Peeping into the Emerging Threat of Novel Influenza D Virus: A Review

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ABSTRACT

In 2011, a new virus was isolated from swine with influenza-like symptoms in Oklahoma, USA. Later in 2013, it was also evidenced in cattle, considered as its natural reservoir, elsewhere in the USA. This new virus has certain resemblance with Influenza C virus (ICV), predominately a human pathogen. Due to its inability to re-assort with ICV, it is now classified as Influenza D virus (IDV) and is a new candidate in the Orthomyxoviridae family. It causes mild respiratory disease in several animal species and replicates in both upper and lower respiratory tract. To date, serological evidence was demonstrated in various animal species and humans in all continents except Australia. It is transmitted through direct contact or through aerosol routes. Not much is known about its potential impact to animal and human health but it poses a potential risk as an emerging threat to cattle-workers. Currently, limited data is available on its global occurrence and distribution. Therefore, in current review, we summarize the global available data regarding epidemiology, pathology, zoonotic potential and future perspectives of this virus. In conclusion, continuous surveillance and risk assessment of this emerging virus is required.

Key words: Emerging infectious diseases, Emerging pathogens, Epidemic, Influenza D virus, Pandemic.

IDV is an enveloped, negative sense, single-stranded RNA virus containing seven genomic segments that are predicted to encode 9 proteins: a glycoprotein hemagglutinin-esterase fusion (HEF); polymerases PB2, PB1 and P3; nucleoprotein; matrix proteins (M1 and CM2); and nonstructural proteins (NS1 and NEP). It uses 9-O-acetylated sialic acid as their cellular receptor on host cells such as ICVs (Collin et al., 2015) (Mitra et al., 2016; Nakatsu et al., 2018; Song et al., 2016; Kerlin et al., 2017). It contrasts with Influenza A and B viruses (IAV and IBV), which contain eight segments of the genome (Desselberger et al., 1980; Lee and Seong, 1998). Phylogenetic analysis demonstrated its 50% homology with ICV (Hause et al., 2013) but there is no cross-reactivity between IDV and human ICV induced serum (Collin et al., 2015), thus supporting the need of separate genus. Hause et al., (2014) performed detailed phylogenetic studies on IDV and revealed that the virus isolated from swine and cattle was different from ICV. Additionally IDV circulates much more frequently in bovines as compared to other hosts (Jiang et al., 2014). Considering several of these differences to ICV, IDV was officially classified as a new genus of the Orthomyxoviridae family. Recently, complete genome sequence of IDV strain from swine origin has been demonstrated in United States (Thielen et al., 2019). This virus is reported to be transmitted through direct contact and through aerosols (Salem et al., 2019). Infected calves can shed the virus resulting in infection of non-treated penmate calves as evidenced through presence of virus in respiratory tract and sero-converted (Ferguson et al., 2016). It colonizes in the upper and lower respiratory tract and replicates in nasal turbinate, trachea, bronchus and lungs.

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It causes mild respiratory disease associated with inflammation of the trachea (Ferguson et al., 2016; Hause et al., 2017; Salem et al., 2019). (Ferguson et al., 2016) observed dry cough, mucoid nasal discharge, serous ocular discharge and tracheal inflammation in IDV-infected calves. However, other parameters of clinical significance like respiratory rate, heart rate, rectal temperature, total white cell counts and lymphocyte counts were unchanged. In another study, suppurative rhinitis was observed in the infected calves (Hause et al., 2017). (Salem et al., 2019)
observed respiratory disease with the clinical manifestations of bronchopneumonia and interstitial pneumonia in IDV infected animals. Here, we review the epidemiology, virology and patho-biology of IDV and the possibility of transmission among various hosts and potential to cause human disease. We also explain the association of this virus with bovine respiratory disease (BRD) complex and highlight the associated research gaps (host range, distribution, seasonality, rapid diagnostic tools, transmission and pathogenesis). The data produced from this study will help in future control and eradication of this important zoonosis using one health approach.

