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A NEW GENUS OF INFLUENZA VIRUS — *Influenza D virus*
(review)

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Abstract

Influenza D virus (IDV) discovered in swine in 2011 and then in cattle and other animals was subsequently classified as a separate genus *Influenza D virus* (*Orthomyxoviridae*, *Deltainfluenzavirus*) (B.M. Hause et al., 2014). It is assumed that influenza D virus descended from human influenza C virus (ICV) from 300 to 1,500 years ago (Z. Sheng et al., 2014; S. Su et al., 2017). Its virion contains seven segments of RNA. The IDV genome sequence is 50 % different from ICV, no recombinants are formed between IDV and ICV, and no cross-reactivity of the antibodies occurs as well (B.M. Hause et al., 2011). Retrospective analysis showed that the virus has been circulating in North America since 2002 at the latest (M. Quast et al., 2015). Cattle is the main reservoir of the pathogen (L. Ferguson et al., 2015) but it also infects small ruminants, horses (H. Nedland et al., 2018), camels (E. Salem et al., 2017), and pigs (Z. Yan et al., 2018), including in wildlife (L. Ferguson et al., 2018). The virus provokes bacterial infections which affect the lung parenchyma, slowing growth, decreasing milk yields, and causing reproductive delay. In severe acute disease, IDV can move into the bloodstream in cattle and goats via penetration through capillaries lining respiratory tract. Calves possess passive immunity due to natural feeding that weakens in the 6-8-month-old animals, making them susceptible to the infection. Small ruminants serve as a reservoir for IDV and can transmit infection to other livestock. Wild boars can also be dangerous as IDV vectors between wild and domestic animals. IDV has not yet been found in poultry. At present, three types of influenza D virus are circulating simultaneously. The experiments have shown that the virus infects polecats (B.M. Hause et al., 2011) and guinea pigs (C. Sreenivasan et al., 2015). IDV successfully replicates in human's respiratory epithelial cell culture at 33 to 37 °C (M. Holwerda et al., 2019). The selection pressure for IDV is higher in pigs than in cattle and goats, so IDV, if successfully adapted, can spread widely among pigs. Therefore, a new public health risk could arise given the similarity in receptors between pig and human. The accumulated data on the ability of IDV to infect humans are ambiguous and require further in-deep study. Particular attention should be paid to persons involved in the management of farm animals susceptible to IDV. The pathogen is widespread across the planet and poses a potential threat to agriculture in countries where the breeding of cattle, small ruminants and pigs is of great importance to the economy. The fact that the virus is capable of infecting a wide range of hosts makes it potentially harmful to humans too.

Keywords: influenza D virus, influenza C virus, large cattle, small ruminants, pigs

Influenza viruses comprise four genera of *Ortomyxoviridae* family, the *Influenza A* (*Alphainfluenzavirus*), *Influenza B* (*Betainfluenzavirus*), *Influenza C* (*Gammainfluenzavirus*) isolated in 1930-1940, and *Influenza D* (*Deltainfluenzavirus*) discovered in 2011 in a pig and then in cattle and other animals [1-3]. The formal assignment to the genera is based on no serological cross-reactivity determined by antigenic properties of the internal proteins (ribonucleoproteins) of the virion.

Influenza viruses can infect and cause disease in humans, mammals, birds, and possibly other members of the animal kingdom. This pathogen is able

to overcome the interspecies barrier [4, 5]. Its variability is due to two mechanisms, the genetic drift (point mutations) and reassortment. The reassortment occurs when multiple viruses replicate in a host cell during co-infection. When the progeny viruses are assembled, the original viral RNA segments are shuffling and a pathogen with new properties appears [6]. The body's immune system fails to provide proper protection against an altered virus, which results in re-infection of the host macro-organism [7]. This virus spreads over a population, causing severe pandemics [8-10].

This review summarizes the latest data on *Influenza D virus*, its global spread and the range of host species susceptible to this pathogen.

