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Antigenic switch potential of influenza D virus

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Abstract

The antigenic variability of Influenza D virus (IDV), a recently identified pathogen with significant implications for livestock and zoonotic diseases, presents unique challenges in virology, epidemiology, and public health. This review stands out by focusing explicitly on IDV's distinct antigenic shift and drift mechanisms, which are underexplored compared to other influenza viruses. Unlike previous studies that broadly address influenza evolution, this research emphasizes IDV's specific molecular and ecological traits, particularly its hemagglutinin-esterase fusion (HEF) protein, which plays a critical role in antigenic reconfiguration. The study integrates genomic sequencing, structural bioinformatics, and epidemiological surveillance to deliver a comprehensive understanding of IDV's evolutionary potential and cross-species transmission risks. This review uniquely highlights IDV's moderate propensity for antigenic switching, particularly in livestock reservoirs such as cattle and swine, which act as amplification hosts for viral dissemination. By rigorously mapping the virus's antigenic architecture, this work provides novel insights into its adaptive mechanisms and evolutionary trajectory, offering practical implications for vaccine development, immune evasion strategies, and interspecies transmission control. The methodological foundation includes an exhaustive review of peer-reviewed literature, in silico simulations, and phylogenetic analyses, setting this study apart as a detailed exploration of IDV's antigenic dynamics. Findings emphasize the challenges posed by IDV variability for sustainable vaccine development, necessitating regular updates to address ongoing antigenic shifts. This study significantly advances global efforts to understand and manage IDV evolution, underscoring the urgent need for enhanced surveillance in agricultural, veterinary, and public health systems. By doing so, it bridges critical knowledge gaps and informs future diagnostic, therapeutic, and preventive strategies tailored to mitigate zoonotic threats.

Key words influenza D virus, antigenic switch, hemagglutinin-esterase fusion, zoonotic potential, host immunogenicity

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Introduction

The Orthomyxoviridae family comprises four distinct types of influenza viruses, namely influenza A, B, C, and D. Influenza A (IAV) and B (IBV) viruses are recognized for their capacity to induce respiratory illnesses in humans, often resulting in severe health complications and seasonal influenza epidemics, with IAV possessing the potential to instigate a pandemic. In contrast, Influenza D represents the sole type of influenza virus predominantly affecting cattle, with occasional spillover occurrences into other species. Since the inaugural identification of the Influenza D virus (IDV) in 2011, it was initially isolated from a pig exhibiting severe respiratory symptoms in Oklahoma, USA. Despite its widespread presence in agricultural animals such as cattle and swine, little is known regarding the implications and pathogenesis of IDV on human health [1, 2, 3, 4, 5, 6, 7, 8, 9]. In 2020, As Liu et al. [10] noted, “The virus has since been documented to circulate among cattle and swine populations globally”. Influenza D virus (IDV) is classified into four primary lineages: D/OK, D/660, D/Yama_2016, and D/Yama_2019, with a potential fifth lineage, designated D/CA2019, recently identified in California, demonstrating genetic and antigenic divergence from the other four lineages. Initially classified as C/Oklahoma/1334/2011 (C/OK), this variant exhibits only 50% amino acid similarity to ICV. Nevertheless, subsequent investigations uncovered more closely related viral variants to the now-recognized D/OK variant, reinforcing the notion of a novel and distinct influenza virus type. IDV is an enveloped, segmented, single-stranded, negative-sense RNA virus. It encodes a singular glycoprotein derived from the hemagglutinin-esterase-fusion (HEF) gene, alongside seven segments that code for the polymerase essential proteins 1 (PB1) and 2 (PB2), the polymerase acidic protein (PA), the nucleoprotein (NP), the matrix proteins (M1/M2), and non-structural proteins 1 and 2 (NS1/2) [10, 11, 12, 13, 2, 14, 15, 16, 17, 18, 19, 20, 21, 22].

Furthermore, the binding characteristics of Influenza D exhibit variability across different virus clades and wildlife species. A tissue microarray system was employed to investigate the respiratory tissues of wild and domestic animals, demonstrating that IDV can adhere to the respiratory tracts of wildlife, thereby potentially promoting transmission [23, 24]. The influenza D virus is closely related to the human influenza C virus. It is suggested to be a natural reservoir in cattle, potentially contributing to the bovine respiratory disease complex. While the pathogenic potential of IDV in humans remains largely unexplored, it poses a significant risk as an emerging pathogen for individuals working with cattle. IDV exhibits a broad host range and can cross species barriers. Emerging threats from influenza A viruses (IAVs) arise from genetic drift and shift, resulting in frequent epidemics and the necessity for annual vaccine reformulations. Pigs, quails, and bats serve as mixing vessels for IAVs, as they co-express both SAα2,3-Gal and SAα2,6-Gal receptors, which are essential for binding to avian and human IAVs [25, 26, 27, 28, 29, 30, 31].

Finally, the influenza D virus has been increasingly detected in cattle and swine populations across the globe, demonstrating exceptional thermal and acid stability along with a broad host range. Cattle have been identified as the natural reservoir and amplification host for IDV, with infections contributing to mild or moderate respiratory illnesses in cattle and playing a significant role in the bovine respiratory disease (BRD) complex. This complex is the most common and economically impactful cattle industry disease. Recent advances in understanding the biology and epidemiology of IDV have highlighted its pathogenesis and potential zoonotic risks. Antibodies specific to IDV have been found in several species beyond cattle and swine, including horses, small ruminants, feral swine, buffalo, camels, and humans, particularly among those exposed to cattle. These findings underline the increasing significance of IDV as a pathogen with potential interspecies transmission. These considerations will further elaborate on various critical aspects of influenza viruses, such as the antigenic shift across all types, the agricultural theory behind IDV, and vaccination and epidemiological studies. The role of swine as intermediate vectors, along with treatment, prevention strategies, vaccine development, and prospects, will also be discussed, offering a broad and diverse range of insights into these pressing issues **Table 1** [32, 33, 26, 3, 4, 24, 34, 35, 36, 37, 38, 6, 39, 40].

Results and discussion

A research investigation in North America revealed that wild white-tailed deer (WTD) had been exposed to the influenza D virus (IDVs), suggesting the possibility of infecting various hosts, including wild animal populations. The study analyzed 264 serum samples from WTD and utilized hemagglutination inhibition assays against two co-circulating viruses. In 2020, Guan et al. [40] noted, “Exposure of white-tailed deer in North America to influenza D virus” was evident, with seropositive samples for IDV identified among both juvenile and adult deer, encompassing individuals of both sexes [40]. A novel in vitro system utilizing caprine airway epithelial cell (AEC) cultures has been established to investigate caprine respiratory viruses and bacteria. As in 2021, Strässle et al. [57] highlight that this system involves "the establishment of caprine airway epithelial cells grown in an air-liquid interface system to study caprine respiratory viruses and bacteria". This platform has been validated through experiments involving Influenza D Virus infection and colonization by Mycoplasma mycoides subsp. Capri, indicating its promising applications in animal welfare research [57, 58]. A study investigating the synergistic interplay between influenza D virus (IDV) and Mycoplasma bovis respiratory infections in cattle revealed that initial IDV infection facilitates M. bovis superinfection by enhancing bacterial replication and inducing pulmonary damage. Furthermore, IDV was shown to compromise the innate immune response by reducing pro-inflammatory cytokines and chemokines. Stimulation assays involving cytosolic helicases and Toll-like receptors indicated that the primary activation of RIG-I/MDA5 leads to a desensitization of TLR2 activation, akin to the effects of IDV infection. This non-additive response modifies the TLR2-mediated signaling cascade responsible for regulating the infection [59, 58, 60]. A research initiative has established a reverse-genetics system (RGS) for the Influenza D virus, facilitating the exploration of its infection biology. The viruses derived from the RGS closely mimic their parental counterparts, enabling in-depth investigations into replication, tropism, and pathogenesis. This plasmid-based system produces infectious viruses with replication kinetics akin to wild-type strains following cultured cells' transfection. Additionally, the minigenome replication assay has revealed mutations that influence the activity of the IDV ribonucleoprotein (RNP) complex (**Figure 1**) [61, 62, 4, 20, 15, 63, 64].

