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Influenza D virus in cattle (review)

Svetlana V. Koteneva, Alexander G. Glotov, Tatyana I. Glotova, Alexey V. Nefedchenko

Siberian Federal Scientific Centre of Agro-BioTechnologies, Russian Academy of Sciences, Institute of Experimental Veterinary Science of Siberia and the Far East, Krasnoobsk 630501, Novosibirsk Oblast, Russia

ABSTRACT

The influenza D virus was first detected and identified in 2011. The overall amino acid sequence of influenza D virus shares approximately 50% identity with that of influenza C virus, suggesting that both viruses had a common ancestor. Cattle is considered to be the primary natural reservoir for influenza D virus. The involvement of this virus into the bovine respiratory disease complex has been confirmed. The virus causes mild to moderate disease in calves and replicates in both the upper and lower respiratory tracts, promoting bronchopneumonia. The influenza D virus can be transmitted by contact or aerosol over short distances, has a high transmission rate and can potentiate the effects of other respiratory pathogens. There are currently no vaccines or specific treatment for influenza D virus. This virus can replicate and be transmitted by direct contact in ferrets and guinea pigs, which are surrogate models of human influenza infection, as well as in well-differentiated human airway epithelial cells (hAECs). Currently five distinctive lineages of influenza D virus have been identified, co-circulating in worldwide bovine and pig populations that may facilitate genetic reassortment between different viral strains. The virus has a zoonotic potential, and if its pathogenicity for humans changes, its importance for public health will be great. Very high seropositivity rates among persons working with cattle in the USA and Italy have been reported. There is no data in the available literature on the circulation of the influenza D virus in the Russian Federation. Research is needed to study this new virus, as well as monitoring of the virus spread and circulation in our country to understand its role in bovine respiratory disease complex and its zoonotic potential.

Keywords: review, influenza D virus, cattle, respiratory disease complex, genetic lineages, zoonotic potential

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For correspondence: Tatyana I. Glotova, Dr. Sci. (Biology), Professor, Chief Researcher, Laboratory of Biotechnologies – Diagnostic Center, Institute of Experimental Veterinary Science of Siberia and the Far East, Siberian Federal Scientific Centre of Agro-BioTechnologies, Russian Academy of Sciences, Krasnoobsk 630501, Novosibirsky District, Novosibirsk Oblast, Russia, *e-mail: t-glotova@mail.ru*

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Вирус гриппа D у крупного рогатого скота (обзор)

С. В. Котенева, А. Г. Глотов, Т. И. Глотова, А. В. Нефедченко

Сибирский федеральный научный центр агробиотехнологий Российской академии наук, Институт экспериментальной ветеринарии Сибири и Дальнего Востока (ИЭВСиДВ СФНЦА РАН), р. п. Краснообск, 630501, Новосибирская область, Россия

РЕЗЮМЕ

Вирус гриппа D впервые был обнаружен и идентифицирован в 2011 г. Его аминокислотная последовательность примерно на 50% идентична аминокислотной последовательности вируса гриппа C, что предполагает наличие общего предка у обоих патогенов. Основной резервуар вируса гриппа D – крупный рогатый скот. Установлено участие данного возбудителя в комплексе респираторных болезней крупного рогатого скота. Вирус вызывает у телят заболевание легкой и умеренной степени тяжести и реплицируется как в верхних, так и в нижних отделах дыхательных путей, способствуя возникновению бронхопневмонии. Возбудитель гриппа D передается контактным и воздушно-капельным путем на короткие расстояния, имеет высокую частоту передачи и может усиливать действие других патогенов. На сегодняшний день вакцин или специфического лечения не существует. Агент способен размножаться и передаваться при прямом контакте в организме хорьков и морских свинок, являющихся суррогатными моделями для изучения человеческого гриппа, а также в культурах высокодифференцированных эпителиальных клеток дыхательных путей человека hAEC. В настоящее время определены пять генетических групп вируса гриппа D, циркулирующих в популяциях крупного рогатого скота и свиней во всем мире, что может способствовать генетической рекомбинации между различными штаммами. Возбудитель обладает зоонозным потенциалом и, если произойдет резкое изменение его патогенности для человека, может явиться серьезной проблемой для общественного здравоохранения. Сообщалось о высоком уровне серопозитивности к вирусу среди персонала животноводческих ферм в США и Италии. В доступной литературе нет данных о циркуляции возбудителя гриппа D на территории Российской Федерации. Необходимы исследования, направленные на изучение этого нового вируса, а также

проведение мониторинга распространения и циркуляции патогена в нашей стране для понимания его роли в комплексе респираторных заболеваний крупного рогатого скота и зоонозного потенциала.