Currently, influenza A viruses (IAVs) are the most widespread, diverse, and epidemiologically significant. IAVs differ in two surface proteins, the hemagglutinin and neuraminidase (18 and 11 subtypes, respectively). Waterfowl is the IAV reservoir, with the exception of H17N10 [11] and H18N11 [12] viruses detected only in bats [13, 14]. IAVs are isolated from a large number of wild and domestic animals. However, reports of IAV infection in cattle are rather rare compared to other agricultural mammals [15]. Over a long period of observations, only few works have addressed the problem of IAV infection in ruminant ungulates. One of the first was the report on the detection of antibodies to H3N2 in yaks in Nepal in 1974 [16]. In 1977 IAV was isolated from a calf [17]. Later, IAV was shown to infect various domestic ruminants without causing massive serious diseases [18, 19] but with a decrease in milk yield [20, 21]. In a number of studies, antibodies to the seasonal human influenza viruses H1N1 and H3N2 were detected in cattle [22-24]. It was serologically evidenced that cultured bovine respiratory epithelium is permissive for the growth of equine H3N8 influenza virus in vitro [25] and that calves, when infected experimentally, can support replication of the H5N1 virus isolated from cats [26].

In the human population, two antigenically distinct influenza B virus (IBV) strains, Victoria and Yamagata [27] capable of reassorting [28] circulate. Their primary host is humans, but since 1999, the virus has been isolated from seals (*Phoca vitulina*) [29, 30], and in the last decade, data on susceptibility of domestic animals to the pathogen have appeared [31]. Influenza C viruses (ICVs) are widespread in humans. As a rule, the disease is asymptomatic or a mild respiratory distress occurs in children under 6 years of age [32, 33]. Six genetically and antigenically different lines have been described [34] that form reassortants during co-circulation [35]. The main reservoir is humans, although ICVs are also detected in domestic pigs [36, 37] and dogs [38, 39]. In pigs, the transmission of the virus from one animal to another has been experimentally shown [40, 41]. Interspecies transmission of influenza C virus between humans and pigs is possible in vivo [42]. It was recently found that camels have antibodies to ICV [43], and in 2016, ICV which was 95 % similar to human influenza viruses was isolated from a sick calf in the United States [44, 45].

A novel genus of influenza virus. D/swine/Oklahoma/1334/2011 (D/OK) influenza virus isolated in April 2011 in Oklahoma from a 15-week-old pig exhibiting influenza-like illness, was only 50 % similar to human ICVs. The isolate was initially designated as C/OK. Like ICV, the isolate has a segmented RNA genome (seven segments). Phylogenetic analysis found that the divergence between human ICV and C/OK is similar to that between influenza A and B viruses. Hemagglutination inhibition (HI) assay showed no cross-reactivity between human ICV and C/OK. Serological screening revealed prevalence of C/OK antibody diagnostic titers in 9.5 and 1.3 % sera from pigs and humans, respectively. In cell culture, the C/OK virus exhibits a broader cellular tropism than ICV. In ST cells (swine testis cell line) on day 3, this virus, like the influ-

enza virus, caused cytopathic effects. In addition, the new virus was easier to culture than ICV [1]. It was found that ICV and C/OK failed to form reassortants. On this basis, the authors proposed to classify the new group as influenza D virus (IDV), a separate genus of the *Orthomyxoviridae* family [46].

Further investigations showed the widespread distribution of IDV on other continents and the ability of the pathogen to infect other mammalian species (cattle, goats, sheep, etc.). This pose a potential threat of IDV to the agriculture and public health around the world, including in the Russian Federation, the countries of the former USSR, and Mongolia, where the breeding of cattle, small ruminants and pigs is economically important.