**Diagnosis**

For field specialists, the most decisive diagnostic tools are herd history and clinical signs. However, development of a rapid diagnostic test for this virus is a challenging task. Representative samples for isolation and identification of this virus can be obtained from oral fluid, nasal swabs and lungs (Foni et al., 2017), but the viral density decreases as we move toward the lower respiratory system (Hause et al., 2017). It can be diagnosed in laboratories using molecular and serological diagnostic tools. In molecular diagnostic tools, RT-PCR, real-time RT-PCR and gene sequencing are being used (Faccini et al., 2017; Hause et al., 2013). (Faccini et al., 2017) developed and evaluated a qRT-PCR protocol to detect the IDV in short time. (Kishimoto et al., 2017) have developed a one run RT-PCR protocol for the detection of IDV and other 15 respiratory pathogens simultaneously. Recently, (Henritzi et al., 2019) described the development of tetraplex qRT-PCR assay for simultaneously screening of IAV, IBV, ICV and IDV. Hemagglutination assay (HA) and hemagglutination inhibition assay (HI) can also be performed according to the ‘World Health Organization (WHO)’ manual on animal influenza diagnosis and surveillance by using turkey RBCs in U-bottom 96 well plates (Ferguson et al., 2015; Hause et al., 2013). Virus isolation, micro-neutralization test and ELISA are also being performed in laboratories (Faccini et al., 2017; Ferguson; et al., 2016; Foni et al., 2017). In comparison to HI test, (Moreno et al., 2019) developed and validated a monoclonal antibody-based competitive ELISA for the detection of anti-IDV antibodies.

**Epidemiology**

IDV was first reported in swine followed by its detection in cattle, swine, small ruminants, horses, camel and humans. On the basis of epidemiological, serological and pathological studies, cattle are considered as natural reservoir for this virus (Ducatez et al., 2015; Ferguson et al., 2015; Hause et al., 2014; Jiang et al., 2014). Anti-IDV antibodies were also detected from equine population (Nedland et al., 2018), small ruminants (Quast et al., 2015), camel (Salem et al., 2017) and humans (McDaniel et al., 2016). On the basis of epidemiological, serological and pathological studies, cattle are considered as natural reservoir for this virus (Ducatez et al., 2015; Ferguson et al., 2015; Hause et al., 2014; Jiang et al., 2014). Fig 1 presents the epidemiology of IDV in cattle, swine, small ruminants, horses, camel and humans. Worldwide sero-prevalence and virus prevalence of IDV and/or similar circulating viruses in animal species from different geographical areas are presented in Table 1 and Table 2. IDV is an emerging infectious disease of domestic animals particularly bovines reported in various states of North and South America continents. The sero-prevalence of this virus was highest (13.5-95.1%) in cattle (Luo et al., 2017;
Peeping into the Emerging Threat of Novel Influenza D Virus: A Review

Ferguson et al., 2015) and was lowest (5.2%) in sheep (Quast et al., 2015) as shown in Table 1. Data on the evidence of this virus in buffalo and camel is lacking and future studies will be needed. Furthermore, 42.7% seropositivity rate of HI indicates the circulation of the virus in pigs (Ferguson et al., 2018). Findings of (Ferguson et al., 2018) suggest that swine could offer an important role in the ecology of this novel virus. This study further revealed that co-infection of IDV and IAV in a same host can increase the chances of re-assortment and development of novel virus strains. They further explained that cattle shed the virus as long as nine days post IDV infection, while swine shed the virus up to five days. This variation could be due to the predominance of IDV in the upper respiratory tract in cattle and lower respiratory tract in swine. The prevalence of this virus in cattle is high particularly in calves. Few studies revealed that newborn calves (~95%) showed high maternal antibody titers against this virus which diminished after six months of age, leading to increased risk of disease in young calves (Ferguson et al., 2015; Luo et al., 2017). Thus, it seems that cattle are more vulnerable to IDV in younger age. Moreover, these studies demonstrate that it has been circulating in Unites States cattle population much earlier than it was identified as a novel virus. Findings from archived sera suggest the circulation of this virus dates back to almost 2003 (Ferguson et al., 2015; Luo et al., 2017). A past report revealed that it was more prevalent in cattle with BRD complex than healthy cattle (Luo et al., 2017). (Collin et al., 2015) reported that 4.8% cattle were positive against IDV in the United States associated with BRD complex. A serological survey showed a prevalence rate of 5.2% in sheep and 8.8% in goats across multiple states of the United States but not among the chicken and turkey (Quast et al., 2016). Anti-IDV antibodies have also been detected in horses. (Nedland et al., 2018) demonstrated that horses are susceptible to two lineages of this virus (D/OK and D/660) and these strains are present in equine populations throughout the multiple Midwestern states of the United States.

