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ВСПЫШКА БОЛЕЗНИ СЛИЗИСТЫХ ОБОЛОЧЕК У КРУПНОГО РОГАТОГО СКОТА, ВЫЗВАННАЯ *PESTIVIRUS H*

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Описана вспышка инфекции, вызванной *Pestivirus H* (вирус вирусной диареи – болезни слизистых оболочек третьего вида, BVDV-3), в молочном хозяйстве, сопровождающаяся высокой заболеваемостью и летальностью животных разных возрастов. У части больных животных зарегистрировали полный комплекс ярко выраженных симптомов, характерных для «классической» болезни слизистых оболочек крупного рогатого скота: эрозии и язвы на носовом зеркальце и языке, выделение пены из ротовой полости, серозные выделения из носа, геморрагическое воспаление и выраженные продольные эрозии на слизистой пищевода, сычуга и кишечника. Коровы абортировали на разных стадиях стельности. Коэффициент плодотворного осеменения снизился до 20%. Течение болезни осложнилось вовлечением в инфекционный процесс вируса герпеса крупного рогатого скота 4-го типа, бактерий семейства Pasteurellaceae и *Clostridium* spp. Геном BVDV-3 обнаружили в широком спектре внутренних органов абортированных плодов, телят и взрослых животных. По данным секвенирования возбудитель отнесли к субтипу 3a. Филогенетический анализ участка 5'-нетранслируемой области генома вируса (5'-UTR) показал близкое его родство со штаммами, выделенными в Италии и Бразилии, большинство из которых ранее идентифицированы как контаминанты эмбриональной сыворотки и живых вакцин против вирусных инфекций крупного рогатого скота. В настоящее время средства специфической профилактики против инфекции, вызванной BVDV-3, не разработаны, поэтому необходимы обновление и совершенствование методов диагностики, оптимизация противоэпизоотических мероприятий для недопущения распространения вирулентных штаммов возбудителя, контроль безопасности используемых вакцин.

Ключевые слова: крупный рогатый скот, болезнь слизистых оболочек, *Pestivirus H*, ПЦР, филогенетический анализ

AN OUTBREAK OF MUCOSAL DISEASE IN CATTLE CAUSED BY *PESTIVIRUS H*

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An outbreak of infection caused by *Pestivirus H* (virus of bovine viral diarrhea – mucosal disease of the third kind, BVDV-3) in a dairy farm with high morbidity and mortality in animals of different ages is described. In some sick animals a full complex of pronounced symptoms characteristic of "classical" bovine mucosal disease was registered: erosions and ulcers on the nasal mirror and tongue, foaming from the mouth, serous discharge from the nose, hemorrhagic inflammation and pronounced longitudinal erosions on the mucosa of the esophagus, rennet stomach and intestine. Cows miscarried at different stages of pregnancy. The coefficient of effective insemination decreased

to 20%. The course of the disease was complicated by the involvement of the bovine herpes virus type 4, bacteria of the family Pasteurellaceae and *Clostridium* spp. in the infectious process. The BVDV-3 genome was found in a wide range of internal organs of aborted fetuses, calves, and adult animals. According to sequencing data, the pathogen was classified as subtype 3a. Phylogenetic analysis of the 5'-untranslated region of the virus genome (5'-UTR) showed its close relationship to the strains isolated in Italy and Brazil, most of which were previously identified as contaminants of fetal bovine serum and live vaccines against viral infections of cattle. No specific prophylaxis against BVDV-3 infection has been developed at this time, therefore, it is necessary to update and improve diagnostic methods, optimize control measures to prevent the spread of virulent strains of the pathogen, and control the safety of the vaccines used.

Keywords: cattle, *pestivirus H*, mucosal disease, PCR, phylogenetic analysis

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Conflict of interest

The authors declare no conflict of interest.

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INTRODUCTION

Pestiviruses of cattle are the causative agents of bovine viral diarrhea, a disease of the mucous membranes (BVD-MD), which is characterized by a variety of clinical manifestations including immunosuppression, respiratory and reproductive pathologies, erosive-ulcerative lesions of the mucous membranes of the oral cavity and gastrointestinal tract, enteritis, acute infections with hemorrhagic syndrome, and mucous membrane disease[1–3] [1, 2].