Ключевые слова: обзор, вирус гриппа D, крупный рогатый скот, комплекс респираторных заболеваний, генетические линии, зоонозный потенциал

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Для корреспонденции: Глотова Татьяна Ивановна, д-р биол. наук, профессор, главный научный сотрудник лаборатории биотехнологии – диагностический центр ИЭВСиДВ СФНЦА РАН, р. п. Краснообск, 630501, Новосибирский район, Новосибирская обл., *Россия, e-mail: t-glotova@mail.ru*

INTRODUCTION

Bovine respiratory disease (BRD) complex is one of the most costly multifactorial diseases, affecting predominantly young cattle in the whole world. The pathogens most often responsible for respiratory conditions are infectious rhinotracheitis virus and viral diarrhea virus (mucosal diseases), respiratory syncytial infection, parainfluenza-3, bovine coronavirus infection and *Pasteurella multocida* (*P. multocida*) *Mannheimia haemolytica* (*M. haemolytica*), *Mycoplasma bovis* (*M. bovis*), *Histophilus somni* (*H. somni*) bacteria [1, 2, 3, 4].

Bovines were not considered susceptible to influenza viruses until the discovery of influenza D virus (IDV). This new species has been identified as a new etiological agent involved in BRD [3]. The interest in research on IDV is increasing and this highlights the importance and global impact that this new virus may have, which mainly affects cattle, although there is a wide range of other species that can act as hosts.

Influenza viruses are RNA viruses belonging to the family *Orthomyxoviridae*, which encompasses four monotypic genera, classified on the basis of antigenic differences between their nucleoprotein (NP) and matrix (M) proteins: *Alphainfluenzavirus*, *Betainfluenzavirus*, *Gammainfluenzavirus* and *Deltainfluenzavirus*, each having one species – Influenza A virus (IAV), Influenza B virus (IBV), Influenza C virus (ICV) and Influenza D virus (IDV). Influenza A, B and C viruses are known to cause respiratory diseases in humans [5].

Unlike other influenza virus types that affect a wide range of mammals and birds and cause epidemics and pandemics, cattle serve as the reservoir of IDV, but its circulation among other mammalian species can not be excluded [3, 6, 7, 8, 9].

Influenza D virus was initially isolated from a diseased pig with the severe respiratory symptoms in Oklahoma (USA) in 2011. It shared approximately 50% homology with the human ICV and was initially thought to be its new subtype [10]. Subsequently, genetic, antigenic and biological differences were identified [11]. In August 2016, the International Committee on Taxonomy of Viruses (ICTV) officially classified IDV as a new species that belongs to the genus *Deltainfluenzavirus* of the *Orthomyxoviridae* family. Cattle are thought to be the primary natural reservoir for IDV according to further studies [11, 12]. Specific antibodies were also found in horses, small ruminants, wild pigs, buffaloes, camels and humans, especially in those who had been in contact with cattle [10, 13, 14, 15, 16], this does not exclude a wide range of hosts and transmission from cattle to humans or other animal species.

This review provides information on recent advances in IDV study, the prevalence of the virus and its role in the bovine respiratory disease complex.

INFLUENZA D VIRUS CHARACTERISTICS

Influenza D virus presents an envelope and a segmented genome, composed of seven negative-sense, single-stranded RNA segments. The virus lacks neuraminidases, as does ICV. Virions are 80–120 nanometers in diameter [17]. The segmented IDV genome encodes nine proteins [18]. The three longest segments produce the proteins PB2, PB1 and P3, needed for replication and viral mRNA synthesis. The fourth segment encodes the hemagglutinin-esterase-fusion (HEF), which aids virus entry into host cells, as well as is the main target of neutralizing antibodies. The broader cell tropism of IDV compared to ICV is explained by receptor-binding pocket in the HEF protein of IDV, which allows it to bind to various cell surface molecules [19, 20]. The fifth segment produces the nucleoprotein NP, which constitutes the viral ribonucleoprotein complex [19]. The sixth segment encodes matrix proteins M1 and M2 covering the viral membrane on it's the inside and exhibiting ion channel activity [21]. The seventh segment produces non-structural proteins NS1 and NS2, which are involved in neutralization of the cellular interferon response and mediate the nuclear export of ribonucleoprotein [22].

