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Chapter 54

Viral Gastroenteritis in Ruminants

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INTRODUCTION

Diarrhea is one of the leading causes of morbidity and mortality in infants and young animals in both developing and developed countries. It has been estimated that over 500×10^6 cases of diarrhea occur annually in humans, leading either directly or indirectly to approximately 10×10^6 deaths (Editorial, 1978). Accurate estimates of diarrhea cases in ruminants are not available, but they would appear to be at least as high as in humans on a percentage basis, thus indicating the economical importance of this disease syndrome.

Until recently, the agents responsible for most cases of nonbacterial gastroenteritis were not identified. However, since the discovery in 1969 by Mebus (Mebus et al., 1969) that a virus was present in feces of calves suffering from diarrhea, it has been proven that rotaviruses can infect calves and cause diarrhea. This discovery prompted the search for related viruses as a cause of diarrhea in other animals. As a result of these investigations, rotavirus has been found to be a major cause of nonbacterial gastroenteritis in most mammals and in fowl (Flewett and Woode, 1978; McNulty, 1978; Woode, 1982), and it is now accepted that up to 60% of nonbacterial gastroenteritis cases may be caused by rotavirus. The remaining cases of diarrhea are caused by a variety of viral agents, which may include *Coronavirus, Torovirus, Calicivirus, Parvovirus, Enterovirus, Adenovirus, Astrovirus, Minireovirus* or rota-like viruses (Table 35). However, the role and prevalence of many of these agents in causing diarrhea has not been firmly established, neither in ruminants nor in other mammals.

Although as microbiologists we try to identify a specific etiological agent as a cause of diarrhea, it must be emphasized that diarrhea is often multifactorial and that interactions of various factors with infectious agents can exacerbate the disease. These factors can be broadly grouped into immunological, environmental and nutritional. In each category there are large numbers of components that can interact and alter both the degree of diarrhea and the final outcome of the disease. For example, diarrhea is often associated with inclement weather, i.e. storms, sleet, cold, etc. This is probably associated with increased stress due to temperature fluctuations which can alter the animals' defense mechanisms and increase the probability of infection due to increased animal congregation.

The viruses that cause gastroenteric infections can generally be divided into two groups. For viruses of the first group, replication is restricted to the gastrointestinal tract; they induce disease as a result of direct effects only on the cells of the intestine (Fig. 179). Most of these agents enter the host directly, via the oral cavity, and pass into the gastrointestinal tract. Viruses of the

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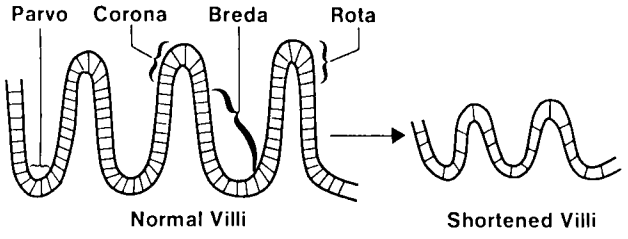

Fig. 179. Sites of infection and cell destruction by some enteric viruses.

second group enter the host via the oral cavity and replicate in the gastrointestinal tract but they do not remain localized. These viruses may spread to other target organs such as lymphoid tissue (Kahn, 1978) or even the CNS (Nathanson, 1979).

At least eleven different viruses can cause intestinal damage and diarrhea in ruminants under appropriate conditions (Table 35). All of these agents produce the most severe clinical signs during the first few weeks of life (Woode and Bridger, 1975; Little and Shadduck, 1982). However, there are reports of virus shedding associated with diarrhea in older animals as well (Von Bonsdorff et al., 1976; McNulty et al., 1978; Jones et al., 1979). In most cases the infection of older animals is subclinical, and it has been suggested that they serve as virus carriers and are a source of infection for young susceptible animals. In fact, recent reports suggest that removal of carrier animals from a herd reduces or eliminates the disease. The reason for increased severity of diarrhea in younger animals and a higher mortality is that the viruses generally cause greater villous atrophy in the younger animals.

