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UDC 575.174.015.3:619:616.98:578.833-036.2:636.22/.28 **Review article**

Bovine Pestiviruses (*Flaviviridae, Pestivirus*) genomic diversity and global distribution

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Abstract

The bovine viral diarrhea virus (BVDV) is a member of the genus *pestivirus* of the family Flaviviridae and is capable of infecting cattle in many countries; it is characterized by genetic diversity and various diverse clinical manifestations. Bovine pestiviruses belong to three species: *Pestivirus bovis* (BVDV-1), *Pestivirus tauri* (BVDV2) and *Pestivirus braziliense* (BVDV-3 or HOBIE-like pestivirus). There are 21 subtypes of BVDV-1, 4 of BVDV-2, and 4 of BVDV-3. The most widespread in the world, BVDV-1 is widespread in cattle and is most often detected in European countries. The largest number of subtypes of this virus have been identified in cattle in Italy and China. The virus is wides pread in the Central region of the Russian Federation (subtypes 1a and 1m). A number of BVDV-1 subtypes have been detected in Turkey, including BVDV-1a, 1b, 1c, 1d, 1f, 1h, 1i, 1l, 1r, and 1v. A total of 11 subtypes are presentin native and imported animals in Siberia: 1a (5%), 1b (35%), 1c (5%), 1d (10%), 1f (20%), 1g (2.5%), 1i (2.5%), 1j (5%), 1k (5%), 1p (5%), and 1r (5%). BVDV-2 is the most virulent and is found less frequently, primarily in the United States, Canada, Brazil, Argentina, Uruguay, in European countries (Germany, Slovakia, Turkey, and Italy), and in Asian countries (South Korea, Japan, and Mongolia). Three subtypes have been identified in Siberia: 2a (25%), 2b (10%) and 2c (5%). BVDV-3 circulates in Europe, Asia, and South America. The main route of virus introduction is via contaminated biological products. In Russia, BVDV-3 of the Italian Brazilian group (3a) was identified in seven lots of fetal serum. The existence of virus polymorphism complicates disease diagnosis and reduces the effectiveness of vaccination and control programs.

Keywords: review; *pestiviruses*; cattle; viral diarrhea; genetic polymorphism; species; subtypes; distribution.

Introduction

Bovine viral diarrhea virus (BVDV) is a worldwide disease in cattle, causing widespread outbreaks and significant economic losses; it can infect a wide range of domestic and wild species, including sheep, goats, deer, camelids, pigs, and wild ruminants [1]. It is a *pestivirus* of the *Flaviviridae family*, which also includes other important animal viruses, such as classical swine fever virus and border disease virus. BVDV is a single-stranded RNA virus that can be taxonomically divided into three species: *Pestivirus bovis* (commonly known as BVDV-1), *Pestivirus tauri* (BVDV-2), and *Pestivirus brazilense* (BVDV-3 or HoBi-like pestivirus), which are further divided into subtypes based on genetic analysis [2-5]. At least 21 subtypes of BVDV-1 (1a-1u), 4 subtypes of BVDV-2 (2a-2d), and 4 subtypes of BVDV-3 (3a-3d) have been described [6]. However, additional subtypes have recently been suggested [7].

BVDV is an important pathogen causing reproductive, respiratory, and gastrointestinal diseases in cattle. In addition, it causes endemic infections and significant economic losses in cattle herds worldwide.

Most often, bovine *pestiviruses* are distributed in those countries where industrial animal breeding is developed with high concentrations in limited areas in the absence or non-observance of preventive diseases. The epizootic state is determined by the pathogenetic mechanisms by which these viruses are preserved in cattle populations. *Pestiviruses* of all types usually cause the same forms of pathologies in animals: acute infections with immunosuppression, enteritis, resorption of embryos, abortions at different stages of pregnancy, congenital malformations of the fetus, and the birth of weakened non-viable calves, infertility, pathology of the respiratory system and diseases of the mucous membranes [8-15]. Many researchers pay attention to the possibility of contamination of biological preparations with pestiviruses, which include embryonic serum, cell culture lines used in the biotechnological industry in the production of vaccines for humans and animals, trypsin, other biotechnological preparations, embryos, stem cells, sperm from breeding bulls, etc. [16-23].