Prevalence and hosts of influenza D virus. The IDV was first isolated from pigs, but further studies have shown that cattle play a major role in IDV circulation [47, 48]. Currently, IDV has been found in cattle in China [49], France [3], USA [50], Italy [51], Mexico [52], Japan [53], Ireland [54], Luxembourg [55], Great Britain [56]. IDV plays an important role in the Bovine Respiratory Disease Complex (BRDC) and can significantly reduce animal performance indicators in animals. It is most likely that IDV provokes the development of bacterial infections [57] with a damage to the pulmonary parenchyma, slowing growth rate, and delayed puberty onset. The death of animals, a decrease in milk and meat production, and the cost of treatment cause huge losses to the economy of farms.

Using cell cultures, Hause et al. [46] detected another five isolates that were more than 96 % identical to the D/swine/Oklahoma/334/2011 virus, with 18 % of animals being infected. Later Ferguson et al. [50] showed that 6-8-month-old calves at pre-sale points (Mississippi, USA) are massively infected. The virus was detected in 2.4 % of healthy animals and in 23.6 % of animals with BRDC symptoms [50]. By this age, passive immunity due to natural feeding weakens and the calves become susceptible to infection.

IDV is detected in USA, France, Italy, Ireland, and Great Britain, when studying outbreaks of respiratory diseases in cattle, including those associated with the death of animals. Collin et al. [2] identified IDV in 4.8 % of sick animals from Kansas, Texas and Nebraska and established co-circulation of two lines, the D/swine/Oklahoma/1334/2011 (D/OK) and D/bovine/Oklahoma/660/2013 (D/660). The reassortment between viruses of these two lines has also been found [2]. Ducatez et al. [3] examined archival cattle samples (2010-2014) and proved that IDV has been circulating in France since at least 2011. In the Po Valley (Northern Italy), IDVs have also been isolated during outbreaks of respiratory disease [51]. In 12 provinces of Italy, 6.5 % of 895 dead animals died from influenza D virus [58].

In 2014-2016, IDV was detected in Ireland in nasal swabs in cattle with clinically diagnosed respiratory diseases [54]. In the UK, in 8.7 % of dead animals with respiratory infection syndromes, influenza D virus was usually detected as the only viral agent, always combined with bacterial infection [56]. To date, all viral sequences described in European countries are grouped in clade D/swine/Oklahoma/1334/2011.

In China, IDV has been circulating since 2014. In a screening surveillance, the RNA of the virus was found in 0.7-2 % of animals that had no signs of the disease cases, which indicates an asymptomatic infection [49, 59]. In the study of nasal washings in cattle with various clinical sings of diseases in 2016, Zhai et al. [59] found the virus in 12.8 % of cases in the Holstein breed and in 7.3 % in the local yellow cattle and established the penetration of the virus into the circulatory system through the capillaries lining the respiratory tract. The homology of isolates from China ranged from 95.35 to 99.22 % as compared to

the American isolates [49].

Seroprevalence of animals is an important indicator of the IDV prevalence. In 2014 Hause et al. [46], using D/OK and D/660 as antigens, found geometric mean titers for both viruses at a dilution of 1:40 and higher in cattle from different states. Interestingly, in a retrospective study of the blood sera of adult animals from the state of Nebraska (USA) in 2003-2004, Luo et al. [60] identified 81.9 % of animals with antibodies to IDV at all 40 randomly selected farms. Therefore, IDV emerged in this territory at least in 2003. In 2014, testing of paired serum samples from 242 calves revealed that 98% and 76% of animals were seropositive for IDV at 1 week and 3 months, respectively, while antibody titers in most calves decreased. These results prove that newborn calves have high levels of maternal antibodies against IDV. Similar data were reported for eight prefectures of Japan in 2010-2016 (1267 samples from 166 farms): the IDV seropositive samples averaged 30.5 %, increased with the age of the animals and did not depend on the breed. This means that IDV has been circulating in Japan since at least 2010. Currently, the virus is widespread in cattle populations throughout the country [61]. Antibodies to IDV were detected in 92.4 % of animals from 42 farms in Northern Italy (the Province of Mantova) [58], in 80.2 % of adult animals without respiratory symptoms in Luxembourg [55]. From 31 to 70 % (47.2 % on average) of animals were seropositive in the regions of France [62]. IDV prevalence has also been shown in North (Morocco, 2012-2015) and West Africa since 2012 (Togo and Benin, 2014) [43]. The authors associate the emergence of this new pathogen with the import of animals from Europe to Morocco.