Antigenic shift of all types of influenza viruses

The neuraminidase enzyme associated with influenza. Neuraminidase, a type II membrane-anchored glycoprotein on the surface of influenza virions, is essential in ensuring adequate protection. Nonetheless, neuraminidase's limited potency and stability in existing influenza vaccines present significant obstacles to eliciting robust immune responses. Strategies such as isolating and characterizing broadly reactive monoclonal antibodies against neuraminidase have been explored to augment

Table 1. Exploring the complex effects and mitigation approaches of influenza D virus across diverse biological systems.

Target tissues	Description	Control strategies	Vaccine (year, country)	Negative/Positive parameters	Clinical phase	Mechanism of action	Future prospects	References
Respiratory Tract (e.g., lungs, trachea)	Influenza D virus primarily targets the respiratory epithelium, causing respiratory illnesses in cattle, swine, and other animals. Viral replication leads to inflammation and damage to respiratory tissues.	Biosecurity: Improved biosecurity in farms. Vaccination: Development of species-specific vaccines. Surveillance: Enhanced global livestock and intermediate vectors surveillance to monitor viral mutations.	Ongoing research (no licensed vaccines yet; vaccine trials in development globally).	Positive: Shows antigenic variation, expanding host range. Negative: Cross-species transmission poses risks for zoonotic spillover—potential for reassortment with other viruses, increasing its adaptation to new hosts.	Preclinical (animal models)	Hemagglutinin-esterase fusion protein binds to sialic acid receptors, facilitating viral entry and replication in respiratory epithelial cells. Mutations enhance receptor-binding efficiency and immune evasion.	Cross-species transmission: Future research may focus on the development of multi-species vaccines. Surveillance: Global monitoring for mutations and viral evolution that could enhance zoonotic potential and the virus's adaptability to new environments.	[41, 42, 43]
Gastrointestinal Tract	Some studies suggest that IDV may target the gastrointestinal tract, particularly in cattle, causing mild symptoms. Gastrointestinal involvement is still under investigation.	Hygiene and Sanitation: Reducing fecal-oral transmission through improved sanitation in farming environments. Antivirals: Testing potential antiviral drugs targeting viral replication.	It is in progress (various trials in cattle and swine).	Positive: Reduced pathogenicity in gastrointestinal infections. Negative: Limited understanding of the virus's replication in non-respiratory tissues may lead to underestimating transmission routes.	Experimental	Viral replication in gastrointestinal tissues may rely on similar mechanisms to respiratory replication, particularly receptor-mediated entry into epithelial cells.	Antiviral Treatments: Future antiviral therapies could target respiratory and gastrointestinal infections to mitigate disease spread. Mutagenesis Studies: Understanding how mutations influence tissue tropism could open new therapeutic avenues.	[6, 44]
Immune System (Innate and Adaptive)	Mutations in the hemagglutinin-esterase fusion protein allow the virus to evade immune responses and avoid detection by neutralizing antibodies.	Immune Modulation: Use of immunomodulatory therapies to boost innate immunity in affected animals. Adjuvant Vaccines: Development of vaccines that enhance adaptive immune responses to overcome immune evasion mechanisms.	Development stage in North America (2022 trials in cattle).	Positive: Moderate stimulation of innate immune responses in early infection. Harmful: Evasion of adaptive immune responses through antigenic variation, leading to long-term immunity and vaccine efficacy challenges.	Phase I (vaccine trials)	Mutations in vital antigenic sites allow the virus to escape neutralizing antibodies, while altered surface proteins enhance immune evasion. This allows persistent infection or rapid spread in immunologically naïve populations.	Vaccine Enhancement: Future vaccines may incorporate novel adjuvants to improve immunogenicity. Genetic Engineering: Potential for using reverse genetics to produce attenuated strains that stimulate more robust immune responses.	[45, 46]

Table 1. Exploring the complex effects and mitigation approaches of influenza D virus across diverse biological systems (continued).

Target tissues	Description	Control strategies	Vaccine (year, country)	Negative/Positive parameters	Clinical phase	Mechanism of action	Future prospects	References
Endothelial Cells	IDV may infect endothelial cells, contributing to vascular inflammation and exacerbating respiratory symptoms. Although not fully established, endothelial involvement is suspected in severe cases.	Anti-inflammatory Strategies: Investigating anti-inflammatory drugs to minimize vascular damage. Prophylactic Antiviral Use: Use broad-spectrum antivirals in herds experiencing outbreaks to limit viral spread.	There is no current vaccine. Early research into endothelial effects is ongoing.	Positive: Vascular involvement may increase understanding of severe cases. Damaging: The lack of confirmed data on endothelial cell infection limits the ability to develop targeted therapies.	Exploratory studies	Potential infection of endothelial cells could contribute to vascular inflammation, though the exact mechanism of interaction between IDV and endothelial cells remains under investigation.	Host Range Expansion: Future studies could examine the potential for IDV to affect the vascular systems of non-traditional hosts, leading to a greater understanding of severe pathogenicity in humans.	[47, 48]
Neurological System (possible)	Though rare, neurological symptoms in affected animals, such as swine, have been reported in severe cases, likely secondary to systemic infection rather than primary neural invasion.	Neurological Surveillance: Increased monitoring of neurological symptoms during outbreaks. Anti-inflammatory Drugs: Testing anti-neuroinflammatory drugs in severe cases where neurological involvement is suspected.	No vaccine addressing neurological impacts.	Positive: Limited neurological involvement in most cases. Negative: Neurological symptoms may complicate treatment and prognosis in rare instances of severe systemic infection.	Not applicable	Secondary neurological effects may arise from systemic inflammatory responses rather than direct infection of neural tissues. The mechanisms remain unclear and require further investigation.	Neurological Research: Studies into potential neurotropic characteristics could be vital for assessing IDV's pathogenicity in non-traditional hosts, including humans.	[25, 49]
Reproductive System (in swine)	Possible reproductive impacts on swine are under investigation. Although evidence is limited, preliminary studies suggest that IDV may have mild effects on reproductive tissues.	Reproductive Health Monitoring: Regular monitoring of reproductive health in swine herds during IDV outbreaks. Preventive Measures: Research into vaccine development aimed at reducing reproductive effects.	Research is in progress (no specific vaccines address reproductive impacts).	Positive: No significant reproductive health effects have been observed so far. Negative: Limited research may underestimate the virus's potential impact on reproduction, leading to prevention and control measures gaps.	Preclinical (animal studies)	Direct reproductive system infection is unlikely; reproductive impacts may be secondary to systemic disease, similar to other influenza viruses.	Long-Term Studies: Future longitudinal studies could assess whether IDV affects reproductive health over multiple generations in livestock, particularly swine, and its possible effects on fertility and neonatal health.	[50, 48]

Table 1. Exploring the complex effects and mitigation approaches of influenza D virus across diverse biological systems (continued).