AGENTS INVOLVED

Rotaviruses

Rotavirus-induced disease was first described by Cheever and Mueller

TABLE 35

Some enteric viruses of ruminants

Virus	Site of replication	
	Horizontal	Longitudinal
Rotavirus	enterocytes/villus tip	small intestine
Rota-like virus	enterocytes/villus tip	small intestine
Coronavirus	enterocytes/top half	small, large intestine, colon
Corona-like virus	enterocytes/top half	small intestine
Torovirus (Breda)	mid villus/crypts	small intestine, colon
Astrovirus	?	?
Calicivirus	?	?
Parvovirus	crypts, lymphoid	small, large intestine
Adenovirus	enterocytes	small intestine
Reovirus	?	?
Enterovirus	?	?

? Insufficient data available for definitive statements to be made.

(1948); later rotaviruses were established as important infectious agents in mice by Kraft (1957, 1958). However, rotavirus was not recognized as an important pathogen in domestic animals until Mebus et al. (1969) identified it as a cause of neonatal diarrhea in calves. Since then it has been demonstrated to play a major role in nonbacterial gastroenteritis in most mammalian species. In most outbreaks the disease occurs suddenly and spreads rapidly to other susceptible individuals. The reason for this rapid spread is that the concentration of virus can reach 10^{11} particles per gram of feces, which is equivalent to 10^7 infectious doses (Flewett and Woode, 1978; Woode et al., 1976a, b). Experimental inoculation of bacteria-free filtrates containing rotavirus causes diarrhea within 12–24 h in susceptible young animals. Diarrheic animals are also anorexic and can vomit. The reason for such rapid clinical signs is that in the absence of passive antibody or local acquired immunity, the virus infects the enterocytes of the villi, rapidly killing them. The replication cycle of rotavirus is approximately 12 h (Carpio et al., 1981).

Rotavirus infection is generally limited to the small intestine in calves, pigs and humans (Middleton et al., 1974; Mebus and Newman, 1977; McAdaragh et al., 1980), but antigen can be found in the colon of lambs (Snodgrass et al., 1977), pigs (Theil et al., 1978) and mice (Little and Shadduck, 1982). Viral infection occurs in the enterocytes of the upper half of the villi of the small intestine, resulting in rapid death and sloughing of the cells (see Fig. 179). With death, the villi become shortened and loose their adsorptive capacity (Woode and Crouch, 1978). The cells at the tips of the villi are responsible for production of lactase which aids in digestion of lactose. Thus the combination of reduced adsorptive capacity and reduced enzyme activity accounts for the diarrhea. Since the crypt cells are not damaged, regeneration of the enterocytes and recovery of the villi is generally rapid after the infection is overcome. Animals that recover from the disease return to normal body weight within 10–28 days after infection.

Coronaviruses

Coronaviruses can cause both respiratory and gastrointestinal infections in humans and animals (Robb and Bond, 1979). Transmissible gastroenteritis virus of swine was one of the first coronaviruses identified as a cause of diarrhea in animals (Doyle and Hutchings, 1946). Coronaviruses have also been identified as a major cause of calf diarrhea (Stair et al., 1972; Mebus, 1978; Storz et al., 1978a). Bovine coronavirus diarrhea, like rotavirus diarrhea, occurs within 15–24 h p.i. Early in infection the villous epithelial cells appear morphological normal but they contain large amounts of antigen. Since diarrhea occurs before denudation and loss of enterocytes it is postulated that it is a direct result of infection of the cell and the ensuing redirection of cellular functions from absorption to virus replication. If absorption does not occur there is accumulation of digestive fluids. As the infection proceeds cells are lost from the villi and are replaced by immature squamous to cuboidal epithelial cells which lack the enzymes required for digestion of milk. They also have a reduced absorptive capacity as is the case in all other virus infection of the gastrointestinal tract.

Other enteric viruses

Caliciviruses, astroviruses (Woode and Bridger, 1978) and parvoviruses (Storz and Bates, 1973) may be responsible for causing gastroenteritis and may account for a significant portion of the cases of diarrhea which are not caused by rotaviruses or coronaviruses. However, there are still 20–30% of diarrhea

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cases for which no etiological agent has been identified. As the search continues for etiological agents other viruses are discovered. One such new agent is the Breda virus (Woode et al., 1982) which has recently been identified. In the case of Breda virus infection, the lesions at first appear similar to coronavirus infections with respect to location of lesions. However, on closer examination it becomes obvious that the disease is different, since the lesions and infected cells are visible in the lower 50% of the villi and in the crypts of the small intestine. In the colon, infected cells are present throughout the villi and in the crypts. In addition, structurally this virus is not identical to coronaviruses and is related to an equine virus described in Europe (Horzinek et al., 1984). Recent studies also suggest that other species may have antibody to this group of viruses, which has been tentatively designated as toroviruses (Horzinek et al., 1987).