Reports on the isolation of the virus in different countries over the past years and retrospective studies of blood sera for anti-IDV antibodies indicate that IDV began circulating in cattle no later than in 2003 and is now common on different continents. The high percentage of seropositive animals suggests that the virus spreads rapidly and leads to a decrease in milk yield, weight gain in young animals, and even death.

Interspecies transmission of IDV can occur when keeping different species of farm animals together. A survey of 648 animals from 141 farms in the United States and Canada showed the presence of anti-IDV antibodies in 5.2 % of sheep and 8.8 % of goats [63]. In a retrospective study of the sera of 64 goats and 85 sheep (2001-2007), one goat sample contained antibodies to IDV (Massachusetts, 2002). This allowed the authors to believe that IDV has been circulating in the United States since at least 2002, and has become most widespread since 2011. It was found that on the North American continent, small ruminants have antibodies to two lines, the D/bovine/Oklahoma/660/2013 (D/660) and D/swine/Oklahoma/1334/2011 (D/OK) isolated from a cow and a pig. It can be concluded that these species are susceptible to the new virus and have been in contact with it in different states of the United States and provinces of Canada. Salem et al. [43] found antibodies to IDV in small ruminants in North Africa (Morocco) and West Africa (Togo and Benin) in 2013 and found the virus to be similar to D/Bovine/Nebraska/9-5/2012 strain. In 2016 in China (the Guangdong Province), RT-PCR detected IDV infection in 33.8 % of goats with various symptoms of diseases and in one of eight rectal smears from animals with severe diarrhea [59]. In France, antibodies were found in 1.5 % of small ruminants [62]. Consequently, small ruminants serve as an IDV reservoir and can transmit infection to other animal species, change the biological characteristics of the virus, and contribute to its evolution.

The pig is the animal from which IDV was first isolated [1]. Wild pigs are mobile and contacting with sources of infection, primarily cattle, and can

spread the virus. In 2012-2013, in the states of Gawai, North Carolina, Oklahoma and Texas (USA), from 7.8 to 28.6 % of wild boar populations had antibodies to IDV [64]. Also, 42.7 % of 96 IAV seropositive samples (2010-2013) contained antibodies to IDV. This study showed that wild boars pose a danger with regard to IDVs and also other viruses as vectors of infection between wild and domestic animals.

IDV is rapidly spreading among domestic pigs in the USA, Italy, China, and Luxembourg. During outbreaks of respiratory diseases in the Po Valley (Northern Italy), IDV RNA was detected in a nasal swab of a sow, and, furthermore, D/swine/Italy/199723-3/2015 was isolated on cell cultures [51]. During the same outbreak, other authors examined 845 clinical samples from 448 pig farms, identified IDV RNA in 2.3 % of the specimens, and isolated three strains closely associated with D/swine/Oklahoma/1334/2011 cluster [65]. The serological screening that they also performed for 3698 pig blood sera from the archived collections of 2009 and 2015 found 0.6 and 11.7 % seropositive samples, respectively. In Guangdong Province (PRC) in 2016, RT-PCR detected 36.8 % of nasal washes positive for IDV in pigs with respiratory symptoms and 28.9 % of lung samples positive for IDV from dead pigs [59]. In Luxembourg, a study of nasal lavages from healthy domestic pigs showed a low spread of the virus, 0% in 2009 and 0.7% in 2014-2015, and the low concentration of viral RNA in the samples did not allow nucleotide sequencing [55]. Low seroprevalence in pigs indicates that they are less involved in IDV circulation than cattle, but as a result of the evolution of the virus, it may become more dangerous for this species. It has been shown that the selection pressure on the virus in pigs is higher than in cattle and goats [66]. It cannot be ruled out that successful adaptation of the virus will lead to its wide spreading among domestic pigs and even among humans, given the similarity of pig's and human's receptors.