Influenza viruses have exploited a variety of strategies to increase their genome coding capacities. Splicing has been demonstrated in the NS and/or M segments of influenza viruses. All types of influenza viruses have a similar mechanism for generating NS1 and NS2 proteins. However, each viral type exploits a unique strategy to generate M1 and/or M2 proteins. Herewith IDV also exhibits a new mechanism for generating the M1 protein when compared to ICV. It uses a proteolytic cleavage strategy similar to the ICV strategy to produce M2 protein from P42

protein, while unlike the ICV M segment, which generates M1 protein through splicing, that solely introduces a termination codon, the splicing of the IDV M segment adds an additional 4-amino-acid peptide into the preceding exon [11].

Studies by J. Yu et al. showed that IDV has exceptional stability at high temperatures and acidity due to the role of HEF glycoproteins and it is considered the most stable of the four influenza viruses [17]. Influenza D virus could resist and retain its infectivity even after exposure to a temperature of 53 °C for 120 min. Furthermore, IDV only lost 20% of the original infectivity when subjected to a low pH of 3.0 for 30 min, compared with the rest of influenza viruses that were completely inactive at low pH. The stability of HEF at extremely low pH highlights a new aspect of IDV replication that requires further study [23].

PATHOGENESIS

Influenza D virus has tropism for epithelial cells upper and lower respiratory tracts and can cause mild to moderate interstitial/bronchointerstitial pneumonia. The virus was also detected in the nasal mucosa, trachea, bronchioles and lung tissues 8 days after infection of calves. It was also detected in the tracheobronchial and mediastinal lymph nodes [3]. The highest viral load of IDV was observed in the nasal cavity. High IDV RNA loads were also found in the olfactory bulb and tonsils in sentinel animals that were infected via aerosol, but IDV tropism for these tissues could not be confirmed by immunohistochemistry test or virus isolation [24].

Salem E. et al. [3], Ferguson L. et al. [18] showed that IDV causes mild respiratory disease in calves experimentally infected by direct contact. Influenza D virus infection can alter the structural integrity of the respiratory epithelium and as a result trigger a significant increase in neutrophils in the trachea of infected animals [18]. This pathological effect seems to suggest an etiological role of IDV in bovine respiratory disease complex. Further investigation of IDV pathogenesis and host responses in calves showed that IDV infection resulted in moderate bronchopneumonia with restricted lesions of interstitial pneumonia and significant activations of pathogen recognition receptors and chemokines CCL2, CCL3, and CCL4 [3]. The signaling pathway to activate the type I interferon response was not substantially activated in the lower respiratory tract of IDV-infected calves [25].

The IDV genome was detected in serum samples from seriously sick cattle, which implies that the virus could cause temporary viremia and spread to other organs; IDV was detected by RT-PCR in feces on day five post infection and in the jejunum on day six post infection, which corresponds to the time of greatest viral RNA replication in the respiratory tract. Yu J. et al. suggested that IDV could replicate within the intestinal tract in a similar way to IAV and IBV. This possible enteric tropism of IDV could be due to the high acid stability of this virus [17]. In addition, the high thermal and acid stability of the virus means that IDV has a high resistance potential abroad, which could explain its high transmission efficiency [3].

A number of researchers have demonstrated that infection in guinea pigs or ferrets is asymptomatic [10, 26]. In guinea pigs, the virus has been detected in both the upper and lower respiratory tracts. However, lungs from infected guinea pigs showed severe and extensive inflammatory changes in the alveolar space with inflammatory cell infiltration, perivascular cuffing, and destruction of bronchiolar epithelium with exudation [26]. Animals also demonstrated apoptosis in epithelial cells of the lungs. In ferrets, IDV replicated in nasal turbinates and was not detected in the lungs [10]. Clinical signs were not observed in infected mice. Influenza D virus replication in mice was observed mainly in the upper respiratory tract, less often in the lower respiratory tract. Low titers of IDV were found in mice intestines [27]. Infected mice showed a significant increase of neutrophils and lymphocytes in the lung [28]. Influenza D virus replication in mice led to activate proinflammatory genes including gamma interferon (IFN-*γ*) and chemokine CCL2 [27].

Taken together, cattle infection experiments collectively suggest that IDV is a mild to moderate respiratory disease pathogen of bovines and acts as an important cofactor of clinical bovine respiratory disease complex.

INFLUENZA D VIRUS SPREAD IN THE WORLD

Influenza D virus is widespread among cattle in North and South America [14, 18, 29, 30, 31, 32], Europe [33, 34, 35, 36, 37], Asia [38, 39, 40] and Africa [41, 42].