The disease is widespread worldwide. The economic consequences of the infection are mainly associated with the impact of the pathogen on the reproductive system of animals, resulting in reduced fertility rates, abortions, the birth of persistently infected calves, or young animals with developmental defects[4] [3].

Since 2017, representatives of the genus *Pestivirus* in the family Flaviviridae have been classified into 11 genetically distinct types. Three antigenically and genetically distinct species infect cattle: Pestivirus A (bovine viral diarrhea virus type 1, BVDV-1), *Pestivirus B* (bovine viral diarrhea virus type 2, BVDV-2), and *Pestivirus H* (Hobi-like pestivirus, bovine viral diarrhea virus type 3, BVDV-3). Each of them is further subdivided into subgenotypes: *Pestivirus A* has 23 subtypes (1a to 1w), and *Pestivirus B* and *Pestivirus H* have four sub-

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types[5] each (a to d) [4]. All BVDV types cause similar pathologies in animals. The forms of infection vary from subclinical to severe, acute cases with hemorrhagic syndrome and high mortality. The course of the disease depends on the immune status and age of the animal, virulence of the strain, as well as the conditions of housing and feeding [6–13] [2, 5–8]. BVD-MD in cattle is often enzootic, which hinders efforts to eradicate it.

Pestivirus A is widespread worldwide, while *Pestivirus B* is more virulent and less common. These two types are typical representatives of their genus and have been well studied. *Pestivirus H*, on the other hand, was identified relatively recently and classified as an atypical bovine pestivirus. Until now, its role as an etiological agent of BVD-MD in cattle has been poorly understood. It was first discovered in Germany in 2004 in a batch of embryonic bovine blood serum for the biological industry manufactured in Brazil (see footnote 11) [8]. A year later, it was detected in South America in an infected cell culture and buffalo blood[14]. In 2010, the virus was isolated from calves during a respiratory disease outbreak and in cases of persistent infection in Italy (see footnote 9). Subsequently, cases of respiratory disease in calves caused by *Pestivirus H* [9] were reported in Brazil and China, accompanied by gastrointestinal symptoms and high mortality rates [10].

BVDV-3 can be transmitted through airborne droplets, fecal-oral route, and vertical transmission from dam to fetus. In addition to infected animals, live vaccines made using virus-contaminated embryonic bovine blood serum for cell culture cultivation can serve as a source of the virus[15] [10, 11].

Italian researchers have conducted *in vitro* studies showing that BVDV-3 can replicate in the same cell cultures as typical bovine pestiviruses without showing cytopathic effects [7].

On the territory of the Russian Federation, infection of animals caused by *Pestivirus H* was first registered in 2022 [11].

The purpose of this study is to describe a case of an outbreak of mucous membrane disease in cattle caused by *Pestivirus H* in a dairy farm, examine the characteristics of the infection, and provide a phylogenetic analysis of the pathogen.

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MATERIAL AND METHODS

The research was conducted in a livestock farm with a total population of 1750 cattle, including 740 cows. Samples of biomaterial were collected from diseased, deceased, and euthanized animals of different age and sex groups exhibiting characteristic clinical signs. They were tested for the presence of infectious bovine rhinotracheitis virus (IBR), viral diarrhea-mucosal disease (VD-MD) of three types, respiratory syncytial virus (RSV), bovine herpesvirus type 4 (BHV-4), and bacteria of the *Clostridium* genus, as well as *Salmonella dublin*, *Pasteurella multocida*, and *Mannheimia haemolytica*, using PCR-based real-time assay systems developed by us [12].

Pestivirus H was detected using primers and probe sequences: PVspF-5-ccatrcccttag-taggackagc-3; PVHR-5-tccttgatgcgtcgaacca-3; PVHZ-5-(FAM) tagtggtagca-gtgagctccttggat (BHQ1)-3, targeting a 110 bp fragment. The reaction mixture consisted of PCR buffer (60 mM Tris-HCl, pH 8.5; 1.5 mM MgCl2; 25 mM KCl; 10 mM 2-mercaptoethanol; 0.1% Triton X-100), 0.2 mM dNTPs, 0.2 μg of each primer, 0.1 μg of the probe, 1.25 U of Taq DNA polymerase, and 5 μl of DNA template. The PCR temperature profile was as follows: 95 °C for 5 min - 1 cycle; 95 °C for 10 sec, 55 °C for 15 sec, 72 °C for 30 sec - 45 cycles. The experiments were performed using the CFX96 amplification system (Bio-Rad, USA). Fluorescence was measured at 55 °C using the FAM channel. Samples with a Ct value not exceeding 40 were considered positive.