The forms of clinical manifestation and the features of the course of the disease depend on the following factors. The main one is the virulence of the virus strain infecting the animal. The state of the animal's immune system and its milk production also play a role. In this case, the conditions of feeding and keeping animals should be taken into account in each specific case [24, 25]. The characteristics of the epizootic state and the stationarity of foci of infection are always directly dependent on the constant circulation of the virus and its evolution, as well as new foci of infection. During the emergence of new disease outbreaks, a wide range of clinical manifestations of the disease may be observed, as described in the scientific literature [26-28].

The literature describes cases of the pathogen spreading among cattle associated with the use of vaccines that were contaminated with non-cytopathogenic strains of pestivirus during production. It is known that cell cultures and fetal serum are used in the production of viral vaccines, which may contain non-cytopathogenic strains of viruses [18-20].

The purpose of this review was to obtain new scientific information on the distribution of genetic diversity of *pestiviruses* among cattle in different countries of the world.

Pathogen

All *pestiviruses* have a complex genome structure, which is represented by a single-stranded positively charged RNA consisting of 12.3 thousand nucleotides. It has an open reading frame (ORF) about 4000 codons long, encoding four structural proteins (C, Erns, E1, and E2) and eight nonstructural proteins (Npro, p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B), flanked at the 5′ and 3′ ends by untranslated regions (5′ UTR and 3′ UTR) [9, 29]. The nonstructural proteins of the virus are involved in viral replication, transcription, and translation, individually or together [9]. Among all regions of the viral genome, the 5′UTR, Npro, and E2 regions are widely used for differentiation (comparative studies) and phylogenetic analysis [29, 30]. The 5′UTR is the most conserved region, contains secondary structures, and acts as an internal ribosomal site of insertion and regulates the conversion of the ORF to the active state upon its insertion into an animal cell; it is most often used for phylogenetic analysis [9].

Numerous studies have proved that changes in the *pestivirus* genome can be caused by three different processes, which are accompanied by the appearance of different mutants (subtypes) of the virus. These include: (1) accumulation of point mutations due to errors in RNA-dependent RNA polymerase; (2) non-homologous RNA recombination; and (3) homologous RNA recombination. It has been established that these mutations in their frequency coincide with the frequency of these processes in other representatives of RNA viruses. As a rule, one point mutation per replication cycle is introduced into the *pestivirus* genome [31, 32]. The average rate of evolution of the virus strains for the 5′UTR region was estimated to be 9.3×10-3 substitutions/site/year, with a confidence interval between 4.8 and 14.7 substitutions per 1000 nucleotides [26]. Taxonomically, BVDV is divided into three species: BVDV-1, BVDV-2, and BVDV-3. The role of each of these three *pestivirus s*pecies in the development of pathology in cattle has not yet been studied in detail. It has been established that all *pestiviruses* are divided into cytopathogenic (cause changes in the monolayer of cell cultures) and non-cytopathogenic (do not cause changes in the structure of the monolayer of cell cultures) [9, 28, 31]. The identified variability of pestiviruses affects the effectiveness of disease diagnostics and control programs. There is no information yet on cross-protection between existing *pestivirus* species [33, 34]. BVDV-1a and BVDV 1b are the most common viruses worldwide, and they, along with BVDV-2a, are included in most commercial vaccines [35].

Epizootology

It is known that viruses can use a strategy based on the following principles to circulate in a cattle population: "infect and disappear" (relay transmission) and "infect and persist". In the first case, this is accompanied by the development of an acute transit form of infection. With this form of infection, susceptible animals transmit the virus to other animals. In the second case, animals develop a persistent form of infection, in which the virus evades the host's immune system. The mechanism of such evasion is characteristic only of *pestiviruses* [36]. Animals with a transit form of infection are short-term and dead-end sources of the virus. Persistently infected animals play a decisive role as a permanent endogenous source of the pathogen in the herd. They maintain a state of stationary distress on the farm [15].