IDV has been reported in domestic animals in various regions of Europe like Ireland (Flynn et al., 2018), Italy (Rosignoli et al., 2017), Luxembourg (Snoeck et al., 2018) and France (Ducatez et al., 2015). In Europe, highest seroprevalence range was found in cattle 80.2-92.4% (Snoeck et al., 2018; Rosignoli et al., 2017) and lowest in swine 0.0-11.7% (Chiapponi et al., 2016; Snoeck et al., 2018) as illustrated in Table 1. In Italy, 92.4% and 0.6-11.7% cattle and swine respectively were found sero-positive against this virus (Chiapponi et al., 2016; Foni et al., 2017; Rosignoli et al., 2017). Currently, there is limited data available on the presence of IDV in other animals. (Foni et al., 2017) conducted a survey on the herds of both swine and cattle and reported that two species should not be mixed by farming practices. They detected this virus from swine with the clinical signs of respiratory disease, fever, abortion and mortality. In Ireland, it was only identified in cattle on the basis of real-time RT-PCR with the prevalence of 5.62%

| Regions                  | Cattle (SP) | VP | Buffalo (SP) | VP | Sheep (SP) | VP | Goat (SP) | VP | Equine (SP) | VP | Camel (SP) | VP |
|--------------------------|-------------|----|---------------|----|------------|----|-----------|----|-------------|----|------------|----|
| North and South America  | 13.5-95.1   | 4.8| 1.33-5.62     | 0.66-7.8| 0.6-11.7  | 0.67-2.3 | 0.0-1.4 | 0.35-0.35 | 99.0 |
| Europe                   | 80.2-92.4   | 28.6-30.5| 0.66-7.8 | 0.0-1.4 | 0.0-2.2  | 99.0 |
| Asia                     | 33.8        | -  | 95.4         | -  | 95.4 | -  |
| Africa                   | 0.0-35.0    | -  | 99.0         | -  | 99.0 | -  |
### Table 2: Worldwide prevalence of different IDV strains reported in various animal species.