The target fragments were purified from non-specific reaction products and reagents using Agencourt AMPure XP magnetic beads (Beckman Coulter, USA). Subsequently, the concentration of the samples was assessed using the NanoDrop One/OneC Microvolume UV Spectrophotometer (Thermo Scientific, USA). For sequencing, 10 ng of the purified product was used in the reaction with BrilliantDye™ Terminator v1.1 Kit (NimaGen, Netherlands) following the manufacturer's instructions on the Applied Biosystems 310 Genetic Analyzer (Applied Biosystems, USA). Nucleotide sequences were determined for both DNA strands. The primary sequencing data were analyzed using the Sequencer 4.0.5 software (Gene Codes, USA).

The nucleotide sequences of the synthesized fragments were aligned with published sequences of other pestivirus strains using the BioEdit 7.0.0 program. The maximum evolution method in MEGA v.7 software was used to construct a dendrogram. The reliability of the topology was assessed by a bootstrap test (1000 replicates)[16, 17].

RESULTS AND DISCUSSION

The outbreak of BVD-MD in cattle in the farm began in February 2020. The first affected animals were 18-month-old calves housed in the same facility. They showed signs of feed refusal, foamy oral discharge, hyperemia and ulcers on the oral mucosa, excessive salivation, white plaque and erosions on the tongue (see Fig. 1a), erosions on the nasal tapetum (see Figure 1b), conjunctivitis, and diarrhea.

Respiratory symptoms then appeared, including serous nasal discharge (see Figure 2a), rhinitis, and frothy discharge from the oral cavity (see Figure 2b), accompanied by a dry and wet cough. Later, erosive lesions were observed on the skin of the neck and the inner surface of the thighs.

During post-mortem examination, hemorrhagic inflammation of the esophageal and intestinal mucosa was observed, and in some animals, well-defined longitudinal erosions were found on the abomasum mucosa (see Figure 3).

Within 6 months, the morbidity rate reached 90% among the animals, with a 100% fatality rate based on the number of clinically affected individuals. Treatment was ineffective, so all the calves were culled over several months. From 2021 to 2022, animals of various ages (from a few days to several years) housed in

[16] *Kumar S., Stecher G., Tamura K.* MEGA 7: Molecular Evolutionary Genetics Analysis version 7.0 for bigger datasets // Molecular Biology and Evolution. 2016. Vol. 33. pp. 1870–1874. DOI: 10.1093/molbev/msw054.

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different facilities also became ill. They showed symptoms such as feed refusal, conjunctivitis, prolonged diarrhea, and weight loss. Cows aborted at various stages of gestation.

Using PCR, genomes of BVDV-3, herpesvirus type 4, and DNA of *Pasteurella multocida* and *Clostridium* spp. were detected in the samples of pathological material collected from the animals. The table presents the results of the examination of samples from internal organs of deceased and culled animals, as well as from aborted fetuses.

Pestivirus H was detected in a wide range of internal organs (spleen, lymph nodes, lungs, intestines, brain) of the animals of different age groups, including aborted fetuses.

Analyzing the data of the epizootiology, clinical manifestations of the disease, pathological autopsy, and laboratory research results, it was concluded that the primary etiological agent of the disease in the farm was *Pestivirus H*. Its role in the occurrence of abortions, reduced fertility rate, manifestation of systemic infection and enteritis in calves and adult animals, as well as mucosal diseases, was identified.

The characteristic feature of all pestiviruses is their immunosuppressive effect on the animal's body, which increases susceptibility to secondary infections (see footnotes 2, 3) [2]. In this farm, the course of the disease was complicated by the involvement of bovine herpesvirus type 4, bacteria of the *Pasteurellaceae* family, and *Clostridium* spp. in the infectious process.