Parvoviruses can infect a wide variety of animals, ranging from pets to large domestic animals (Kahn, 1978; Storz et al., 1978b). In contrast to the other viruses discussed so far, this virus family can produce systemic disease as well as enteritis. Since the virus generally replicates in rapidly dividing cells, the lesions are seen in the crypts of both the small and large intestines as well as in lymphoid tissue. Because of the replication in lymphoid tissue this disease can be more severe, especially in small animals, than other viral infections, because of interference with immune responses and damage to the crypts. However, the role of parvoviruses in diarrhea of ruminants is probably small compared to that played by the other agents.

One common feature of all of the agents described to date is that infection occurs by ingestion of the virus. Since the virus does not have to spread systemically, the incubation period is extremely short, with villus shortening and reduced fluid adsorption, dehydration and death if diarrhea is severe enough. For a differential diagnosis of the actual cause of diarrhea attempts must therefore be made at demonstrating the presence of the specific agent. However, regardless of the agent treatment will be the same.

Although these viruses have been associated with diarrhea, there are also many instances where they are present but no disease occurs. Furthermore, it is not always possible to reproduce the disease in conventional or even gnotobiotic animals to the extent that it occurs naturally. Under experimental conditions most attempts to reproduce the disease are made with a single pathogen and more importantly with plaque purified isolates. Replication of these pure populations may be restricted to very localized regions of the intestine; therefore, they do not cause sufficient damage throughout the intestine (longitudinally) to cause the damage required for disruption of intestinal function and diarrhea. Under natural conditions there may be multiple strains of a virus (Sabara et al., 1982) that infect different areas of the intestine, thus causing severe diarrhea. Another explanation for poor reproducibility of diarrhea under experimental conditions could be that avirulent strains grow in culture more rapidly than the virulent strains (Woode, 1982). If these are used to challenge animals no disease occurs. Another explanation could be related to immunity. If low levels of active or passive immunity are present this would keep the virus infection rate low so as to allow only few viruses to initiate new infections, as is often the case with persistent local infections. However, during stress the immune defense is reduced and virus shedding and diarrhea may occur. When the immune system returns to normal, diarrhea stops but virus may continue to be shed. This type of carrier state would insure the continued presence of the virus in the environment for infection of susceptible neonatal animals. Such carrier states have been demonstrated to occur both in vivo (Leece and King, 1980; Benfield et al., 1982; Crouch et al., 1985) and in vitro (Misra and Babiuk, 1980).

DIAGNOSIS

Many of the viral agents involved in causing diarrhea are not easily cultivable in vitro by conventional methods. The reason for this may be related to the virus tropism for differentiated cells. Because of the difficulty in growing enteric viruses a large variety of tests have been developed to diagnose these agents directly (Yolken, 1982). Most tests are based on the observation that there are high levels of virus particles present in the feces of diarrheic animals and humans (Woode et al., 1976a, b; Flewett and Woode, 1978; McNulty, 1978). It is therefore easy to observe virus in feces by EM techniques. However, direct observation is less efficient than if combined with serological tests, as is the case with IEM, where the virus is aggregated by specific sera and can be visualized much more easily. The availability of specific antisera and monoclonal antibodies to numerous viruses makes this a very attractive means of diagnosis. Some enteric viruses may infect cells without causing a CPE or producing infectious virus. In these cases viruses may be identified by culturing in vitro and testing for the presence of viral antigen in infected cells.

A number of points must be considered when choosing a test, including efficiency, speed, relative costs and the specific purpose for making a diagnosis (Table 36). If trained personnel and proper equipment are available then IEM, RIA and ELISA appear to be very good, with respect to specificity and speed. ELISA tests are especially useful for automation and diagnosing large numbers of samples. Furthermore, ELISA can be read by eye if readers are not available, making this test very attractive. If serotyping is also desired then many of the tests listed can be adapted if specific antisera and preferably monoclonal antibody produced against each serotype are prepared.