| Country/States | Year of study | Diagnostic tools | Specie of animal | Total No of samples | Positive percentage | References |
|----------------|---------------|------------------|------------------|---------------------|---------------------|------------|
| North and South America | 2012-13 | HI | Feral swine | 256 | 19.1% | (Ferguson et al., 2018) |
| | 2010-13 | HI | Feral Swine | NS | 42.7% | (Ferguson et al., 2018) |
| | 2003-04 | HA, HI, NI | Cattle | 293 | 81.2% | (Luo et al., 2017) |
| | 2003-04 | HA, HI, NI | Cattle | 40 | 91-100% | (Luo et al., 2017) |
| | 2011 | HA, HI | Swine | NS | 9.5% | (Ben M. Hause et al., 2013) |
| | 2014 | HA, HI | Cattle | 89 | 22.5% | (Ferguson et al., 2015) |
| | 2014 | HA, HI | Cattle | 55 | 32.7% | (Ferguson et al., 2015) |
| | 2014 | HA, HI | Cattle calf | 284 | 95.1% | (Ferguson et al., 2015) |
| | 2013 | HA, HI | Cattle calf | 164 | 92.1% | (Ferguson et al., 2015) |
| | 2004 | HA, HI | Cattle | 241 | 18.3% | (Ferguson et al., 2015) |
| | 2005 | HA, HI | Cattle | 223 | 14.8% | (Ferguson et al., 2015) |
| | 2006 | HA, HI | Cattle | 141 | 13.5% | (Ferguson et al., 2015) |
| | 2014 | qRT-PCR | Beef cattle | 16 | 15a | (Ferguson et al., 2015) |
| | 2015 | qRT-PCR | Cattle | 208 | 4.8% | (Collin et al., 2015) |
| | 2015 | HI | Equine | 364 | 12% | (Nedland et al., 2018) |
| | 2015 | HI | Equine | 364 | 11% | (Nedland et al., 2018) |
| | 2015 | HI | Equine | 364b | 11% | (Nedland et al., 2018) |
| | 2014 | HI | Sheep | 557 | 5.2% | (Quast et al., 2015) |
| | 2014 | HI | Goat | 91 | 8.8% | (Quast et al., 2015) |
| | 2014 | HI | Chicken and Turkey | 250 | 0 | (Quast et al., 2015) |
| Europe | | | | | | |
| Italy | 2016 | Cell culture, q-RT PCR, sequencing | Swine | 150 | 0.67% | (Chiapponi et al., 2016) |
| | 2016 | Cell culture, q-RT PCR, sequencing | Cattle | 150 | 1.33% | (Chiapponi et al., 2016) |
| | 2014-16 | RT-PCR | Cattle | 837 | 6.5% | (Rosignoli et al., 2017) |
| | 2014-16 | HI | Cattle | NS | 92.4% | (Rosignoli et al., 2017) |
| | 2015-16 | q-RT PCR | Swine | 845 | 2.3% | (Foni et al., 2017) |
| | 2015 | HI | Swine | 3106 | 11.7% | (Foni et al., 2017) |
| | 2015 | HI | Equine | 364a | 0.6% | (Foni et al., 2017) |
| | 2014 | HI | Sheep | 557 | 5.2% | (Quast et al., 2015) |
| | 2014 | HI | Goat | 91 | 8.8% | (Quast et al., 2015) |
| | 2014 | HI | Chicken and Turkey | 250 | 0 | (Quast et al., 2015) |
| | | | | | | |
| Ireland | 2016 | q-RT PCR | Cattle | 320 | 5.62% | (Flynn et al., 2018) |
| | 2012 | HI | Swine | 450 | 80.2% | (Snoeck et al., 2018) |
| | 2012 | HI | Swine | NS | 0% | (Snoeck et al., 2018) |
| | 2014-2015 | HI | Swine | 287 | 5.9% | (Snoeck et al., 2018) |
| Luxembourg | 2016 | q-RT PCR | Cattle | 134 | 4.5% | (Ducatez et al., 2015) |
| France | 2011-14 | q-RT PCR | Cattle | 134 | 4.5% | (Ducatez et al., 2015) |
| Asia | Japan | 2016-17 | qRT PCR | Cattle | 377 | 2.1% | (H. Mekata et al., 2018) |
| | 2016 | HI | Cattle | 82 | 28.6 | (Murakami et al., 2016) |
| | 2010-16 | HA, HI | Cattle | 1267 | 30.5% | (Horimoto et al., 2016) |
| China | 2016 | RT-PCR | Native yellow cattle | 55 | 7.3% | (Zhai et al., 2017) |
| | 2016 | RT-PCR | Pigs | 19 | 7.8% | (Zhai et al., 2017) |
| | 2016 | RT-PCR | Dairy cattle | 193 | 7.8% | (Zhai et al., 2017) |
| | 2016 | RT-PCR | Buffaloes | 51 | 5.9% | (Zhai et al., 2017) |
| | 2016 | RT-PCR | Goats | 80 | 33.8% | (Zhai et al., 2017) |
| | 2016 | RT-PCR | Pigs | 45 | 28.9% | (Zhai et al., 2017) |
| | 2014 | RT-PCR | Cattle | 453 | 0.66% | (Jiang et al., 2014) |
Peeping into the Emerging Threat of Novel Influenza D Virus: A Review

Table 1 continues...