Based on the sequencing results, the investigated strain of BVDV-3 was classified as subtype 3a. Phylogenetic analysis showed that it is most closely related to strains of the Italian-Brazilian group (see Figure 4). It is known that the severe manifestation of mucosal diseases with a fatal outcome in animals occurs as a result of the mutation of the circulating non-cytopathic variant of the virus into a cytopathic variant, which further superinfects virus carriers, creating a so-called "viral pair"[18]. Another cause may be the introduction of a virulent strain of the virus into a non-immune herd from an external source, resulting in infected animals exhibiting the full spectrum of clinical symptoms described in the literature. Regarding the investigated farm, animals from other sources

а *б*

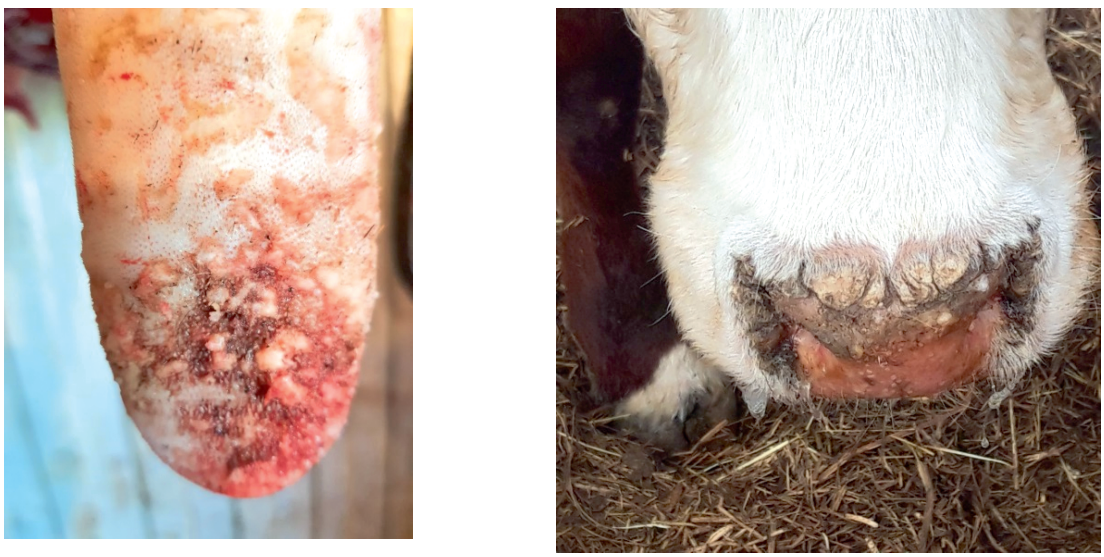

Рис. 1. Клинические признаки заболевания, вызванного BVDV3 у телят:
а – эрозии на языке; *б* – эрозии на носовом зеркальце

Fig. 1. Clinical signs of the disease caused by BVDV3 in calves:
а – erosions on the tongue; *б* – erosions on the nasal speculum

[18]*Goens S.D.* The evolution of bovine viral diarrhea: a review // Canadian Veterinary Journal. 2002. Vol. 43 (12). pp. 946–954.