Serological studies showed that IDV had been already prevalent in cattle in the USA (Mississippi and Nebraska) since 2003 [12, 29]. A serosurveillance across the USA in 2014 and 2015 showed a high overall seropositive rate of 77.5% nationally; regional rates varied from 47.7% to 84.6%. Seropositive samples were found in 41 of the 42 states [30]. A metagenomic virome study conducted in nasal swab samples from the feedlot cattle collected in the USA, Canada and Mexico found a significant association of IDV with other respiratory diseases [43, 44]. Antibodies to IDV were also detected in sheep and goats in North America, in 5.2 and 8.8% of blood serum samples, respectively [13]. Horses also turned out to be IDV carriers – 15.7% (n = 364) of serum samples were positive for specific IDV antibodies [15]. A recent study evaluated the seroprevalence of IDV in feral swine and found that 57 of the 256 (19.1%) tested sera were positive for IDV and may play a certain role in IDV ecology [14].

The presence of IDV in South America has also been demonstrated by serological studies. In a study from Argentina, 85 (73%) of the 116 farms analyzed had at least one positive animal. Of the 165 serum samples from bulls over three years of age that had been collected in 2013, originally to estimate the seroprevalence of reproductive diseases by HI assay, 112 (68%) were seropositive to IDV [31]. Molecular detection of IDV from a case of bovine respiratory disease has also been reported in Brazil [32].

Influenza D virus is widespread in European countries, including France, Italy, Luxembourg, Ireland and the United Kingdom.

Influenza D virus genome was detected by PCR in 6 (4.5%) samples of lung tissue and nasal swab taken from healthy and clinically sick calves in France in 2015. Coinfections with *P. multocida*, *M. haemolytica*, *H. somni*, bovine respiratory syncytial virus and/or bovine herpesvirus 1 were detected in four out of the six IDV positive samples. In the other two samples, no coinfections with the respiratory pathogens analyzed were detected [33]. Additionally, in France, a serological study was performed on bovine sera (n = 3,326) collected from 2014 to 2018,

in five regions. The resulting total seroprevalence was 47.2%, but the results varied depending on the geographical region (31.0–70.0%) [34].

Samples of nasal swabs and lung tissues were tested between the years 2014 and 2016 in Italy. Of the samples taken from cattle with BRD, there was a prevalence of 8.0%, and of the samples taken from cattle without BRD, there was a prevalence of 3.4% Of the 48 IDV positive samples that came from cattle with BRD, in 62.5% of the cases, IDV was the only viral agent detected, which further supports the hypothesis that IDV may play a primary role in the occurrence of BRD. In 37.5% of the remaining samples, IDV was found together with other respiratory viruses, especially bovine coronavirus. Influenza D virus RNA was detected more often in nasal swabs (9.4%) than in lung tissues (3.4%), which reinforces the finding from experimental infection studies that the upper respiratory tract is probably the preferred site of replication for this virus. Serological studies performed in Italy in 2015, demonstrated high prevalence of IDV (92.4%) in dairy farms [2]. In Luxembourg, IDV seroprevalence among animals was 80.2% in 2012–2016 [35]. In Ireland, during 2014–2016, 320 bovine nasal swab samples from 84 farms were tested by RT-PCR. It was determined that 18 calves (5.6%) were positive for IDV from 10 different farms (11.9%) [36].

In the UK, IDV was found in 8.7% of samples from calves exhibiting signs of respiratory infections. In all cases, the causative agent of influenza was detected in combination with bacterial agents and in some cases as part of viral-bacterial associations. Viral RNA was present in both the upper and lower respiratory tract and pathological changes in lung tissues were observed alongside signs of concurrent bacterial infections. Sequencing of one UK isolate revealed that it is similar to viruses from the Ireland and Italy [37].

Influenza D virus was reported for the first time in 2014 in China, where viral genome was detected in 0.7% of samples, collected from clinically health cattle [38]. It is assumed that IDV has been circulating in Asian cattle since 2011. It was found that IDV was widespread among cattle, buffaloes, pigs, sheep and goats in southern China in 2016–2017 [39].

In Japan IDV was detected in cattle in 2016 and was highly contagious [25]. A recent study on the seroprevalence of IDV in sera collected between 2009 and 2018 showed 57% in average. It was proved that the virus of Japanese lineage has been circulating since 2010 [40]. IDV infection of cattle was first reported in Turkey in 2020 [45].