Influenza D virus infection in horses was first reported in 2018. Two IDV lines were shown to co-circulate in populations in the western United States [67]. Antibodies were detected in 15.7 % of the sera of adult horses. Out of 57 positive samples, 23 were positive for both lines.

Currently, IDV infection has arisen in one-humped camels in Kenya [43] and Ethiopia [68]. In some territories of Ethiopia, up to half of the camels have antibodies to IDV, with both detection rates and titers being the highest for the strain from Japan, the D/bovine/Yamagata/10710/2016 as compared to D/swine/Oklahoma/1334/2011 and D/bovine/Nebraska/9-5/2013. Nevertheless, in Mongolia, no antibodies were detected when testing the blood sera of two-humped camels [68].

When animals of various species have the same grazing area and watering points, frequent contacts between them enable the virus to adapt to a new host. Possibly, this is happening with IDV which was initially capable of infecting cattle, and now its various strains can infect other mammalian species as well. Given the features of the evolution of other genera of the influenza virus, especially IAV, IDV adaptation to humans is quite possible. Therefore, IDV which is spread worldwide among domestic animals and can affect a wide range of hosts, is potentially dangerous to humans and birds. Although Quast et al. [63] in a study of 150 blood sera of turkeys and 100 chickens from 25 poultry farms in the states of Minnesota and Iowa in 2014 did not reveal antibodies to IDV, it is impossible to reject the ability of IDV to infect birds.

Experimental infection of mammals with IDV. The experimental infection with IDV was studied in domestic and wild pigs, ferrets, guinea pigs, and cattle. In the first experiment, pigs aged 2.5 months had D/swine/Oklahoma/1334/2011 virus replicating in the turbinates and found in nasal swabs, but

not in the trachea and lungs, that is, its replication could be limited to the upper respiratory tract. No clinical symptoms or lesions characteristic of influenza were observed. Virus was transmitted to "clean" animals through direct contacts with infected animals [1]. An experiment with 4-month-old healthy calves showed the likelihood of D/bovine Mississippi/C00046N/2014 infection with moderate signs of the disease (dry cough, nasal flow, apathy). The virus was detected in the turbinates, trachea, bronchi and lungs and was also transmitted by contact when infected and healthy calves were kept together [48]. A similar experiment with wild boars captured in nature also showed the transmission of the virus between animals [64].

The ferret is one of the best experimental models for respiratory infections in mammals, as it develops signs of disease similar to humans, and these animals are also able to become infected through aerosols. In experimental infection, D/swine/Oklahoma/1334/2011 was detected in the turbinates and absent in the lower respiratory tract of the ferret. Infection occurred as a result of direct contact of animals, but no airborne transmission of the pathogen was observed. Clinical symptoms and lesions characteristic of IAV were absent [1]. No transmission of the virus from calves to ferrets was observed when toys soaked with nasal secretions from a calf infected with IDV were used as fomite [48] to infect 30-day-old guinea pigs. In guinea pigs, unlike ferrets, replication of D/bovine/Oklahoma/660/2013 virus occurred in both upper and lower respiratory tracts and the lungs, but no clinical symptoms appeared. The transmission of the virus from infected to "clean" animals occurred only through direct contact [69]. The Table summarizes information on susceptibility to IDV.