Target tissues	Description	Control strategies	Vaccine (year, country)	Negative/Positive parameters	Clinical phase	Mechanism of action	Future prospects	References
Ocular Tissue (rare cases)	IDV's effect on ocular tissues remains understudied, but there have been occasional reports of conjunctivitis and other mild ocular symptoms in infected animals, typically associated with respiratory distress.	**Ocular Treatment:** Use of anti-inflammatory eye drops in symptomatic animals. **Ocular Surveillance:** Monitoring ocular symptoms in animals during outbreaks to assess correlation with respiratory infections.	There are no current vaccines for ocular impacts (rare symptomology).	**Positive:** Mild and self-limiting ocular involvement. **Damaging:** Lack of specific treatment protocols for ocular symptoms can lead to animal discomfort during respiratory infections.	There is no particular phase for ocular involvement.	Mild ocular symptoms may arise from inflammatory responses associated with respiratory infection rather than direct ocular infection by the virus.	**Ocular Involvement:** Further studies could clarify whether IDV can directly infect ocular tissues or whether observed symptoms are purely secondary to systemic respiratory inflammation.	[51, 52]
Cardiovascular System	Cardiovascular effects are suspected but not well-documented in IDV infections. In cases of severe respiratory distress, secondary cardiovascular symptoms may arise due to systemic inflammation.	**Cardiovascular Monitoring:** Enhanced monitoring of cardiovascular health during outbreaks. **Anti-inflammatory Drugs:** Testing of cardiovascular-targeted treatments in severe systemic infections to reduce inflammation.	No current vaccine addressing cardiovascular impacts (limited research).	**Positive:** Rare cardiovascular symptoms observed. **Negative:** In cases of severe systemic infection, cardiovascular involvement could exacerbate morbidity and complicate treatment efforts.	No clinical trials for cardiovascular effects yet.	Systemic inflammation associated with severe respiratory infections could lead to cardiovascular symptoms, although direct infection of cardiovascular tissues is unlikely based on current evidence.	**Future Research:** Studies into the potential secondary cardiovascular effects could improve understanding of severe cases, particularly in livestock with pre-existing cardiovascular conditions, and inform treatment strategies.	[41, 54, 55]

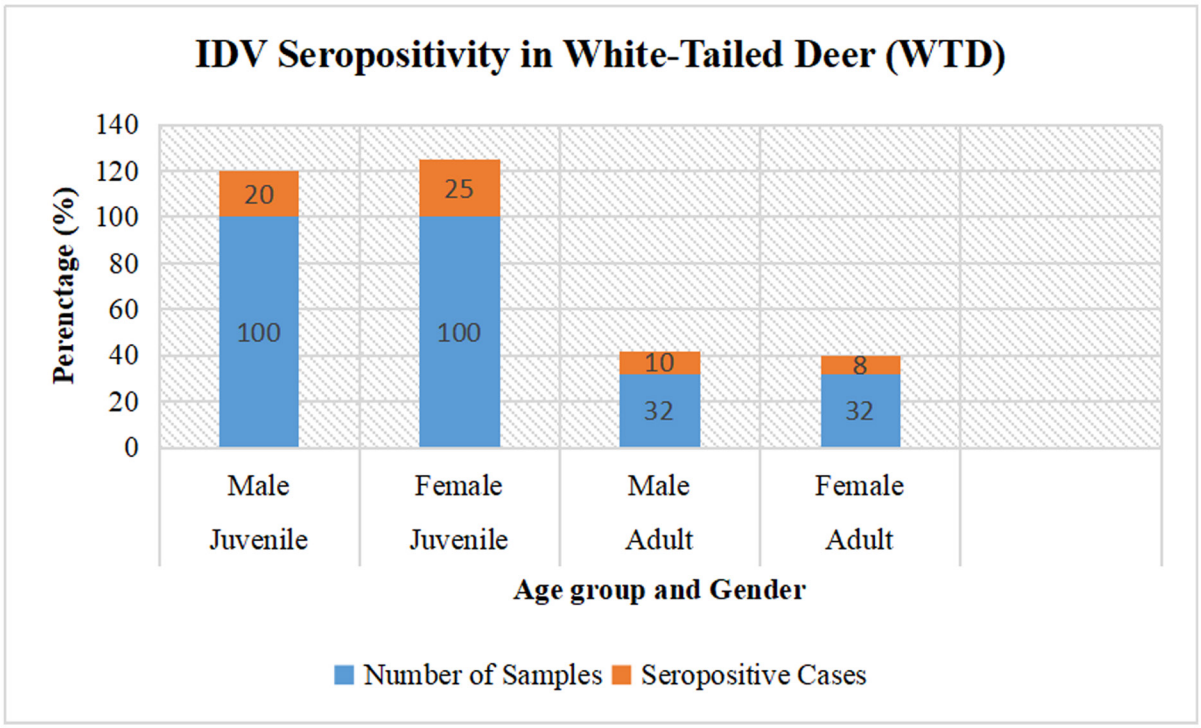

Figure 1. The illustration provides a comprehensive breakdown of specimens categorized by age cohort, gender, total sample size, and incidence of seropositive cases. Within the juvenile cohort, 100 male specimens were analyzed, yielding 20 seropositive results, while 100 female specimens indicated 25 seropositive cases. For the adult cohort, 32 male specimens were assessed, with 10 returning seropositive, and among the 32 female specimens, 8 were identified as seropositive.

anti-neuraminidase immune reactions. The catalytic site located within the head domain of each promoter is highly conserved and serves as a target for antiviral drug and monoclonal antibody development. Cathode ions are critical for enzymatic activity and thermal stability, while the architecture of the neuraminidase stalk domain exhibits variability. Variations in the neuraminidase globular head exposure can significantly influence viral infectivity, transmission, and immunogenicity. Furthermore, the surface of the neuraminidase protein may be extensively glycosylated, contributing to its structural integrity, functionality, specificity, thermal stability, antigenic properties, and immunogenic potential. Removing glycans from the neuraminidase apex enhances protective efficacy [65, 66, 67, 68, 69, 70, 71, 24, 72, 73].

Subsequently, the reassortment between Swine H3N2 and the 2009 Pandemic H1N1 in the United States has resulted in influenza A viruses exhibiting a variety of genetic constellations. A study conducted from 2009 to 2016 identified 44 distinct genotypes of H3N2 influenza A viruses (IAV) in swine, with the predominant genotype (32.33%) characterized by a clade IV-A hemagglutinin (HA) gene, 2002-lineage neuraminidase (NA) gene, an M-pdm09 gene, and other gene segments derived from a triple reassortant internal gene (TRIG) source. This genetic diversity poses challenges for disease management within the swine industry. It presents potential public health risks, mainly if swine-adapted viruses containing H1N1pdm09 genes exhibit an elevated propensity for human infection [74, 75, 68, 76, 77, 78, 79, 80, 48, 81, 18, 82, 83, 84, 50]. A study has identified four H3N2 canine influenza viruses (CIVs) as a potential public health concern due to their close genetic affinity with human strains. The virus was isolated from nasal swabs of dogs in China between 2018 and 2020, and phylogenetic analysis uncovered 15 distinct genotypes, with genotype 15 dominating among dogs since 2017. Molecular characterization revealed several adaptive substitutions in mammals, including HA-G146S, HA-N188D, PB2-I292T, PB2-G590S, PB2-S714I, PB1-D154G, and NP-R293K. A novel adaptive mutation, HA-V223I, was detected in H3N2 viruses from humans and swine, indicating its potential significance in mammalian adaptation. Human H3N2 vaccines do not protect H3N2 CIVs, underscoring the necessity for vigilant surveillance and monitoring [85, 86, 76, 78, 71, 87, 88, 89, 81, 90]. Shandong Province, China, has identified 21 reassortant G4 genotype Eurasian avian-like (EA) H1N1 subtypes of swine influenza viruses (SIVs) that pose potential health risks. These viruses harbor genes from multiple lineages and possess mutation sites that may enhance mammalian fitness and pathogenicity in murine models. The study advocates for improved surveillance to evaluate the pandemic potential of these viruses. SIVs are highly contagious respiratory pathogens in pigs and can infect various animal hosts, including humans, birds, dogs, cats, horses, ferrets, minks, and seals [91, 86, 92, 79, 87, 48, 89, 84].