Sources and routes of pathogen transmission

Viruses use a complex strategy for their survival in animal populations, which is based on two principles. They are based on relay transmission of the virus, in which they "infect and disappear" from the body of the infected animal, and also - "infection and preservation" in the body. During relay transmission of the virus, acute clinical forms of infection occur in animals (transit infection). In the second case, the virus is constantly present in the body of the infected animal, causing a persistent form of infection. In this case, the virus evades the effects of the host's immune system using special mechanisms that have no analogues in other viruses [36]. It has been established that animals with a transit form of infection are temporary sources of the virus. Animals with a resistant form of infection serve as a permanent endogenous source of infection in the herd. They play a major role in maintaining the state of stationary distress on farms [12, 15, 25].

The virus is transmitted horizontally. The main modes of transmission are airborne and feco-oral. In this case, the virus was transmitted from an infected animal to a susceptible animal via aerosol inhalation or swallowing of material contaminated with body secretions (saliva, eye and nasal discharge, urine, feces, uterine discharge, and amniotic fluid). There is also a vertical route of transmission from the mother to the offspring [12, 15].

Distribution of virus species

The most widespread species among animals worldwide is BVDV-1, but it is more often registered in European countries. Analysis of nucleotide sequences showed that the majority of virus isolates were BVDV-1 (88.2%). BVDV-2 was detected much less frequently (11.8%). BVDV-1b was the most common, followed by 1a and 1c [37]. The largest number of BVDV-1 subtypes (up to 21) were found in cattle in Italy [38] and China [39].

In Russia, studies on the phylogenetic analysis of virus isolates are limited. A wide distribution of BVDV-1 in cattle in the Central region of the Russian Federation has been established [40]; two antigenically distinct strains of the virus, 1a and 1m, have been identified in the populations of domestic cattle and wood bison [41].

In the Siberian region of Russia, 11 BVDV-1 subtypes were found to circulate among native and imported animals on dairy farms: 1a (5%), 1b (35%), 1c (5%), 1d (10%), 1f (20%), 1g (2.5%), 1i (2.5%), 1j (5%), 1k (5%), 1p (5%), and 1r (5%). The predominant subtype was BVDV-1b, which was detected in both native animals and those imported from other countries with different clinical forms of the disease [36-37]. BVDV-1c and BVDV-1d were detected in serum samples from calves with clinical forms of respiratory tract lesions. These calves were born from heifers imported from Holland and France. BVDV-1f was detected in a calf born from a heifer imported from Holland and in three serum samples from cows and heifers of local breeds from three regions of Siberia. BVDV-1i was detected in the blood serum of a calf of domestic origin. BVDV-1p was detected in a calf born from a heifer from Germany. BVDV-1a was detected in the internal organs of aborted fetuses and in the blood serum of calves of Austrian and Dutch origin. BVDV-1g was detected in a calf of German origin, and BVDV-1k was detected in a calf from a heifer from France. Contamination of fetal serum samples and cell cultures with the BVDV-1j subtype was established [42, 43]. BVDV-1f was also detected in Slovenia [44] and Austria in calves with persistent infection. Cases of detection of this virus subtype have been described in Italy [45] and Turkey, but without description of clinical syndromes of the disease. BVDV-1i was first identified in samples from the United Kingdom (England and Wales) in 1997 [4, 46]. This subtype was first reported in the United Kingdom, where the incidence of cattle affected by this subtype increased from 3% to 6% over a decade [47]. One strain, 436FaUY/052014, was isolated and classified