Mammals susceptible to *Influenza D virus* (*Orthomyxoviridae*, *Deltainfluenzavirus*), the pathogen detection and spread of

Species	Detection	Country	References
Cattle (*Bos taurus*)	RT-PCR, isolation, ELISA, experimental infection	USA, China, France, Italy, Ireland, Luxembourg, Morocco, Togo, Benin	[2, 3, 43, 46-56, 58-62]
Buffalo (*Bubalus arnee*)	RT-PCR	China	[59]
Sheep (*Ovis aries*)	ELISA	USA, Canada, Togo, Benin	[43, 62, 63]
Goat (*Capra hircus*)	RT-PCR, ELISA	China, USA, Canada, Togo, Benin	[43, 59, 61, 62]
Pig (*Sus scrofa*)	RT-PCR, isolation, ELISA, experimental infection	USA, China, Italy, Luxembourg	[1, 51, 55, 59, 64, 65, 79]
Horse (*Equus ferus caballus*)	ELISA	USA	[67]
Dromedary (*Camelus dromedarius*)	ELISA	Morocco	[43, 68]
Ferret (*Mustela putorius*)	Experimental infection		[1, 50]
Guinea pig (*Cavia porcellus*)	Experimental infection		[69]
Human (*Homo sapiens*)	ELISA, in vitro	USA	[1, 77, 78]

Note. RT-PCR — reverse transcription PCR, ELISA — enzyme-linked immunosorbent assay.

Based on the study of hemagglutinin-esterase-fusion (HEF) glycoprotein which drives the fusion between viral and host cell membranes, Song et al. [70] hypothesized the mechanisms that provide influenza D virus with a broader cell tropism to different hosts compared to influenza C virus.

IDV origins, differences, and diversity. Although research on IAV, IBV, and ICV began in the 1930s-1940s, IDV was not discovered until 2011. Probably, it previously circulated in another unknown animal [1], and after adaptation to cattle it quickly spread across the globe. IDV is identical to ICV in structure, has a negative sense RNA genome represented by seven segments of single-stranded RNA. The IDV and ICV genome sequences are shown to be only half similar [1] while the six known lines of ICV are 95 % identical [34].

The IDV virion is composed of four structural proteins M2, M1, NP and a hemagglutinin esterase (HEF) fusion protein, three subunits of the RNA polymerase complex P3, PB1 and PB2, and two non-structural proteins NS1 and

NS2. IDV is an enveloped virus. The outer layer of the virion envelope is a lipid membrane with the matrix protein M2 which forms ion channels. The lipid membrane also contains an envelope glycoprotein HEF that penetrates the wall of a host cell and plays the role of hemagglutinin (HA) and neuraminidase (NA) of IAV and IBV. The matrix protein M1 is located under the lipid membrane, forms the inner layer of the virus envelope, and gives stability and rigidity to the outer lipid envelope. Ribonucleoprotein complex vRNP (a nucleoprotein in a complex with the genomic RNA) contains RNA fragments attached to a nucleoprotein (NP) and three proteins of the polymerase complex (PB1, PB2, and PA) [1, 71, 73].

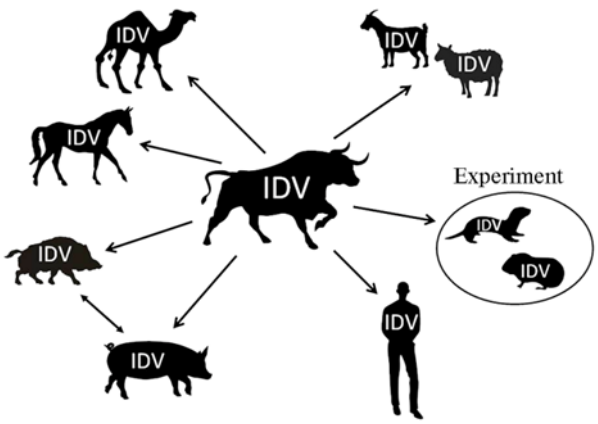
In vitro experiments found no convincing evidences of the ICV and IDV reassortment. Using two strains of human ICV C/Taylor/1947 (C/Tay) and C/Johannesburg/66 (C/JHB), a pig strain D/OK, and a cow strain D/660, Hause et al. [46] found that recombination only occurred between human viruses C/Tay and C/JHB or between animal viruses D/OK and D/660.