Antigenic Diversity Among IDVs Utilizing Immune Antisera. To investigate the antigenic variation of IDV HEF proteins, hemagglutination inhibition (HI) and viral neutralization (VN) assays were performed. These assays utilized mouse polyclonal antibodies generated against specific viral strains, including D/OK, D/660, D/Yama2016, and D/Yama2019 lineages. A recombinant virus (rCA/OK) was also tested. Results confirmed that while all antisera reacted to homologous and heterologous viral strains, reactivity to heterologous viruses exhibited reduced titers. This variation underscores potential antigenic diversity among IDV HEF lineages. Notably, homologous strains showed the highest titers, while heterologous reactions were often eight-fold lower in the HI assay and up to 16-fold lower in VN tests. This pattern highlights possible antigenic differentiation across lineages

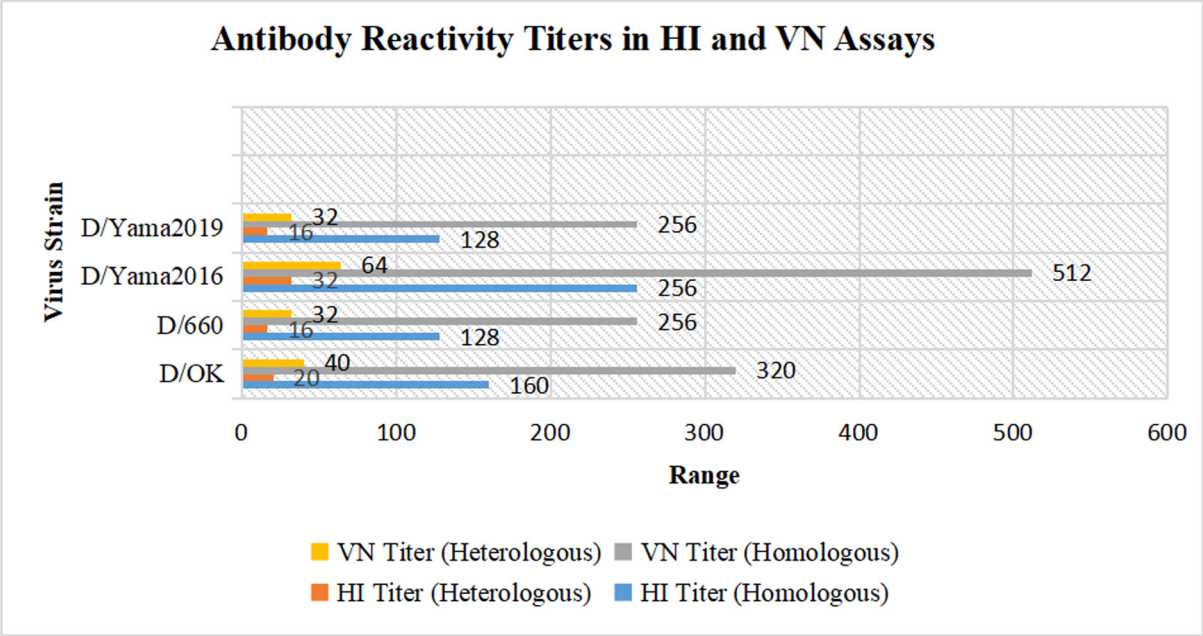

Figure 2. The illustration meticulously delineates virus strains in relation to hemagglutination inhibition (HI) and virus neutralization (VN) titers, stratified by homologous and heterologous responses. For the D/OK strain, the HI titer under homologous conditions registers at 160, with a significant reduction to 20 in heterologous conditions, while the VN titer is elevated at 320 homologously and decreases to 40 heterologously. The D/660 strain presents homologous HI titers of 128, with heterologous titers reduced to 16; VN titers show a homologous value of 256, decreasing to 32 in heterologous conditions. The D/Yama2016 strain manifests robust HI titers of 256 in homologous conditions and 32 in heterologous, accompanied by VN titers of 512 in homologous and 64 in heterologous assays. Lastly, the D/Yama2019 strain exhibits homologous HI titers of 128, with a marked reduction to 16 under heterologous conditions, and homologous VN titers at 256, declining to 32 heterologously.

(**Figure 2**).

Antigenic Variation Among IDV HEFs Employing Monoclonal Antibodies. Mouse hybridomas secreting monoclonal antibodies (mAbs) against HEF antigens were produced to analyze antigenicity further. Specific mAbs were found to react either with homologous viruses or across multiple strains. These results suggested the presence of strain-specific epitopes and cross-reactive regions among IDV HEFs.

Identification of Antigenic Epitopes via Monoclonal Antibodies:. Virus neutralization escape mutants were generated to map antigenic epitopes on the HEF protein. Various amino acid substitutions were identified in escape mutants, highlighting the potential regions responsible for VN activity loss. By comparing these mutants' sequences with their wild-type counterparts, specific epitopes crucial for immune recognition were pinpointed.

Mapping of Epitopes on the Hemagglutinin-Esterase Fusion Molecule. The identified amino acid changes were plotted onto the HEF structure, revealing that critical antigenic epitopes were located near the receptor-binding region or within the esterase domain.

Commonality of Hemagglutinin-Esterase Epitopes across Viral Lineages. Some mAbs recognized epitopes in the receptor-binding region that were conserved across multiple viral lineages. This observation suggests that specific epitopes, such as positions 187 and 189, are preserved and critical for cross-lineage antigenic responses **Table 2** [93, 94, 2, 14, 16, 95, 96, 97, 73, 40, 98].

Antigenic Drift and Shift in Influenza. The influenza virus undergoes antigenic evolution through two primary mechanisms: antigenic drift and antigenic shift. These processes involve changes in the virus's surface glycoproteins, specifically hemagglutinin (HA) and neuraminidase (NA), leading to the continuous need for updates in vaccine antigens to match circulating strains.

Antigenic Drift is a gradual process in which small mutations in the HA and NA proteins occur over time, resulting in minor changes to the virus. These mutations can enable the virus to evade the immune responses generated by previous infections or vaccinations, making the immune response generated by existing vaccines less effective.

Antigenic Shift. In contrast, antigenic shift involves a more significant change, typically through reassortment between different viral strains. This can lead to new virus subtypes that the human population has little to no pre-existing immunity against, potentially resulting in pandemics. The constant antigenic changes presented by both drift and shift challenge vaccine development, necessitating a system of global virus tracking and annual vaccine reformulations. The World Health Organization (WHO) is critical in monitoring these changes and selecting appropriate virus strains for inclusion in seasonal influenza vaccines [21, 99, 53, 100, 80, 101].

Epidemiology and vaccinations of influenza D virus

Influenza D virus (IDV) is a significant cause of the bovine respiratory disease complex (BRDC), the cattle industry's most common and costly ailment. A recombinant strain (rD/OK-AL) was engineered to create a candidate vaccine using mutations in the PB2 and PB1 proteins to enhance cold adaptation and high-temperature sensitivity. This strain grew effectively at 33°C but not at 37°C. In mouse models, rD/OK-AL was attenuated after intranasal inoculation, leading to high antibody levels against IDV. Post-challenge with wild-type virus, IDV was undetectable in respiratory tissues, indicating complete protection. These results suggest that rD/OK-AL could be a promising candidate for developing live attenuated vaccines to control BRDC [12, 102, 92,

Table 2. Reactivity profile of mouse antisera against various viral strains.