| Country  | Year 1991-2015 | Species | Prevalence |
|----------|---------------|---------|------------|
| Benin    | 1991-2015*a  | Cattle  | 207 1.9%   |
|          | 1991-2015*a  | Sheep   | 67 0%      |
|          | 1991-2015*a  | Goat    | 34 0%      |
| Togo     | 1991-2015*a  | Cattle  | 201 10.4%  |
|          | 1991-2015*a  | Sheep   | 135 2.2%   |
|          | 1991-2015*a  | Goat    | 205 1.4%   |
| Côte d’Ivoire | 1991-2015 | Cattle  | 100 0%     |
|          | 1991-2015*a  | Swine   | 103 0%     |
| Morocco  | 1991-2015*a  | Cattle  | 200 35%    |
| Kenya    | 1991-2015*a  | Cattle  | 938 0%     |
|          | 1991-2015*a  | Camel   | 293 99%    |

NS: Not Specified, *isolates based on qRT-PCR, †IDV-related human ICV lineage (C/JHB), ‡Archived samples, †Animal farms, ‡Nasal Swab samples, ‡Serum

(Flynn et al., 2018). Detection of this virus from nasal swab samples submitted from routine respiratory disease cases supports the hypothesis that IDV is an important player of BRD complex. In Luxembourg, sero-prevalence of IDV was observed 80.2% in cattle in 2016 while in swine population, it increased during recent years from 0.0% to 5.9% from 2012 to 2015 (Snoeck et al., 2018). The high prevalence in cattle as compared to swine indicates that cattle are the primary reservoir of this virus (Snoeck et al., 2018). In France, the prevalence of IDV in cattle was 4.5%, which was associated with BRD complex (Ducatez et al., 2015).

In Asia, this virus was reported in only three countries such as China (Zhai et al., 2017), Malaysia (Borkenhagen et al., 2018) and Japan (Murakami et al., 2016). In this region highest sero-prevalence was found (28.6-30.5%) in cattle (Horimoto et al., 2016; Murakami et al., 2016) as presented in table 1. In China, cattle 0.6-7.8% (Jiang et al., 2014; Zhai et al., 2017), buffaloes 5.9% (Zhai et al., 2017), goats 33.8% (Zhai et al., 2017) and pigs 7.8-28.9% (Zhai et al., 2017) were found infected with this virus. The high prevalence of this virus in China might be due to poor bio-security measures, high-density feeding mode practices and possible cross-species transmission (Zhai et al., 2017). Almost 30% of the infected animals showed virus viremia with either acute infection or before the death. Detection of IDV in rectal swabs increasing the likelihood of this virus to proliferate within the intestinal tract like other influenza viruses (Zhai et al., 2017). The virus has been circulating in Japan since last seven years and further investigations revealed horizontal transmission of IDV within herd and also demonstrated that viral infection tended to increase with the age of animal (Horimoto et al., 2016).

In the African region, IDV was detected in various countries like Benin, Togo, Morocco and Kenya (Salem et al., 2017). In this region, the highest sero-prevalence was reported in camels 99% (Salem et al., 2017), while lowest in goats 0.0-1.4% (Salem et al., 2017) as mentioned in Table 1. In Benin, the sero-prevalence range of this virus in cattle was 1.9% while, in Togo, 10.4% cattle, 2.2% sheep and 1.4% goat were detected positive against IDV. In Morocco, 35% of cattle were found sero-positive while 99% of camels in Kenya. The study showed that it has been circulating in North and West Africa since 2012 (Salem et al., 2017). Detection of antibodies against influenza C or D virus in dromedary camels of Kenya suggests a new host for novel IDV (Salem et al., 2017). Anti-IDV antibodies have been detected in cattle in Morocco (from 2012 to 2015), cattle in Benin and Togo (2014), small ruminants in Togo (2013) and camels in Kenya (2015).

**Pathological characteristics**

The transmission routes and pathological characteristics of IDV were investigated by giving challenge of IDV to cattle, swine and laboratory animals like guinea pigs and ferrets. In pigs, experimental results showed that virus replicated in nasal turbinate and shedding of the virus was detected in nasal swabs with no typical lesions of influenza virus. Direct contact was determined as a major source of transmission. However, it was not detected in the lower respiratory tract (Hause et al., 2013). In cattle, it was detected both in the upper and lower respiratory tract and was transmitted to healthy animal through direct contact. Viral titers were high in nasal turbinates, while decreased in the lower respiratory tract (Ferguson et al., 2016; Hause et al., 2014; Hause et al., 2017). In ferrets, this virus could be isolated from nasal turbinates but not from the lower respiratory tract. It was transmitted to sentinel animals through direct contact and not through aerosols (Hause et al., 2013). Replication of this virus in guinea pigs was observed in both upper and lower respiratory tract but the sign and symptoms were not observed (Sreenivasan et al., 2015).