as BVDV-1i in Uruguay [48]. A case of acute outbreak of severe pneumonia and hemorrhagic enteritis in calves caused by BVDV-1r has been described in the western region of Turkey [49]. Acute clinical forms of fibrinous pneumonia caused by these virus subtypes have been reported in calves in Russia. It was established that these calves were born both to heifers imported from Austria and Germany and to local cows from the Novosibirsk region. Circulation of a large number of BVDV-1 subtypes has been established among domestic cattle breeds and in imported animals in Siberia [42, 43]. Worldwide, BVDV-2 is less common than BVDV-1. It has been isolated from cattle in the United States [50], Canada [51], Brazil [52], Argentina [53], Uruguay [48], European countries (Germany [54], Slovakia [55] and Italy [26]) and Asia (South Korea [56], Japan [57] and Mongolia [58]). It has been established that the main route of introduction of this subtype of the virus into European countries is fetal blood serum and other biological products, in particular vaccines [26, 59]. BVDV-2 is a more virulent species than BVDV-1. It has been established that it has four subtypes (2a-2d) [59]. Most often, UGO is detected in the United States and Canada, where it reaches 50% of all isolated strains [15]. In Russia, in the Siberian region, three subtypes of BVDV-2 have been identified in animals of imported and domestic origin: 2a (25%), 2b (10%), and 2c (5%) [42-43, 60]. It has been determined that the main etiological agents causing damage to the reproductive organs and the development of systemic infection with severe hemorrhagic syndrome in cattle are subtypes 2a and 2b of the second type of virus [15, 51-53]. In Siberia, BVDV-2a was first isolated in 2008 from a locally-originating cow that had aborted; BVDV-2b was detected in heifers imported from the United States during an outbreak of mass abortions and in calves born up to 30 days old with enteritis and pneumonia [42 ,43, 60].

In Brazil, the following BVDV-2 subtypes were found within the species: BVDV-1a (35.9%), BVDV-2b (31.4%), BVDV-1b (10.1%), BVDV-1d (6.7%), BVDV-2c (2.2%), and BVDV-1e (1.1%). BVDV-2c and BVDV-1e were detected for the first time in this study in Brazil [61]. BVDV-2c is a rare subtype. It was detected during massive acute outbreaks of the disease in seronegative animals of different ages in the period from 2013 to 2014 on farms in Germany and the Netherlands. During this period, a sharp decrease in milk production in infected cows, an increase in body temperature, respiratory damage and the development of hemorrhagic enteritis in calves, heifers and cows were observed [62, 63]. Later, in 2016, the virus caused a massive outbreak of the disease among small cattle in southern Italy [64]. We were able to detect the presence of this subtype of the virus in cattle with persistent and transit forms of infection. The animals were imported to Russia from Germany. We should be cautious about the detection of this virus subtype in our country should be treated with caution, since it has not been detected in biological products (vaccines, fetal serum, cell cultures) [42, 43]. The scientific data we have obtained indicate that the maximum spread of the virus in Russia occurred in 2006-2015 and was due to the mass import of highly productive imported animals, which was associated with the intensification of animal husbandry.

At the same time, cases of detection of individual virus subtypes in native animals kept in closed farms, where other animals were not brought from outside, force us to reconsider this conclusion. We assume that these viruses could have been present in the animal population of Siberia for a long time, but the original source cannot be established [43].

The spread of BVDV-3 is limited to several specific regions. It is due to the use of biological products contaminated with the virus. It was established that BVDV-3 was first isolated from a batch of fetal serum in Germany. Serum was collected from animals in Brazil and packaged and repackaged in Europe [65]. Isolate D32/00_HoBi was considered the prototype of the Brazilian group of viruses. BVDV-3 was later identified in cattle from South America [66-68], Asia [69-71], and Europe [13-14]. Other authors have identified genetically distinct subtypes with regional distributions, including the Thai [68], Indian [69], and Italian groups. Thus far, the presence of four genetic groups of this virus (BVDV-3a–d) has been established. There are reports in the international literature on the detection of the BVDV-3 genome in fetal serum. For example, *M. Giammarioli* et al., were able to detect BVDV-3 in 57.7% of the fetal serum lots tested by PCR. They were obtained between 1992 and 2013, filtered and treated with gamma irradiation. Seven lots came from South America, and one from Australia. The origin of the remaining serum lots was unknown. Thanks to the phylogenetic analysis, the authors were able to classify the detected virus as a Brazilian group of viruses and establish that it was imported to Italy with fetal serum [72]. Later, they tested 90 lots of commercial serum, which was manufactured