PATHOLOGY AND PATHOPHYSIOLOGY OF ENTERIC VIRUS INFECTIONS

In most virus infections of the gastrointestinal tract, regardless of whether the virus has a predilection for the epithelial cells at the tips of the villi or the crypts, there is shortening and occasional fusion of adjacent villi resulting in a reduced absorptive surface (Keenan et al., 1976; Leece et al., 1976; Pearson and McNulty, 1977). Infection generally begins in the proximal part of the small intestine and spreads progressively to the jejunum and ileum and

TABLE 36

Efficiency and practicality of some diagnostic techniques for detection of viruses causing gastroenteritis in animals

Method	Efficiency	Speed	Relative cost
IEM	very good	hour	high
RIA	very good	day	moderate
ELISA	very good	day	moderate–low
IF	good	hour	moderate
Culture	good	days	low–moderate
CIEP	good	hour	low
CF	poor–good	day	low
Immun. Ad. Hemagg.	average	hour–day	low
HA	poor	hour	low
AGID	poor	day	low

The practicality of IEM is good only for single samples; all other methods can be scaled up for multiple sample examination.

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sometimes to the colon (Mebus et al., 1973; Snodgrass et al., 1977). This will, however, depend on the initial infective dose, the virulence of the virus strain (Woode and Crouch, 1978), and the host's immunological status. Thus in the presence of passively acquired antibody, infection can occur but replication is limited to such an extent that either no or only mild diarrhea occurs. In rotavirus and coronavirus infections, which are limited to the cells at the tips of the villi, the absorptive cells are replaced with immature squamous to cuboidal epithelial cells. Until these cells mature their absorptive capacity and enzymatic activity is greatly reduced. Since they also appear to be relatively resistant to virus infection the disease is often self-limiting if dehydration is not so significant as to cause death (Woode, 1982; Garwes, 1982). Crypt cells are not damaged and the rate of recovery is therefore generally rapid. In contrast, after infection with viruses that replicate in the crypt cells there is a limited number of new cells available to migrate up the villi and recovery tends to take longer. It should be stressed that although the degree of villous damage may be influenced by the virulence of the virus and the immunological status of the animal, the rate of regeneration of enterocytes and enterocyte maturation may also vary with the age of the animal and the site of virus infection. Since glucose and sodium adsorption are highest in the proximal and middle part of the jejunum (Shephard et al., 1979; Bachmann and Hess, 1982), damage here would cause most severe diarrhea.

In viral infections, the mechanism of fluid loss is considered to be different from that in bacterial infections; however, the net losses may be the same. In viral infections, water is predominantly lost from the extracellular fluid due to impaired adsorption and osmotic loss primarily due to the presence of undigested lactose in the lumen rather than to active secretion (Lewis and Philips, 1972; Philips and Lewis, 1973; Tennant et al., 1978; Graham et al., 1982). However, replacement of mature adsorptive cells with immature cells, which retain some of their secretory functions, also increases the rate of secretion (Pensaert et al., 1970; Butler et al., 1974; Kerzner et al., 1977). As the virus kills the adsorptive cells there is also a loss of enzymes which are responsible for digestion of disaccharides. Furthermore, loss of differentiated villous cells diminishes glucose, sodium carrier and (Na^+–K^+)–ATPase activities, which result in a loss of sodium, potassium, chloride, bicarbonates and water. The loss of bicarbonate leads to the development of acidosis. However, acidosis also develops as a result of increased microbial activity in response to fermentation of undigested milk (Lewis and Philips, 1978), as well as the increased lactic acid production and decreased utilization in dehydrated animals (Tennant et al., 1972; Lewis et al., 1975). Acidosis can create a K^+–H^+ ion exchange across the cellular membrane and inhibit cellular functions required for maintaining normal potassium concentration with a net loss of potassium from cells. The next step that occurs is hypoglycemia due to decreased intestinal adsorption, minimal glycogen reserves in young animals, inhibited glyconogenesis and increased glycolysis (Lewis and Philips, 1978). This series of complex pathophysiological changes, if not promptly corrected, results in death.