а *б*

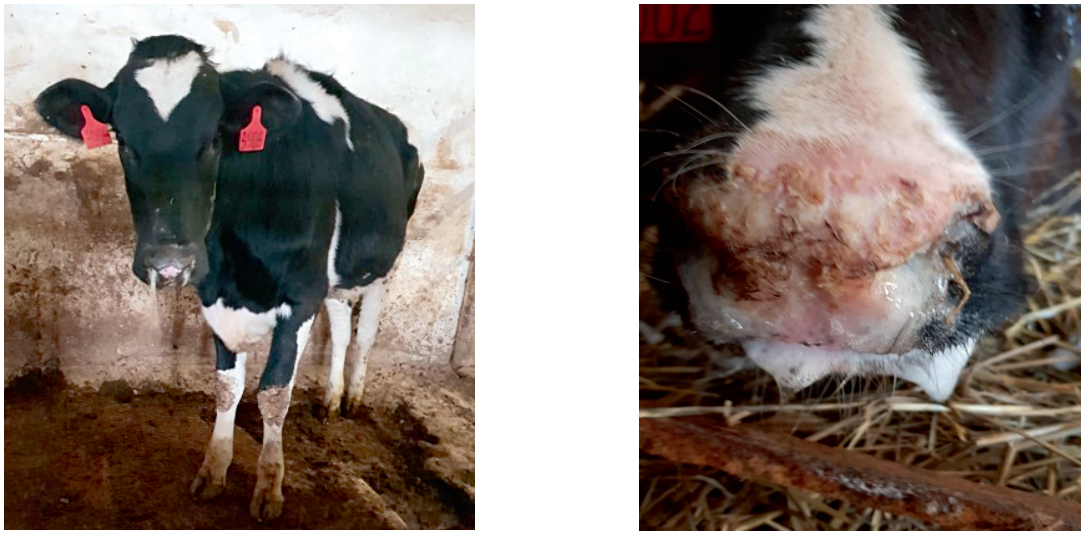

Рис. 2. Клинические признаки респираторного заболевания у телят:
а – серозные выделения из носа; *б* – ринит и выделение пены из ротовой полости

Fig. 2. Clinical signs of respiratory disease in calves:
a – serous nasal discharge; *б* – rhinitis and foaming from the mouth

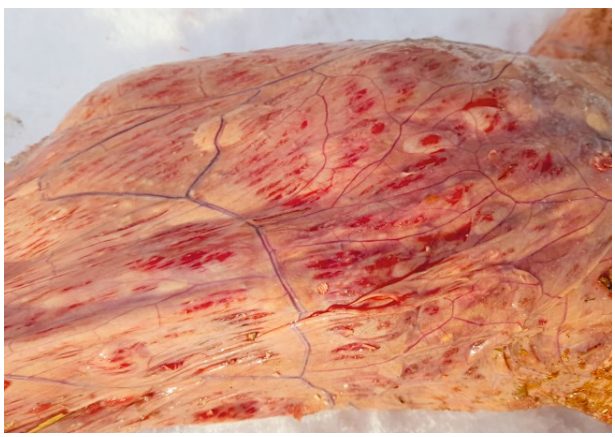

Рис. 3. Эрозии на слизистой оболочке сычуга теленка

Fig. 3. Erosions on the mucous membrane of the abomasum of a calf

have not been introduced there in the past five years, and clinical signs of BVD-MD in cattle have not been previously recorded. It is possible that the introduction of the virulent strain of BVDV-3 could be associated with the use of contaminated live vaccines[19] [13]. Previously, we detected *Pestivirus H* in the samples of imported embryonic serum used for cell culture

Выявление инфекционных агентов во внутренних органах животных при вспышке заболевания
Detection of infectious agents in the internal organs of animals during a disease outbreak

Organ	Viruses		Bacteria	
	Pestivirus H	ВГ-4	*P. multocida*	*Clostridium*
Calves and cows				
Spleen	+	+	–	+
Lymphatic nodes	+	+	+	+
Lungs	+	+	+	–
Kidney	–	+	–	+
Liver	–	–	+	+
Intestine	+	–	–	+
Aborted fetuses				
Visceral organs	+	–	–	–
Brain	+	–	–	–

Note: Pestivirus H - viral diarrhea virus type 3 (BVDV-3); VH-4 - cattle herpesvirus type 4.

[19] *Yurov K.P., Anoyatbekova A.M., Alekseenkova S.V.* New pestivirus-hobi virus - contaminant of vaccines against plague of small ruminants // Veterinary. 2016. N 10. pp. 8–11.