Bailey E. S. et al. [46] reported that IDV was identified in poultry farm bioaerosols in Southeast Asia. Partial genome sequencing of M segment showed that the IDV found in poultry farms was different from virus strains circulating among cattle in North America. In this study, it was not possible to carry out a complete sequencing of the genome, particularly HEF sequence, and identify the lineage of the virus. Further studies on the susceptibility of poultry to infection are needed to investigate IDV infection in this species.

In Africa, IDV has been known to circulate in cattle since 2012. Antibodies to the virus have been detected in cattle, small ruminants and dromedary camels in Morocco, Togo, Cote d'Ivoire, Benin and Kenya [41]. A high level of seropositivity (99.0%) was found in dromedary camels in Kenya, indicating a potential new host for IDV [41]. These results were confirmed by another serological study performed in Ethiopia, where a high seropositivity of dromedary camels to IDV was also observed [42]. Infection among young cattle in African countries is less common, apparently, due to a less intensive animal farming.

The ability of IDV to cause disease in humans has not yet been thoroughly investigated, and it is not clear whether this virus can sustain human-to-human transmission. Viral replication and transmission by direct contact in ferrets and guinea pigs, used for human influenza infection modelling can suggest it [10, 26]. Holwerda M. et al. it has been proved that IDV replicates efficiently in an *in vitro* surrogate model of respiratory epithelium at ambient temperatures that correspond to the human upper and lower respiratory tract. The authors also demonstrated that IDV can be efficiently propagated onto well-differentiated hAEC cultures at both 33 °C and 37 °C [47].

A serological retrospective study conducted in the USA demonstrated the existence of specific antibodies against IDV present in people, finding a prevalence of 1.3% of the human population during 2007–2009 [10]. This means IDV may pose a potential threat as an emerging pathogen to personnel who are in contact with cattle [10]. A very high seroprevalence was observed in the USA (91%) and Italy (46%) in farm personnel. The prevalence of antibodies against IDV in humans implies that the virus can infect humans and pose a potential threat to human health.

The IDV genome was detected by RT-PCR in nasal wash samples of a pig farm worker in Malaysia [49]. In another study conducted in the United States, IDV genome was detected in bioaerosol samples in a hospital emergency room in North Carolina [50] and Raleigh-Durham International Airport [51]. These results suggest that IDV has zoonotic potential. Humans generally have no preexisting immunity against this newly emerging influenza virus.

INFLUENZA D VIRUS GENETIC DIVERSITY

The complete genomes of more than fifty cattle and five pig IDV strains have been sequenced in six countries: USA, France, Italy, Ireland, Japan, and China. According to recent tests IDVs can be classified into five distinct genetic lineages based on HEF [52]:

1) D/OK – detected in Europe (France, Italy and Ireland), America (USA and Mexico) and Asia (China);

2) D/660 – detected in Europe (Italy) and America (USA and Mexico);

3) D/Yama2016 – detected in Asia (Japan);

4) D/Yama2019 – detected in Asia (Japan and China);

5) D/CA2019 – detected in America (USA).

D/OK and D/660 viruses currently circulating in bovine populations in the USA and Europe frequently showed rearrangement events with each other and antigen-antibody cross-reactivity between them which could result in occurring of new antigenic variants that can overcome previously existing herd immunity and pose a threat to livestock health [17]. Chinese D/OK IDV strains differ from strains of the same genetic lineage from the USA and Italy, and are divided into sublineages in each country. D/OK lineage strains isolated from pigs and cattle in the USA and Italy are grouped into one cluster, which suggests a wider distribution of this genetic lineage in the world and virus transmission between these animal species. According to molecular-genetic study the members of IDV D/OK lineage isolated in dairy cows, pigs and goats from Guangdong, PR China showed very low genetic diversity.

In the D/660 lineage, the strains from France and the USA diverged from each other earlier than strains within each country, suggesting that this lineage also evolved into sub-lineages in different countries. Interesting that D/Yama2016, and D/Yama2019 lineages are only present in Japan, and diverge substantially from D/OK and D/660 lineages circulating in other countries. However, in 2022 IDV, identical the D/Yama2019 genetic lineage, was reported from China. During the recent outbreak of bovine respiratory disease in South America, the first case of IDV detection was reported and it was established that the virus circulating in Brazilian cattle herds is divergent from previously described IDV lineages from North America, Europe and Asia according to phylogenetic analysis results [32]. In addition, a new genetic lineage was reported from Turkey (D/Bursa2013) [53] and a new reassorted virus in Namibia [54]. These results highlight the need to monitor the IDV prevalence for better understanding of the viral epidemiology and evolution.