Effective management of diarrhea requires prompt action to prevent continued loss of fluids and electrolytes. This is most economically achieved by removal of milk from the diet. This reduces the amount of undigested lactose in the lumen and therefore reduces fluid loss and acidosis. Therapy should include administration of balanced electrolyte solutions either orally or by the intravenous route. The use of intravenous fluid replacement and careful monitoring of animals could save a large percentage of severely affected animals; however, the costs are generally too high to recommend this as a standard procedure.

MIXED INFECTIONS

Severity of diarrhea is not only related to the virulence of the infectious agent and the age of the animal but also due to the presence of multiple infections. Only a minority of cases of diarrhea in animals is caused by a single virus pathogen (House, 1978). Furthermore, it has been suggested that even if a single pathogenetic virus is involved in an infection there may be heterogeneity within the pathogen (Sabara et al., 1982; Spencer et al., 1983). Therefore, if two viruses co-infect an animal and have different sites of replication, the combined effect may be much more severe than if they infected the animal individually. This may help explain why it is difficult to reproduce enteric infections in conventional calves with single plaque-purified virus isolates. Another important factor is the presence of viral–bacterial synergistic interactions. There is accumulating evidence that many bacterial infections can be more severe if combined with a virus infection (Runnels et al., 1980; Leece et al., 1982). Thus *Escherichia coli* generally produces scours only during the first few days of life. However, if an animal is infected with, for example, rotavirus or coronavirus, *E. coli* can colonize and produce a more severe disease at a later age (Fig. 180). The exact mechanisms by which this occurs is unknown; however, viruses may alter fluid transport by virtue of infecting some cells. This alteration allows the build-up of toxin by bacteria that are normally non-pathogenic. Thus the combination of toxin build-up and decreased mobility of the intestine results in diarrhea. In addition, reduced adsorption of nutrients occurs as a result of virus infection. This provides a more suitable nutritional environment for bacteria to grow, adhere and secrete more toxin.

Additionally, virus infection may reduce the rate of cell maturation. Since it is known that the physiological state of cells may alter adherence, it can be postulated that bacteria actually colonize virus-infected intestines but not normal ones. The virus infection may alter the cells in such a way as to allow direct attachment of bacteria to the viral glycoprotein expressed on their membranes or to altered host cell glycoproteins, as has been convincingly shown for virus–bacterial interactions in the respiratory tract (Sanford et al., 1978; Davison and Sanford, 1981).

Finally, some viruses induce Fc receptors on the surface of host cells. If this occurs, antibody-coated bacteria can bind via the Fc receptor and anchor to the cell, allow secretion of toxin, activation of cyclic AMP and increased fluid loss. Although herpesviruses are the only viruses reported to induce Fc receptors (Westmoreland and Watkins, 1974; Lehner et al., 1975; Costa et al., 1977), preliminary evidence suggests that bovine coronaviruses may also induce them (L.A. Babiuk, unpublished data, 1985).

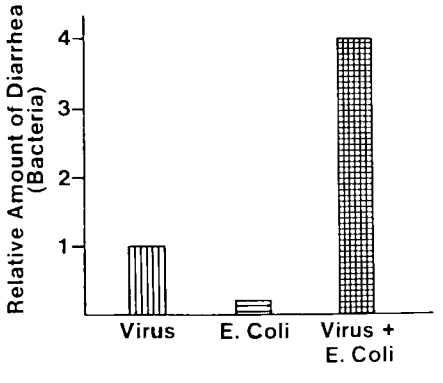

Fig. 180. Effect of the combined infection of virus plus bacteria (*E. coli*) on bacterial shedding and diarrhea.

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IMMUNITY AND IMMUNOLOGICAL CONTROL OF GASTROENTERIC VIRUS INFECTIONS

A major problem with controlling gastroenteric infections in animals is the age at which the animals get the disease. Even if the adult animals are immune and transfer antibody to the young, the antibody must be present continuously in the lumen of the intestine to prevent infection, since serum antibodies are not protective (Woode et al., 1975; Snodgrass and Wells, 1976, 1978a,b). Since many mammalian species do not continue to secrete high levels of antibody in their milk after parturition, the antibody in the intestinal lumen drops rapidly and the young becomes fully susceptible even if it has acquired high levels of serum antibody. Thus, in cattle, the colostrum generally has high antibody levels to most enteric viruses, since the infection rate in adults is high. However, within 5–7 days after parturition antibody levels drop below the threshold required to neutralize virus in the lumen. This is the reason that most enteric virus infections causing neonatal diarrhea in mammals do so after 1 week of age.