It was also found that IDV exhibits a different mechanism in the production of the M1 protein compared to ICV. Another important distinguishing feature of the strains is based on antibody cross-reactivity. It was shown that there is no such reactivity between IDV and antiserum to ICV. The polyclonal antibody to C/Tay does not recognize the D/OK and D/660 antigens, while reacting with the C/JHB antigen. Conversely, the anti-D/OK polyclonal antibody did not recognize human viruses C/JHB and C/Taylor [46]. Using a rabbit antiserum, a cross-reactivity was shown to two IDV lines, D/swine/OK/1334/2011 (D/OK) and D/bovine/660/2013 (D/660) but not to human ICV Victoria/2/2012 (C/Vic) strain [67]. In this case, the D/660 antiserum showed equal reactivity to both D/660 and D/OK, the anti-D/OK antibodies also cross-reacted with D/660 but was more specific for D/OK with titers 4 times higher. Based on these differences, the International Committee on Taxonomy of Viruses (ICTV) assigned the virus to a separate genus *Influenza virus D* of the *Orthomyxoviridae* family and recommended the D/swine/Oklahoma/1334/2011 as the prototype virus.

Analysis of five gene segments showed that IDV could have separated from ICV from 300 to 1200 years ago [73]. Other researchers [74] suggest that IDV originated from human ICV about 1,500 years ago. It can be argued that there are several lines within the genus which demonstrate cross-reactivity, however, it is reduced (up to 10-fold) when using a heterologous serum compared to a homologous. According to Su et al. [74], the two main lines circulating in domestic and wild ungulates (D/swine/Oklahoma/1334/2011 and D/bovine/Oklahoma/660/2013) diverged about 50 years ago. In nasal swabs of a cow with clinical signs of illness, Murakami et al. [53] discovered the influenza D virus (D/bovine/Ibaraki/7768/2016) which had significant differences from the IDVs previously identified in America, Europe and China. In Japan, during the outbreak of the disease in a herd of cows, antibody titers to the strain isolated in Yamagata Prefecture (D/bovine/Yamagata/10710/2016) were 4 times higher compared to strains from Europe and America [75]. That is, there are at least three IDV lines circulating simultaneously. Zhai et al. [59] believe that the variability within the D/660 line indicates its ongoing evolution. However, the low level of nucleotide substitutions characteristic of the known IDVs shows the slow rate of its evolution. The surface glycoprotein is antigenically stable and, therefore, new variants will be infrequent and infection with these viruses can induce long-term immunity. The reason for the slow evolutionary change in IDV proteins is unknown. It can be associated with a low frequency of polymerase errors or with the loss of protein functionality as a result of amino acid

substitutions [74].

Potential risk of the new virus to humans. The ability of IDV to infect ferrets, guinea pigs and other mammals indicates a wide range of hosts for this pathogen and a potential threat to human health. To date, there is little information about the ability of the new virus to infect humans. In 316 sera from patients in Vancouver (British Columbia, Canada) and Hartford (Connecticut, USA) collected during the 2007-2008 and 2008-2009 influenza seasons, antibodies to IDV were detected in four samples of which three samples also had high titers (1:160, 1:320, and 1:1280) to the C/Yamagata/10/1981 strain. One sample had a titer of 1:40 to D/OK and was negative for the tested human ICV strains [1]. Similarly, in 2011, titers to D/OK were detected in 9.5 % of blood sera from 220 pigs aged 3 to 20 weeks, however, only 2.8 % of pig sera had measurable antibody titers to human ICV C/Taylor/1233/47 used to assess the specificity. Therefore, it can be argued that the D OK virus circulates in swine populations, but is not typical for humans [1]. Only ICV was detected by RT-PCR in the study of Scotland archival samples from the human respiratory tract [76]. However, in Florida (USA), antibodies to the new virus (strain D/Bovine/Kansas/1-35/2010) were detected in almost 95 % blood sera of 35 people working with cattle. Also, out of 11 adults who had no contact with animals, two were found to have anti-bodies [77]. Using in vitro human respiratory tract epithelium cells (HAEC), it was found that IDV is able to effectively replicate and be released from cells at temperatures from 33 to 37 °C. The replication proceeded without long-term adaptation to the cell culture used in the work and even more intensively than in ICV [78].



