—	—	1	—	—	1	—

*There are no vaccines licensed in Denmark and Greece; in Luxembourg the vaccines licensed in the neighbouring countries may be employed.

†Including ts-mutant vaccines.

‡Including a subunit vaccine.

Table 3. BHV1 vaccine combinations available in the U.S.A. licensed in the EC countries

Composition BHV1 plus	Type	Number of licenses in the individual countries*									
		B	D	E	F	GB	I	Irl	NL	P	
PI3	Inactivated	—	—	—	—	—	—	1	—	—	1
	Live	2	1	2	—	1	—	—	4	—	
PI3 + BRSV	Inactivated	—	—	—	—	—	—	—	—	—	
	Live	—	—	—	—	—	—	—	—	—	
BRSV	Live	—	—	—	—	—	—	—	—	—	
BVDV	Inactivated	—	—	—	—	—	—	—	—	—	
	Live	—	—	—	—	—	—	—	—	—	
BVDV + PI3	Inactivated	—	—	2	—	—	—	—	—	2 [3]	
(+ BRSV)	Live	—	—	—	—	—	1	—	1	—	
	Inactivated live†	—	—	—	—	—	—	—	—	—	
BVDV + BRSV	Live	—	—	—	—	—	—	—	—	—	
PI3 + Adeno3	Live	1	—	1	—	—	1	—	1	—	
	Inactivated‡	—	—	1 [4]	—	—	—	—	—	1	
Adeno3 + BVDV + REO + PI3	Inactivated	—	—	—	—	1	—	—	—	—	
PI3 + REO 1 + 3 + Adeno 1 + 3	Inactivated	—	1	1	—	—	—	—	—	1	

*There are no vaccines licensed in Denmark and Greece; in Luxembourg the vaccines licensed in the neighbouring countries may be employed.

†The BVD portion is inactivated.

‡Included are antigens of 5 strains of leptospira.

§Included are pasteurilla antigens.

considered as very safe. The same is true for subunit vaccines. Their advantage is considered to be based on lessening the chance of inducing allergic type reactions in animals while at the same time offering the same advantages as the inactivated vaccines based on the inactivation of whole virions [29, 30].

Most manufacturers recommend the use of vaccines, whether live or inactivated in seronegative cattle twice at 4–6 week intervals followed by half year or yearly repeat vaccinations. It has also been demonstrated that it is useless to repeat the vaccination at an interval of 2 weeks [22]. The site of application for parenteral vaccination is the subcutaneous route, whereas live attenuated vaccines should be administered locally, i.e. the respiratory and genital tract. It is also advisable to spray a small amount into the eyes, which will give protection at all the natural entrances.

It must be pointed out that all these vaccines are only able to prevent disease, but not infection followed by the establishment of latency [2].

Future vaccines

In the field of pseudorabies it has been shown that virus vaccines deleted of one or the other glycoprotein can still produce good protection in vaccinated animals and furthermore allow the veterinary profession to differentiate well between those animals which have been vaccinated and animals infected with field virus. The same is possibly true for BHV1 vaccines presently developed by a number of companies. It is, however, already known, that it is not possible to simply copy the pseudorabies vaccine development. The major glycoproteins responsible for the induction of immunity are considered to be gI and gIV.

Whether or not it will be possible to develop efficacious anti-idiotypic vaccine remains to be determined [31]. The same is true for recombinant vaccines. So far experiments have

been conducted using vaccinia virus as a carrier [32]. But there is no question that this virus can only be used for experimental studies. It is unsuitable for use in cattle vaccines on a commercial basis as the population is free of orthopoxviruses to which vaccinia belongs. Unlicensed vaccine trials using vacciniavirus as a carrier for rabiesvirus components have proved to be disastrous. But other vectors may be suitable. BHV4 which has been considered by some investigators is certainly also unsuitable because the immune response to field virus strains is extremely weak.

The question whether or not it will finally be possible to develop peptide vaccines cannot be answered presently. Such vaccines would certainly be best as they would be free of any nucleic acid, could probably be stored almost indefinitely and would most likely not require refrigeration.

Molecular virology

This most important field has so far been neglected, but it has lately been discussed in detail [33]. There it has been described for example, how the various strains can be grouped together, what their composition is like and their relation to practical aspects.

Eradication and sanitation programmes

There seems to be no difference between the two titles, but there is indeed one. Eradication means freedom from BHV1 of the whole cattle population of a country or state; sanitation means to eliminate BHV1 from a herd or a group of organised breeders.

In an eradication programme vaccination is prohibited, in a sanitation programme it may be used. In Europe three countries are conducting an eradication programme: Austria, Denmark and Switzerland.

A prerequisite for such a programme is a low prevalence rate. Switzerland started, for example, when the rate was 4.2% seropositive cattle of the total population. The prevalence rates at the beginning were similar in the other countries. The general idea as to the method of procedure for other countries is outlined in Fig. 6.

The test and slaughter policy is of course dependent on the financial situation of a country because compensation should be paid for breeding animals.

The question of which circumstances which programme should be conducted and whether one should start with live in inactivated resp. subunit vaccines depends not only on the percentage of seropositive cattle in a herd but also on its size.

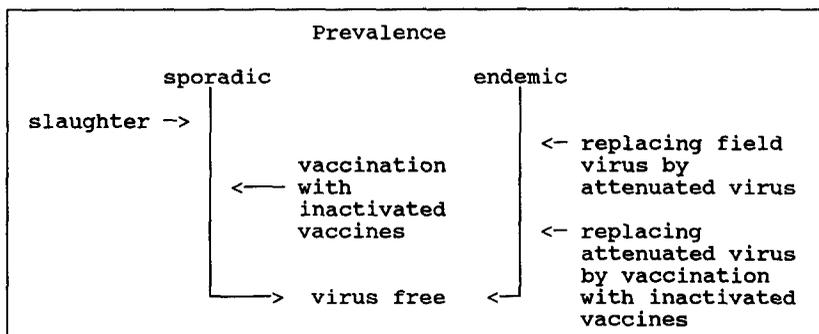


Fig. 6. Proposed scheme for the eradication of field virus.

Herd size	Maximal numbers of seroreactors at the various prevalence rates				Stress factor increase
	up to 10%	20%	40%	50%	
1 - 10	1	2	4	5	↓
11 - 20	2	4	5	10	
21 - 50	5	10	20	25	
51 - 100	10	20	40	50	
>100	>10	>20	>40	>50	

Fig. 7. Scheme for the eradication of BHV1 from infected herds. (■) Vaccination only with inactivated vaccines. No application of corticosteroids. First two vaccinations at 4–6 week interval. Subsequently one yearly vaccination; (▨) first two vaccinations at 4–6 week interval with attenuated live vaccines with inactivated vaccines. Subsequently one yearly vaccination. Also no application of corticosteroids.

A scheme is recommended (Fig. 7) which is based on the knowledge obtained from surveys and experience from field trials. Thereby a risk is accepted, because seropositive animals can always shed infectious virus as mentioned earlier, the higher their number the riskier is the procedure to start with inactivated vaccines rightaway [34].

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