in the United States and packaged in Europe. BVDV-3 was not detected in these serum lots, but BVDV-1 was present in 19 of them, and BVDV-2 in one [73]. According to other researchers, BVDV-3 was detected in a commercial vaccine against peste des petits ruminants in the Republic of Tajikistan [74]. Data have been published on the presence of the virus genome in 7 of 18 fetal serum samples from two manufacturers used in Russia. Viral RNA was detected in two series of fetal blood serum (manufactured by Biolot LLC) and in five series (manufactured by PAA Laboratories). All virus isolates identified by us were assigned to the Italian subgroup [42, 43]. We also established the etiological role of BVDV-3 in the occurrence of mass respiratory diseases in calves. In addition, the virus was isolated in cell culture [75].

Many researchers believe that BVDV-3 affects the decrease in the fertilization rate, plays a role in the etiology of abortions, the development of systemic infection and enteritis in calves and adult animals.

We have established the etiological role of the virus in the occurrence of mass outbreaks of the disease on three large dairy farms. The source of infection was presumably a live vaccine against lumpy skin disease. Analysis of the results of sequencing the nucleotide sequences of three viral isolates obtained from animals established their identity with the BVDV-3 vaccine strain [76]. There is an opinion of Italian researchers that the low frequency of BVDV-3 detection in Italy and the absence of its circulation in other European countries confirm the hypothesis that it was brought with contaminated biological products, and not with infected animals [26]. These results are consistent with the results of other researchers [76].

Conclusion

The conducted analysis of literary sources indicates that BVDV-1 is most widespread worldwide among the cattle population. BVDV-2 is the most virulent. It is most often detected in North American countries. The main source of pathogens is cattle in international trade and contaminated biological products. The spread of BVDV-3 is currently limited to several regions of South America, Europe and Asia. The primary source is contaminated biological products.

According to the literature in Russia, widespread and fairly high heterogeneity of viral diarrhea viruses circulating among cattle of domestic and foreign origin has been established. Phylogenetic analysis revealed the circulation of 12 subtypes of BVDV-1, 3 of BVDV-2, and 1of BVDV-3. The predominant subtypes are BVDV-1b and BVDV-2a. The main reason for the wide distribution and high level of heterogeneity of BVDV-1 in Russia is the intensification of livestock farming, which is accompanied by an increase in the concentration of animals in limited areas, the movement of animals associated with the livestock trade. In addition, the import of highly productive animals from other countries and the lack of a state control program are of great importance. The circulation of two new subtypes of BVDV-2 (b and c) in Russia has been established. It is necessary to be careful about their detection. It is known that no vaccine has been developed against BVDV-3 in the world. The lack of drugs for the prevention of BVDV-3 creates favorable conditions for the spread of the virus in the cattle population worldwide. In addition, it is important to introduce systematic control of biological products to prevent the spread of the pathogen. Biological products contaminated with non-cytopathogenic strains of the virus should be considered as potential sources of the introduction of emerging species and subgenotypes of bovine *pestiviruses* into new regions and countries of the world. The composition of virus subtypes in the cattle population should be monitored continuously. This approach helps maintain effective diagnostic methods and control measures and serves as an early warning system for the introduction of new *pestivirus* subtypes into naive cattle populations.

Authors' Contributions

TG and AG: conceptualized and designed the study, conducted a comprehensive literature search, analyzed the gathered data and drafted the manuscript. Conducted the final revision and proofreading of the manuscript. All authors have read, reviewed, and approved the final manuscript".

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