In contrast to above-mentioned studies about replication and transmission routes of IDV (Ferguson et al., 2016; Hause et al., 2014; Hause et al., 2013, 2017). (Salem et al., 2019) reported that it can replicate not only in upper but also in the lower respiratory tract of cattle. On virological examination of aerosol sentinel animals, airborne transmission of this virus on short distance (3 meters) was noticed. Study of the immune response showed that antibodies (IDV-specific IgG1) were produced ten days post IDV challenge.
For determining the replication kinetics, cell tropism and zoonotic potential of this virus in humans. (Holwerda et al., 2019) conducted a study by using human well-differentiated airway epithelial cell (HAECs) culture model of biological donors. Results demonstrated that replication kinetics of this virus was more efficient at a temperature corresponding to the lower respiratory tract (37°C) of humans. They also reported that progeny of virus obtained from initial experiments was infectious in nature. Replication kinetics for IDV in HAECs cultures was robust and independent from the donor and almost identical to ICV because both viruses share some similarities between the HEF. Overlapping of the virus antigen signal of both IDV and ICV with ciliated markers indicates that both viruses have a predominant preference for ciliated cells.

**IDV and BRD complex**

A confliction is present due to mild symptoms associated with experimental infection that IDV could be associated with a more pronounced disease in the field. It could be possible due to variations in doses and transmission routes of infection or husbandry practices. However, it was also supposed that IDV alone could not cause clinical disease. It might be a part of BRD complex. It may provide optimum conditions for infiltration, proliferation and colonization of other pathogens in both upper and lower respiratory tract (Hause et al., 2017). The exact role of this virus in clinical disease in animals is not yet investigated, while the role of this virus in causing respiratory infections in cattle has been implied. It is supported by a meta-genomic study conducted to identify the virome associated with BRD complex in cattle. They found that IDV was co-infected with bovine adenovirus 3, bovine rhinitis A and B, bovine corona virus, bovine viral diarrhea virus, bovine herpes virus 1, bovine respiratory syncytial virus and bovine para-influenza 3 virus (Mitra et al., 2016). Other studies also revealed that infection rate of this virus was higher in clinically sick animals and tended to be associated with BRD complex (Ferguson et al., 2016; Hause et al., 2014). A study conducted in Japan revealed that IDV was associated with bovine corona virus for the development of BRD complex (Hirohisa, 2018). IDV could play a significant role in developing BRD complex and could facilitate co-infection with other pathogens (Ferguson et al., 2016).

**Zoonotic potential**

Zoonotic potential of IDV is still unclear and in infancy stage. Several studies have been conducted to investigate the prevalence of IDV in humans. A study on respiratory samples of humans in Scotland showed that IDV was not present in any sample (Smith et al., 2016). A serological study on human serum samples found that 1.3% of 316 samples were positive, leading to suppositions that it could have the potential of public health risks (Hause et al., 2013). Serological evidence in two independent studies has revealed that it can potentially infect human beings with occupational exposure to cattle. One of the studies reported 91% of sero-positivity among 35 persons working with cattle from Florida (White et al., 2016), while others reported only 1% sero-positivity among 741 persons with suspected high exposure to this virus (Eckard, 2016). The virus was also detected in the nasal passages of humans (1.3% of 78 samples) with the occupational exposure to the pigs in Malaysia using RT-PCR and real-time RT-PCR (Borkenhagen et al., 2018). Thereafter, a high sero-prevalence (18%) was also observed in those individuals who were not exposed to cattle (Faccini et al., 2017). Clearly, more investigations are needed to know the prevalence rate of this emerging virus in humans.