The observed requirement for local immunity has stimulated the interest in immunizing the newborn. There is presently an oral vaccine on the market for use in newborn calves to provide protection against rotaviruses and coronaviruses. Unfortunately, if the colostral antibodies can protect against virulent virus they will also prevent the attachment of vaccine virus to enterocytes. Thus the supposed early nonspecific protection, possibly by interferon and the later specific immunological protection do not occur unless the animals are immunized prior to ingestion of colostrum. This is often not possible and, therefore, this vaccine has not proven to be as successful as hoped. To overcome this problem a few attempts have been made at in utero immunization but this is impractical at present under field situations (Newman et al., 1978). However, recent advances may make this approach feasible in the near future.

The most recent trend to overcome the requirement of local immunity in gastrointestinal virus infection is hyperimmunization of the dam. This results in a much higher initial level of antibody in the colostrum, which provides excellent early protection. More importantly, even though antibody levels drop they remain above a threshold level which is protective against normal virus challenge doses. The final method of providing high levels of antibody in the lumen is by feeding monoclonal antibody to the animal. This has proven to be very effective in preventing *E. coli* induced diarrhea in calves (Sherman et al., 1982). The combination of various antiviral monoclonal antibodies with anti-*E. coli* antibody should prove effective under certain situations but is probably of limited value in field situations where animals cannot be handled routinely. Furthermore, the presence of serotypes, especially in rotaviruses (Woode et al., 1983) dictates that each serotype is represented either in the vaccine or in the monoclonal antibody mixture.

The recent advances in recombinant DNA technology have great potential for helping control gastroenteric infections in animals. They are especially relevant to producing vaccines against viruses that do not replicate well in culture. Identification of the antigens involved in protection and the genes coding for them should make it feasible to produce sufficient antigen for immunization. Furthermore, it should be possible to identify the sequences involved in protection and synthesize them (Lerner, 1983) for immunization of dams during pregnancy so as to elevate colostral and milk antibodies. The problem of multiple serotypes combined with multiple agents that can cause diarrhea in ruminants emphasizes the need for inclusion of many agents in a vaccine before a great decrease in disease incidence will be seen. In this regard economical production of these vaccines is mandatory.

A final method of reducing enteric infections is by proper management. Since it is assumed that infections either occur as a result of virus shedding from small numbers of adults or from virus in the environment, animals should not be crowded into contaminated areas. Movement of young into clean environments, away from other animals, will greatly reduce the rate of infection and economic loss. Finally, if only a limited number of animals are carriers, it may be possible to eliminate these and thus break the infection cycle. However, this hypothesis is in need of proper testing.

CONCLUSIONS

Although there is a wide variety of viruses that can cause infections of the gastrointestinal tract of animals, most of them are localized in either the crypts or the enterocytes. Infections are initiated in the proximal part of the small intestine and progress sometimes to the colon. Infections result in loss of adsorptive cells, villous atrophy, fluid loss and ion imbalance. These pathophysiological events lead to anorexia, dehydration and death. Since young animals do not have large reserves of fluids and glycogen, mortality can reach 50–80% in severe outbreaks. However, removal of milk and administration of oral electrolytes can significantly reduce losses.

Effective immunization requires that local immunity is present at an early age. Oral immunization with live attenuated vaccines is difficult due to the high levels of maternal antibody in the milk during the first few days of life. To overcome this problem the present trend is to immunize the dam so as to increase the level of antibody in milk above the threshold level required to prevent infection. As more agents and serotypes involved in gastroenteritis are identified, vaccines will have to combine various pathogens and serotypes for protection. Although in some cases vaccines may be produced by conventional methods, recombinant DNA technology may aid in providing sufficient quantities of antigens to vaccinate against viruses that do not replicate well in culture. However, it will be more difficult to test the efficacy of these vaccines under field conditions than that of many other vaccines due to the difficulty in reproducing the disease and its variable incidence from year to year in herds under natural conditions.

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