Antiserum	Test	Titer against OK	Titer against NE	Titer against Y16	Titer against Y19	Titer against rCA/OK
αOK	HI	5,120	1,280	1,280	640	640
	VN	12,800	6,400	3,200	1,600	1,600
αNE	HI	80	640	320	160	80
	VN	100	3,200	6,400	800	200
αY16	HI	320	320	640	80	80
	VN	800	800	3,200	800	200
αY19	HI	640	160	320	640	320
	VN	800	800	1,600	1,600	80

2, 26, 28, 103, 31]. The research investigates the immunogenicity and efficacy of a quadrivalent neuraminidase RNA particle vaccine, Sequivity NA, marketed under the brand name Sequivity® IAV-S NA. This vaccine uses four neuraminidase antigens representing the predominant NA clades of Influenza A virus (IAV) subtypes H1N1, H1N2, and H3N2 prevalent in swine populations across the United States. During the trials, pigs received two vaccinations at three days and three weeks of age, followed by challenges with either homologous or heterologous IAV strains. The vaccine successfully elicited a strong serum neuraminidase inhibition (NI) antibody response. It conferred protection against both homologous and heterologous IAV-S strains, as in 2023, Kitikoon et al. [104] stated: "Quadrivalent neuraminidase RNA particle vaccine protects pigs against homologous and heterologous strains of swine influenza virus infection" (**Figure 3**) [104, 105, 106, 107, 66, 68, 108, 109, 48].

Moreover, Bovine Respiratory Syncytial Virus (BRSV) and Bovine Parainfluenza 3 Virus (BPIV3) are significant pathogens in bovine respiratory disease (BRD), leading to substantial morbidity and economic losses. Their intricate interaction with the host's immune system necessitates the presence of neutralizing antibodies and cell-mediated immunity. According to Makoschey and Berge (2021), combination vaccines targeting both viruses are commonly employed, and understanding their roles within the BRD complex can facilitate the development of effective vaccines [110, 67, 111, 26, 112, 113, 30, 114]. Moreover, research uncovers three newly identified triple-reassortant H1N1 swine influenza viruses from pigs in Tianjin, Northern China. In 2016, Sun et al. [90] stated that "these viruses possess a genetic composition derived from the 2009 pandemic H1N1 strain, Eurasian swine, and triple-reassortant swine lineages". The reassortment occurring in Tianjin presents a potential risk to human health, given that swine influenza, a highly contagious respiratory infection, has led to outbreaks in both the United States and China [115, 20, 67, 80]. Similarly, the Influenza D virus has emerged as a novel contributor to bovine respiratory disease (BRD), leading to notable production and economic setbacks in feedlot operations. As in 2020, Alvarez et al. [116] noted, "IDV infection is endemic in La Pampa, with 68% of the examined samples testing positive." However, the clinical significance of the virus in Argentina remains to be thoroughly investigated [116, 117]. In the same way, a novel influenza virus of genus D has been identified in pigs and cattle in the United States and France, showing a genome similarity of 94% to 99% to its U.S. counterpart. As in 2015, Ducatez et al. [118] state, "The virus, designated C/swine/Oklahoma/1334/2011 (C/OK), replicates in ferrets, which are the preferred animal model for studying influenza in humans." [118, 116, 119, 41, 117]. In Luxembourg, the influenza D virus (IDV) is widespread among cattle farms, with antibodies identified in 80.2% of cattle samples collected in 2016. The seroprevalence of the virus rose significantly from 0% to 5.9% between 2012 and 2015 [120]. The United States revealed that 19.1% of 256 swine tested were seropositive for influenza D virus, with an overall IDV seropositivity rate of 42.7% [121]. Moreover, the Influenza D virus predominantly occurs in cattle across numerous countries, exhibiting a notably high seropositivity rate of 77.5% in the United States. The virus is associated with mild to moderate respiratory ailments. It plays a role in the bovine respiratory disease complex (BRDC), representing the most economically burdensome illness impacting the U.S. cattle industry [122, 28]. The study assessed antibody levels against influenza viruses across seven age cohorts during Poland's 2018/2019 epidemic season. The peak antibody response was observed in the 10-14 age group for the A/Singapore/INFIMH-16-0019/2016 (H3N2) and B/Phuket/3073/2013 Yamagata lineage antigens. Influenza represents a significant risk to vulnerable populations, including individuals over 65, children under two years, pregnant women, and those with chronic health conditions [123, 105, 107]. A novel strain of the Influenza D virus has been isolated from affected cattle in Japan and is linked to respiratory illnesses. The hemagglutinin-esterase-fusion (HEF) gene does not belong to any recognized phylogenetic lineages [125, 11, 14]. At the same time, Tropheryma whipplei pneumonia has been associated with HIV-2 infection in an individual with the virus. Dogs can transmit various pathogens to humans, including canine influenza A and prevalent human influenza viruses. Italy revealed a low prevalence of exposure to influenza D virus among adult household dogs, showing no correlation between IDV infection and clinical manifestations in dogs, as well as a lack of cross-reactivity between IDV and human influenza C virus (ICV) [50, 27, 87]. A study published in Emerging Microbes & Infections investigated the virulence and transmissibility of canine H3N2 influenza viruses (CIVs) isolated from dogs in South Korea between 2009 and 2013. The analysis revealed that these viruses exhibited a close genetic relationship with strains previously identified in dogs from both Korea and China. Notably, the research identified non-synonymous mutations within the canine