In spite of the absence of convincing proof of IDV infection in human beings, we suspect that this virus can infect and replicate in the human population due to the following reasons. Detection of the virus and anti-IDV antibodies in humans particularly with cattle and pig exposure suggest that this virus can infect humans (White et al., 2016; Borkenhagen et al., 2018). Ferrets, surrogates for influenza virus studies and are also susceptible to IDV suggests that the virus can cause infection in humans as well. It replicates strongly at 37°C (Hause et al., 2013), the predominant temperature in the human lungs. The more open receptor cavity of HEF of IDV proposes that it can infect a wider range of cells than ICV (Song et al., 2016). Holwerda et al., (2019) also reported that both IDV and ICV have similar replication kinetics in HAECs cultures and have cell tropism towards ciliated cells of respiratory tract. These proofs might explain that why anti-IDV antibodies can be present in humans with occupational exposure to livestock animals. Therefore, it seems to be no internal impairment for this virus to propagate within the respiratory epithelium of humans and to do so only a couple of adaptations may be required. Although serological investigations suggest that IDV can infect humans. Whereas IDV has not been identified in a large number of human samples, more investigations are needed to come to a reasonable conclusion.

**Control strategies for IDV infection**

Our current understanding about IDV continues to lag far behind than other IVs, perhaps due to relatively mild respiratory disease it causes and lack of rapid IDV-specific diagnostic tests. Rapid diagnostic tests must be devised to timely diagnose the virus to limit the further spread. In response to the spread of infectious diseases through air travel, bio-aerosol surveillance may be beneficial. Pilot study of aerosol surveillance at Raleigh Durham International Airport showed that 17% of the specimens were positive for known respiratory viruses including IDV and Adenovirus (Wan et al., 2018). This study was conducted on small sample size, more epidemiological and prevalence-based studies would be required to strengthen such findings.

Developments in antiviral strategies against IDV have been in action to prevent the outbreaks. Recently, a DNA vaccine expressing consensus HEF protein against two
lineages of IDV (D/OK and D/660) showed protective efficacy in guinea pigs. In this study, the vaccinated animals showed appreciable antibody titers against IDV lineage representatives and were protected against intranasal challenge with IDV. This study is claimed to be first, which is showing that DNA vaccine is efficacious in preventing different lineages of IDV infection (Smith et al., 2016). Another study highlights the development of a homologous inactivated vaccine, which was immunogenic and partially protective against IDV. Vaccinated calves had significantly reduced level of IDV titers as compared to control animals (Hause et al., 2017). Despite the fact that some advancements have been developed to reduce the IDV infection, yet more research would be required to assess the potential of existing and new antiviral strategies to limit the zoonotic transmission to humans and prevent any future IDV outbreaks (Asha and Kumar, 2019).

CONCLUSION

IVs have been the reason of significant concern to human and animal health worldwide. They not only cause high morbidity and mortality, but also lead to socio-economic losses. Influenza D virus is a new genus in the Orthomyxoviridae family that infects cattle (which are apparently its main animal reservoir), pigs, small ruminants and some other domestic animals. Clinical signs after experimental infection are usually small, but are more pronounced in animals infected in the field suggesting that IDV might be a component of the bovine respiratory disease (BRD) complex. Whether IDV is a human health threat is a matter of debate; antibodies are detected in some humans having exposure to cattle, but it is unclear whether IDV causes disease and/or is transmitted between humans. Detection of IDV in domestic animals and feral swine is an indication that further studies should be conducted to check the diversity of this virus in other wild animals and extent of interspecies transmission. More information is needed about the survivability of this virus at different temperature and humidity to know the possible seasonality. It is another threat to the global epidemiological map of the world. Rapid country to country spread of this virus could be due to international travel and import or export of the animals. Cattle are established to be the natural reservoir of IDV. If this virus possesses a public health threat, it can pose an occupational hazard to the farmers, veterinarians, butchers and lab workers etc. Risk assessment is needed to confirm the effects of IDV exposure on bovine production to provide the data that BRD complex is leading cause of economic loss to this industry and to clarify what, if any, it may pose a potential risk to public health.

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Conflict of Interest

None

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