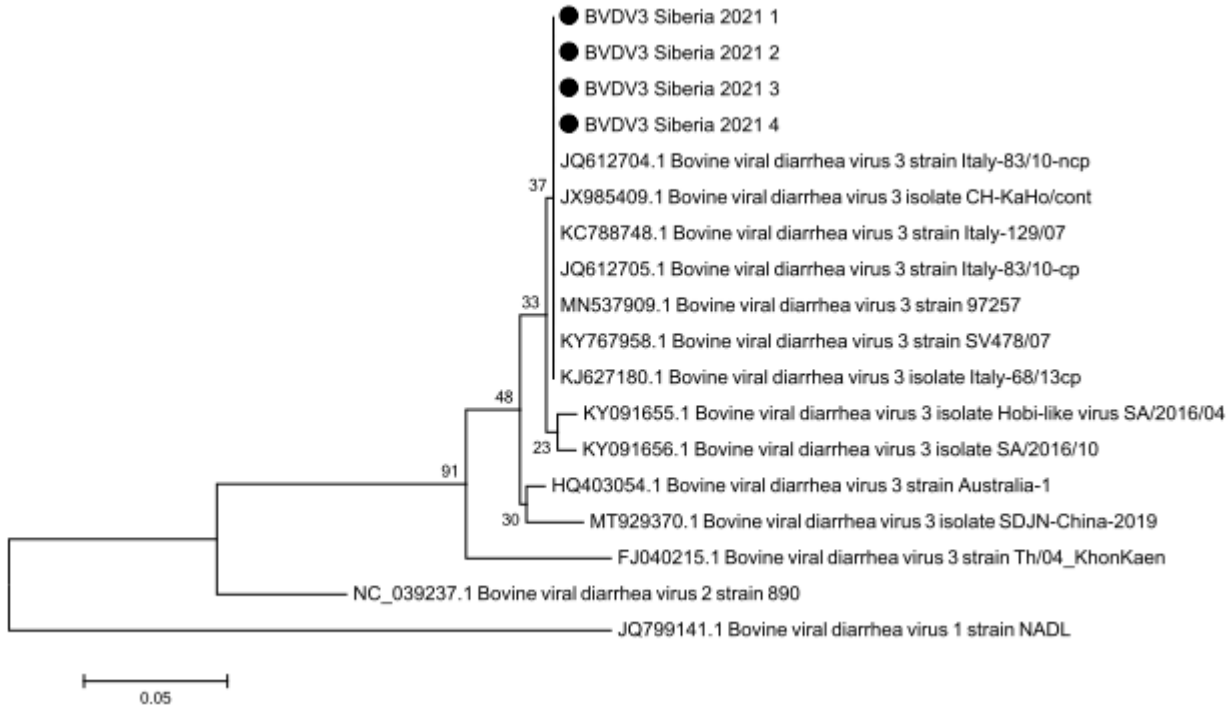

Рис. 4. Филогенетическое дерево, построенное на основе нуклеотидной последовательности области генома 5′UTR *Pestivirus H*; матрица генетических расстояний рассчитана методом максимальной эволюции; указаны индексы статистической поддержки узлов; бутстреп-тест рассчитан для 1000 реплик

Fig. 4. Phylogenetic tree built on the basis of the nucleotide sequence of the 5′UTR *Pestivirus H* genome region, the genetic distance matrix was calculated by the maximum evolution method; indexes of statistical node support are indicated, bootstrap test is calculated for 1000 replicas

cultivation. Based on phylogenetic research results, the isolates were classified as subtype 3a of the Italian-Brazilian group, similar to the strain of BVDV-3 identified in this study [13, 14]. Similar reports exist in the international literature regarding contamination of biological preparations with this virus (embryonic serum, continuous cell culture lines, vaccines for human and veterinary medicine, interferons, trypsin, biotechnological preparations, embryos, stem cells, semen of bull sires, etc.) (see footnotes 12, 15)[20]. Confirmed cases of BVDV-3 spread have been described in relation to the mass use of live vaccines manufactured using contaminated embryonic serum (see footnote 15) [10]. Italian researchers, based on the data on the low frequency of *Pestivirus H* detection in Italy and its absence in circulation in other European countries, concluded that the source of the pathogen was indeed contaminated live vaccines rather than infected animals. Moreover, the isolated BVDV-3 strains belonged to subtype 3a [15].

In Russia, as well as worldwide, specific prophylactic measures against BVDV-3 have not yet been developed, and the use of contaminated biological products may contribute to the spread of the pathogen to different regions of the country. Therefore, strict systematic control of the safety of biological products produced for veterinary purposes is necessary, as well as the updating and improvement of methods for diagnosing and preventing pestivirus infections. The spread of this strain of BVDV-3 in Russia may have significant economic consequences for the domestic livestock industry.

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CONCLUSION

The outbreak of viral diarrhea caused by the virulent strain of *Pestivirus H*, belonging to subtype 3a, with characteristic manifestations of "classical" bovine mucosal disease, has been described. According to phylogenetic analysis of the 5'-UTR genome sequence segment, the isolated virus strain was found to be most closely related to the strains from Italy and Brazil, the majority of which were previously detected in biological preparations for vaccine production. Considering the severe course of the infection, it is necessary to update and improve diagnostic methods, optimize preventive measures to prevent the spread of virulent BVDV-3 strains, and ensure the safety of the vaccines used.

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