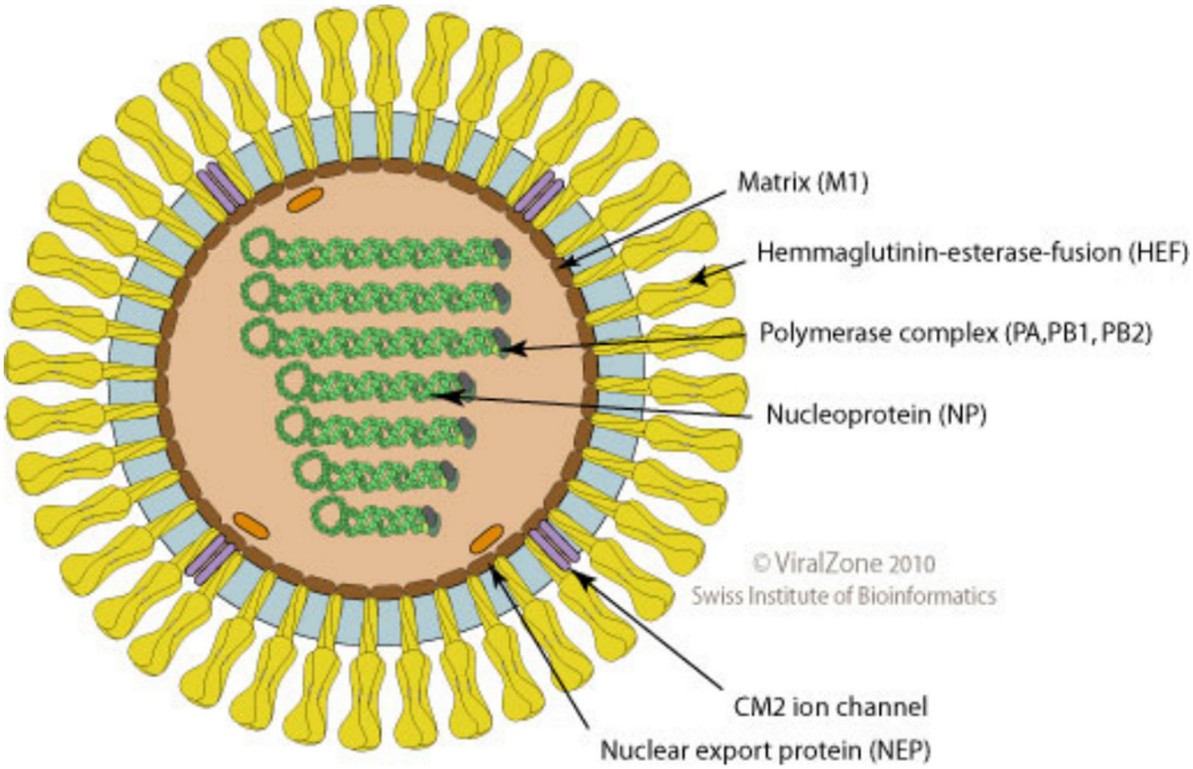

Figure 3. The illustration provides an overview of Influenza D virus (IDV), an enveloped, spherical virus approximately 80-120 nm in diameter, with a segmented, single-stranded, negative-sense RNA genome that encodes seven proteins. Transcription is driven by the viral RNA polymerase complex through a cap-snatching mechanism. A distinctive feature of IDV is its hemagglutinin-esterase (HE) fusion protein, which enables receptor binding, viral fusion, and degradation of the host receptor. IDV shares roughly 50% amino acid identity with human influenza C virus (ICV) and similarly utilizes 9-O-acetylated sialic acid as its receptor, though segment homology levels vary.

viruses, particularly affecting the presumed H3 antigenic sites, the neuraminidase (NA) stalk regions, and various internal genes. Furthermore, the study elucidated the genetic contributions of the NA, nucleoprotein (NP), and matrix (M) genes to the adaptability of CIVs that originated from the avian H3N2 virus [126, 106, 107, 69, 29].

Likewise, the virosomal influenza vaccine administered to pigs exhibited no significant lesions in the lung, spleen, liver, or kidney tissue samples. Nevertheless, follicular lymphoid hyperplasia was detected in 71.87% of the pigs in the G2 group, while mild histiocytic infiltration was noted in 11.11% of the pigs from the G1 group and 15.62% from the G2 group. The polyvalent influenza virosome vaccine demonstrated a commendable safety profile and non-cytotoxicity in pigs, as evidenced by the findings from the TUNEL assay and the absence of adverse reactions following vaccination. Furthermore, in (2023), Haach et al. [127] indicated that "the follicular lymphoid hyperplasia observed in the mediastinal lymph nodes of vaccinated pigs remains to be investigated" [127, 73]. A DNA vaccine, FluD-Vax, has been engineered to safeguard guinea pigs from infection by two distinct lineages of the influenza D virus (D/OK and D/660). This vaccine expresses the consensus hemagglutinin-esterase fusion protein (HEF) and has undergone testing against these lineages in guinea pigs. The vaccine elicited substantial levels of neutralizing antibodies against representatives of the influenza D virus lineages, specifically D/OK and D/660 [128, 42, 129]. The study investigates the innate immune response within the respiratory epithelium of human, porcine, and bovine hosts during influenza virus infection to uncover potential factors influencing viral cross-species transmission [131]. Influenza C and D viruses exhibit genetic similarities and utilize 9-O-acetylated sialic acids for cellular entry. Both viruses target ciliated cells, operating independently of the host and ambient temperature. Temperature pronounced affects influenza C virus (ICV) replication in cultured environments, whereas influenza D virus demonstrates efficient replication regardless of temperature and host species [131, 132, 133, 134]. Influenza viruses, encompassing types A, B, C, and D (IAV, IBV, ICV, and IDV), impact various animal species, including humans. The non-structural protein 1 (NS1) is a multifunctional protein in all influenza types, undermining host antiviral defenses. Despite performing analogous functions, NS1 proteins from various types exhibit minimal amino acid sequence homology [135, 13]. Moreover, in contrast to that for prevention, Wild watermelon, a plant rich in phytochemicals and phytoestrogens, has emerged as a promising functional food in the fight against influenza. The plant's phytochemicals and phytoestrogens, which include polyphenols, flavonoids, and prenylated compounds, demonstrate the ability to inhibit viral growth, entry, and replication. This study emphasizes the potential of wild watermelon as a preventive and therapeutic agent against influenza, exhibiting notable antiviral efficacy. Influenza, a zoonotic disease with significant public health implications, is marked by antigenic mutations that affect transmissibility and drug resistance. While antiviral medications have been developed to target various stages of viral replication,

resistance can develop within a timeframe ranging from years to decades [136, 137]. It has seven RNA segments and one major surface glycoprotein, the hemagglutinin-esterase-fusion. The virus has been identified in several countries, including France, Italy, Luxembourg, Canada, Mexico, China, Mississippi, Japan, and Nebraska. Notably, the virus has been detected in cattle, sheep, swine, horses, and goats. However, its viral genome has been confirmed only in certain animal species, with specific antibodies detected in others. In 2022, a study conducted by Trombetta et al. [138] to evaluate the prevalence of antibodies against two IDV lineages (D/660 and D/OK) in archived serum samples from swine veterinarians in Italy collected in 2004, results indicated that cattle may come into contact with the virus either during transportation or immediately afterward [138, 139]. At the same time, there is research to assess the extent of maternally acquired passive immunity in cattle from Mississippi and its influence on the onset of infectious diseases. Among 55 ailing calves, 32.7% exhibited seropositivity for Influenza D Virus (IDV), with a geometric mean viral titer (GMT) of 172.8 (±7215.7). These calves had been housed at the facility for an average duration of 24 days at the time of sampling and had undergone 1.9 treatments for respiratory illness. Quantitative RT-PCR analysis of respiratory swabs identified IDV in 29.1% (55 out of 189) of the sick calves and 2.4% (2 out of 82) of the healthy calves, supporting the hypothesis that IDV infection correlates with bovine respiratory disease (BRD) in dairy cattle. In 2015, Ferguson et al. [140] state, "Influenza D virus infection was observed in Mississippi beef cattle with a significant percentage showing seropositivity." The calves testing positive for IDV had been at the facility for an average of 19.4 days, implying that active infection may develop within the first week of arrival at the order-buying facility. Two healthy calves, who had only been at the facility for seven days, shared the same pen. BRD is a multifaceted, multi-pathogen disease with various contributing agents. IDV, detected in cattle displaying respiratory symptoms, could potentially be one of the multiple pathogens that compromise host immunity and exacerbate the pathogenesis of respiratory disease in cattle. Metagenomics analysis of respiratory samples from 50 dairy calves with BRD revealed contig reads for bovine adenovirus 3, bovine rhinotracheitis virus A, and IDV in 62% of the specimens. However, other respiratory pathogens might account for the elevated IDV prevalence in sick versus healthy herds. The findings indicated that 94% of neonatal cattle sampled between 2013 and 2014 acquired immunity against IDV through maternal colostrum, though this immunity appeared to wane with age. By six months, many cattle were likely vulnerable to IDV infection [140, 141].