CONCLUSION

The analysis of the publications demonstrates the spread of IDV among animals worldwide. Cattle is considered the main reservoir of the virus and plays a significant role in its spread. Influenza D virus is an important cofactor of clinically BRD complex as it can cause alone a mild to moderate respiratory disease with a high transmission rate, and can potentiate the effects of other pathogens. The increasing number of IDV infection outbreaks in pigs and cattle in recent years may be associated not only with the growing attention to this new pathogen, but also with an increased virulence of the virus. Influenza D virus has the potential for spillover and adaptation to humans, and if there is a drastic change in its pathogenicity to humans, it could be a major public health concern.

The IDV peculiarity is its relative stability in comparison with other influenza viruses, suggesting its evolution is slow. There are currently no vaccines or specific treatment for influenza D virus.

In Russia, studies on IDV spread and its role in the BRD complex have not been conducted. International trade in livestock entails the risks of the virus introduction into our country, which can facilitate the spread of a new infection among animals and pose a potential threat to human health, if no control measures are taken. Therefore, the study of IDV circulation in different regions of the Russian Federation is important to prevent the infection in animals and humans.

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INFORMATION ABOUT THE AUTHORS / ИНФОРМАЦИЯ ОБ АВТОРАХ

Svetlana V. Koteneva, Cand. Sci. (Veterinary Medicine), Leading Researcher, Institute of Experimental Veterinary Science of Siberia and the Far East SFSCA RAS, Krasnoobsk, Novosibirsk Oblast, Russia; *https://orcid.org/0000-0003-2649-7505, e-mail: koteneva-sv@mail.ru*

Alexander G. Glotov, Dr. Sci. (Veterinary Medicine), Professor, Chief Researcher, Institute of Experimental Veterinary Science of Siberia and the Far East SFSCA RAS, Krasnoobsk, Novosibirsk Oblast, Russia; *https://orcid.org/0000-0002-2006-0196, e-mail: glotov_vet@mail.ru*

Tatyana I. Glotova, Dr. Sci. (Biology), Professor, Chief Researcher, Institute of Experimental Veterinary Science of Siberia and the Far East SFSCA RAS, Krasnoobsk, Novosibirsk Oblast, Russia; *https://orcid.org/0000-0003-3538-8749, e-mail: t-glotova@mail.ru*

Alexey V. Nefedchenko, Dr. Sci. (Veterinary), Associate Professor, Leading Researcher, Institute of Experimental Veterinary Science of Siberia and the Far East SFSCA RAS, Krasnoobsk, Novosibirsk Oblast, Russia; *https://orcid.org/0000-0002-4181-4268, e-mail: homeovet@yandex.ru*

Котенева Светлана Владимировна, канд. вет. наук, ведущий научный сотрудник, ИЭВСиДВ СФНЦА РАН, р. п. Краснообск, Новосибирская обл., Россия; *https://orcid.org/0000-0003-2649-7505, e-mail: koteneva-sv@mail.ru*

Глотов Александр Гаврилович, д-р вет. наук, профессор, главный научный сотрудник, ИЭВСиДВ СФНЦА РАН, р. п. Краснообск, Новосибирская обл., Россия; *https://orcid.org/0000-0002-2006-0196, e-mail: glotov_vet@mail.ru*

Глотова Татьяна Ивановна, д-р биол. наук, профессор, главный научный сотрудник, ИЭВСиДВ СФНЦА РАН, р. п. Краснообск, Новосибирская обл., Россия; *https://orcid.org/0000-0003-3538-8749, e-mail: t-glotova@mail.ru*

Нефедченко Алексей Васильевич, д-р вет. наук, доцент, ведущий научный сотрудник ИЭВСиДВ СФНЦА РАН, р. п. Краснообск, Новосибирская обл., Россия; *https://orcid.org/0000-0002-4181-4268, e-mail: homeovet@yandex.ru*

Contribution: Koteneva S. V. – literature searches; Glotov A. G. – text preparation, literature analysis and synthesis; Glotova T. I. – administration, editing; Nefedchenko A. V. – literature searches.

Вклад авторов: Котенева С. В. – подбор литературных источников, работа с литературой; Глотов А. Г. – подготовка текста, работа с литературой, анализ и обобщение; Глотова Т. И. – администрирование, редактирование текста; Нефедченко А. В. – подбор литературных источников.