Host range of *Influenza D virus* (IDV). Arrows indicate the probable routes of infection transmission.

Thus, the new influenza virus IDV is involved in the complex of respiratory diseases of cattle, is widespread in the Europe, Asia, North America and Africa, and has a significant impact on the livestock economy. This virus plays the role of a primary infection, provoking further pathologies caused by pathogenic bacteria which colonize the lower respiratory tract [47, 52, 56, 62]. In addition to cattle, IDV infects a wide range of domestic animals, including goats, sheep, pigs, camels, and horses (Fig.). Experiments on ferrets and guinea pigs have proved the susceptibility to IDV and IDV transmission [1, 69]; IDV also successfully replicates in human cell lines.

The global cattle population amounts to approximately 1.5 billion, small ruminants to more than 2.2 billion, pigs to approximately 1 billion, horses to 61 million, and camels to 35 million, so viral monitoring is necessary not only among cattle, but among other domestic animals. These species play a significant role in the agricultural economy of many countries, including Russia and the bordering countries of the former USSR. Cattle, small ruminants and pigs are the most abundant in the Russian Federation. According to the Federal Customs Service of the Russian Federation, from 2014 to 2018, the import of cattle (primarily of the pedigree black and white Holstein breed from the EU countries) also increased by

54 % due to several projects within the framework of import substitution and a zero VAT rate (until 2019) for the import of bull sires and young animals. Currently, there is no data on the spread of IDV in the Russian Federation and the role of the pathogen in the complex of respiratory diseases of cattle, but detection of the infection in a large number of countries, including those bordering on the Russian Federation, suggests that the virus is circulating in Russia as well. Therefore, surveillance studies in different regions of the country are relevant to obtain data reflecting the Russian specifics of the evolution and pathobiology of IDV.

Since a significant number of people are in daily contact with these animals, the potential threat of IDV to public health cannot be ruled out. Retrospective studies on pigs conducted in different countries have shown that there has been an increase in the number of immune animals since 2009 [55, 65]. Despite the fact that at present there are no confirmed cases of human disease due to IDV infection, attention should be paid to animal farm workers, since there are cases of detection of the virus in pigs and cattle without signs of the disease [79].

In populations of domestic animals, at least three IDV lines co-circulate [73]. Different animal species are often kept together, and these contacts increase the likelihood of interspecies transitions of the virus, its adaptation to new hosts, acceleration of evolution and molecular changes. In 2017, a RT-PCR method was developed to detect IDV [80], in 2018, a test was suggested for detecting antibodies in different animal species by enzyme immunoassay [81]. Epidemiological, biological and immunological research on IDV should continue and, if necessary, a vaccine should be developed to protect humans against this new pathogen. Since IDV reassortants can arise at any time, there is a high probability of the emergence of viruses capable of infecting people and transmitting from person to person. Information on the ability of IDV to infect humans is little and controversial, therefore, further serological and molecular studies of the population professionally associated with animal care is required for timely preventive measures.

Thus, the influenza D virus (IDV) derived from the human influenza C virus and originally infecting mainly cattle is now widespread among the main ungulate farm animals on different continents. The pathogen also circulates in ungulate populations in the wild. Infection with this virus can lead to both asymptomatic and severe pathology, up to the animal death. There is no conclusive evidence yet of infection with this virus in poultry. Nevertheless, information about genetic diversity of the pathogen and an increase in the world population of chickens and other poultry suggests the possibility of interspecific transfer of the virus when conditions are suitable, as it was with other influenza viruses. The fact that the pathogen is actively spreading among domestic pigs makes IDV potentially dangerous for humans.

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