Efficacy of Two Intranasal Vaccines in Mitigating Bovine Respiratory Disease among Neonatal Beef Calves. Bovine respiratory syncytial virus (BRSV) and bovine parainfluenza-3 virus (bPI3V) are significant contributors to bovine respiratory disease (BRD) in neonatal calves globally. Vaccination is extensively implemented to mitigate BRD, with the development of intranasal vaccines for BRSV and bPI3V aimed at circumventing the interference posed by maternally derived antibodies. Numerous experimental challenge trials have demonstrated the efficacy of these intranasal vaccines; however, their effectiveness in practical field settings, particularly among newborn beef calves, has been less frequently validated. This field trial evaluated the comparative effectiveness of a commercially launched commercial BRSV-bPI3V intranasal vaccine against a benchmark counterpart in newborn beef calves raised within a cow-calf management system. A total of 935 calves across 39 farms were randomized into two vaccination cohorts (Bovalto et al. [Vaccine A], n = 468; Rispoval RS + PI3 Intranasal [Vaccine B], n = 467) and closely monitored throughout the in-house risk period, extending up to three months post-vaccination. A non-inferiority analysis assessed the disparity in BRD prevalence between the two vaccine groups. No statistically significant differences were identified between the vaccines concerning clinical outcomes such as morbidity, mortality, the interval between vaccination and BRD onset, and the treatments administered. Given that the upper limit of the two-sided 95% confidence interval for the difference in BRD prevalence between the treatment groups (0.8%) remained below the non-inferiority margin (d = 5%), Vaccine A was deemed non-inferior [142, 122, 113].

Swine intermediate vectors

The genetic shift has given rise to new strains of influenza viruses capable of facilitating efficient human-to-human transmission, thereby contributing to multiple pandemics in history. While cattle are the primary known reservoir for the influenza D virus, other small ruminants and humans have also demonstrated susceptibility to IDV infections under various circumstances [25, 34, 35, 123]. A study examining two canine influenza viruses from Korea, isolated between 2013 and 2014, revealed a close genetic relationship to the predominant H3N2 canine influenza viruses (CIVs), which possess mutations in antigenic and host-determining regions. The investigation also identified minimal genome-wide genetic variation among the H3N2 CIVs. Influenza A virus (IAV) is highly transmissible, infecting humans, mammals, and domestic and wild avian species. Dogs are regarded as intermediate hosts due to their frequent interactions with humans and respiratory tract receptors [52, 143, 107]. In Italy, molecular and virological analyses were conducted on 845 clinical samples collected from 448 pig farms experiencing respiratory distress in the Po Valley from June 2015 to May 2016. Serological evaluations were performed on 3,698 swine serum samples, including archived sera from 2009 and newly collected samples from 2015. Genetic analysis indicated that Italian swine influenza D viruses are closely aligned with the D/swine/Oklahoma/1334/2011 cluster. 2015 IDV was identified in 27 (8.1%) of the 332 cattle herds examined for respiratory pathogens. To gain a deeper understanding of the epidemiology and significance of IDV within the Italian swine population, a series of clinical specimens, sera, and archived samples were subjected to both virological and serological investigations. The serological findings demonstrated the presence of antibodies against IDV in 364 samples across 74 herds, with 59% exhibiting antibody titers of ≥40. Additionally, a serological test was conducted in 27 farms (36%) to validate the presence of IDV in the swine population [144, 117, 145, 137, 88, 34, 146, 147, 78, 148].

The H1N1pdm09 virus has been transmitted from humans to swine in Brazil, with at least 30 distinct introductions occurring between 2009 and 2011 [149]. These introductions are likely characterized by self-limited infections in swine, resulting in minimal or negligible onward transmission. Nevertheless, the virus persisted in certain instances. It continued to propagate successfully among swine, as demonstrated by the clustering of monophyletic clades that encompass three or more swine sequences isolated in Brazil over several years. The HA and NA sequences from swine collected in Brazil exhibited elongated branch lengths, indicative of substantial genetic divergence and limited sampling [149]. Moreover, the D/Yama2019 lineage-like Influenza D virus (IDV) has been detected in cattle in China. The study revealed the identification of an IDV strain with nearly complete genomic sequences within Chinese cattle herds, demonstrating genetic proximity to strains found in Japan while exhibiting significant divergence from previously reported Chinese IDV strains. This finding underscores the necessity for enhanced surveillance of D/Yama2019-like viruses to gain deeper insights into the epidemiology and diversity of IDV in China [150]. The Influenza D virus is a multi-host pathogen predominantly residing

in bovine populations. It specifically attaches to 9-O-acetylated N-acetylneuraminic acid, which confers a selective evolutionary advantage, facilitating an expanded range of potential hosts [151, 152].

Influenza C and D viruses displayed a unique respiratory tissue tropism in pathogenesis in guinea pigs. Community-acquired pneumonia (CAP) in children exhibits a severity greater than that of the influenza B virus yet comparable to CAP associated with the influenza A virus. This investigation aimed to elucidate the replication dynamics, tissue tropism, and pathogenesis of human ICV (huICV) about the swine influenza D virus (swIDV) in guinea pigs. Intranasal inoculation of both viruses did not elicit clinical symptoms; however, the infected subjects shed the virus in nasal washes. The huICV demonstrated replication in the nasal turbinates, soft palate, and trachea but not in the pulmonary tissues, whereas the sword was capable of replicating across all four examined tissues [153, 133, 20, 154, 63, 129, 130]. The Influenza D virus (IDV), a member of the Orthomyxoviridae family, has been identified in various regions, including North America, Europe, Asia, and Africa. In South Korea, the inaugural report regarding the detection of viral RNA and the seroprevalence of IDV was conducted in 2022. Viral RNA was analyzed using real-time RT-PCR assays on 999 nasal swabs and lung tissues from cattle and 2,391 from pigs. The seroprevalence of IDV was assessed by testing 742 cattle and 1,627 pig sera utilizing a hemagglutination inhibition (HI) assay. The positive rate for viral RNA was 1.4% in cattle, while no viral RNA was identified in pigs. The study revealed a viral RNA positivity rate of 1.4% among cattle, with seropositivity rates recorded at 54.7% for cattle and 1.4% for pigs. The geometric mean antibody titers (GMT) were 68.3 in cattle and 48.5 in pigs. This study marks the first documentation of both viral RNA and antibodies to IDV in the Republic of Korea. IDV can infect and disseminate among a broad spectrum of hosts, including domestic cattle, pigs, sheep, goats, horses, camels, poultry, and wild species such as feral pigs. Cattle are recognized as the principal reservoir for IDV, with infections linked to mild to severe respiratory clinical manifestations. The recently identified IDV is believed to primarily cause respiratory illness in cattle, with significantly lesser effects on pigs. In 2022, Korean native and non-indigenous beef cattle constituted 90% of the national cattle population, while dairy cattle accounted for merely 10%. The relatively small proportion of dairy cattle in the national herd can be attributed to the lesser significance of dairy products in the traditional Korean diet [155, 117].

Clinical Manifestations, Diagnosis, and Prospective Vaccines. Influenza D virus is transmitted via direct contact and aerosolized particles over short distances. The majority of available data regarding this disease's clinical manifestations pertain predominantly to cattle infections. Notably, the potential existence of asymptomatic carriers has also been documented in bovine and various other animal species.

1. Cattle: Cattle serve as the primary reservoir for IDV, with extensive serological studies confirming high seroprevalence across North America and Europe and evidence of the virus's potential contribution to BRD.

2. Swine: IDV circulation has been confirmed in swine populations in several countries, but seroprevalence is generally lower than in cattle, suggesting further investigation into pigs' roles in IDV ecology is warranted.

3. Camels: High seroprevalence of IDV has been observed in camels from Africa and Asia, indicating they may also act as significant reservoirs for the virus.

4. Small Ruminants: Sheep and goats exhibit lower IDV susceptibility than cattle and camels, with varying seroprevalence observed in North America and Africa.

5. Horses: Horses show some seroprevalence to IDV, indicating potential interspecies transmission, although the virus does not appear to cause respiratory disease in equines.

6. Wild Animals: Feral swine and wild deer in North America exhibit varying seroprevalence to IDV, suggesting a possible role in the virus's ecology and transmission between domestic and wild species (**Figuure 4**) [156, 39].

Serology of influenza D virus

The study explored the potential cross-reactivity between Influenza D/swine (IDV) and Influenza C/Victoria (ICV) by utilizing rabbit reference anti-sera targeting two IDV lineages: Influenza D/swine/OK/1334/2011 (D/OK) and Influenza D/bovine/660/2013 (D/660), in conjunction with a human ICV strain, Influenza C/Vic. The anti-serum specific to the D/660 strain exhibited equivalent reactivity toward both viruses, achieving a hemagglutination inhibition (HI) titre of 1,280 for each, while displaying no detectable reactivity with C/Vic. In contrast, the anti-serum produced against the D/OK strain demonstrated greater specificity for the D/OK virus, yielding an HI titre of 2,560, although it also displayed cross-reactivity with D/660, attaining a titre of 640. The anti-serum directed against C/Vic was specific to the C/Vic virus, with an HI titre of 2,560 and no observable activity against either IDV lineage. The investigation involved the analysis of 364 horse serum samples collected in 2015 from six states, along with an additional 100 samples gathered in 2016 from four states. Each sample was examined for virus-specific antibodies through the standardized hemagglutinin inhibition assay (HI) conducted in triplicate. Among the 230 individual serum samples included in the analysis, 36 tested positive for antibodies against D/OK, 28 for D/660, and 37 for C/JHB. Out of the 57 total positive samples for IDVs from the 2015 serum cohort, 23 (6.3%) exhibited positivity for both IDV lineages (D/OK and D/660), while 21 (5.8%) and 13 (3.6%) were positive solely for the D/OK or D/660 lineages, respectively. Based on the cross-reactivity data from the two IDV lineages evaluated with reference rabbit anti-serum, it was hypothesized that the 23 horses with detectable antibodies to both lineages were primarily infected by D/660 or D/660-like viruses, as the D/660 anti-sera recognized both lineages with equal efficacy in the HI assay. Additionally, it remains plausible that the samples testing positive for both IDV lineages may indicate superinfection or co-infection with D/660 and D/OK, a determination complicated by the cross-reactive properties of these viral lineages and the absence of temporal data regarding the collected samples. A separate analysis of the 2015 horse serum samples from the HI trials revealed a robust positive correlation between the antibody titres of the two IDV lineages (D/660-D/OK) and one ICV strain. However, negative correlations were identified between the ICV strain and the two IDV strains. In 2016, 100 horse serum samples were collected to assess the presence of IDV- or ICV-specific antibodies, revealing three (3%) samples positive for antibodies against D/OK, two (2%) for D/660, and eight (8%) for C/JHB. The observed discrepancies in overall seroprevalence among the samples may be attributed to the smaller sample size and the more restricted population of horses involved [157, 14, 137, 158, 34, 147, 78, 148]. In conclusion, Influenza D virus (IDV) is a pivotal component of the bovine respiratory disease (BRD) complex, having been identified in livestock throughout China. Notably, during the 2022-2023 period, live IDVs were successfully isolated from cattle, revealing a remarkably high seroprevalence of 91.4% during the winter season. Furthermore, IDV RNA was detected in 11.1% of cattle across the nation, marking the first instance of IDV serosurveillance in China. In contrast, pigs and goats exhibited exceedingly low seroprevalence rates. Additionally, the study uncovered a D/660 lineage-like IDV in Chinese cattle, a variant not previously documented in Asia. Therefore, further research

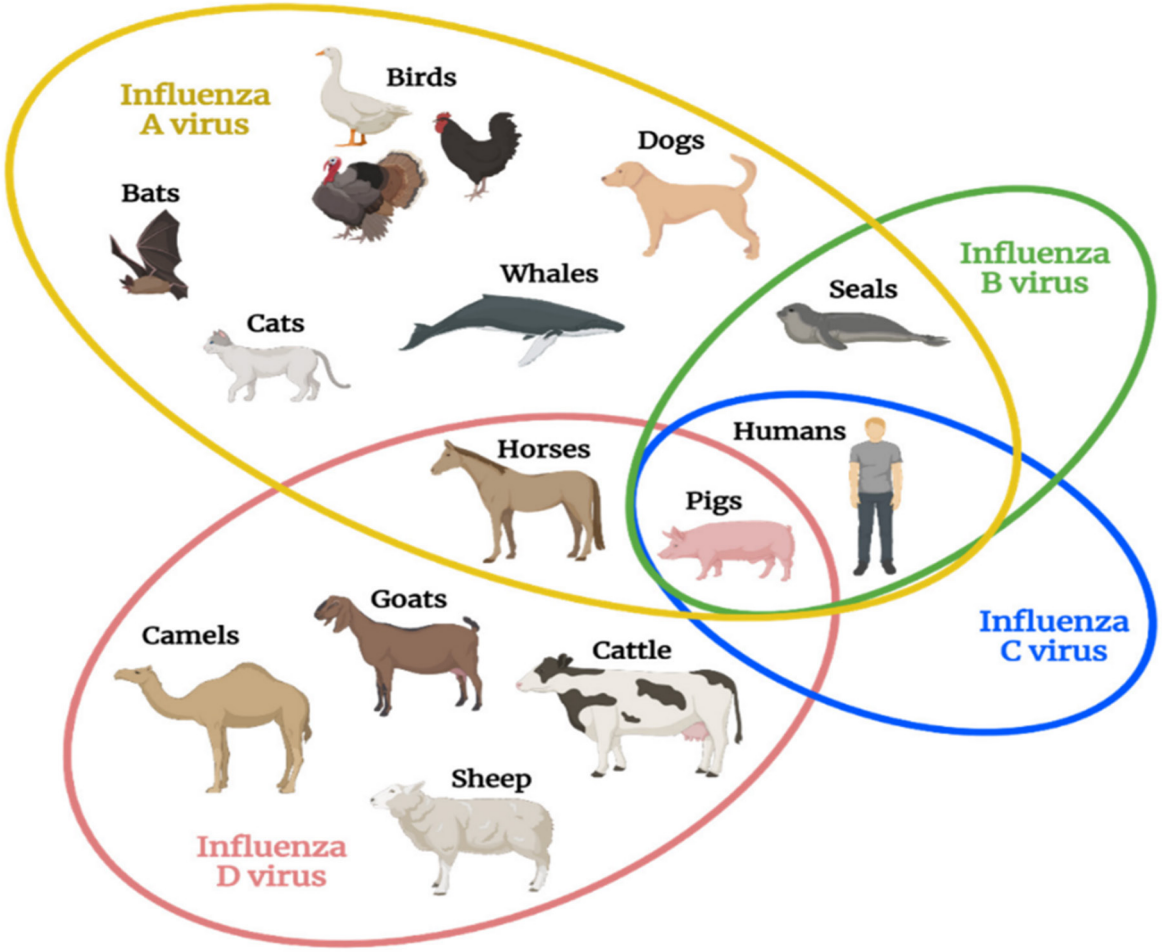

Figure 4. The illustration elucidates the natural host range of distinct influenza virus types, accentuating the principal species intrinsically susceptible to each variant, with certain overlaps manifesting among the different strains. Significantly, swine represent the exclusive species documented to harbor all four influenza virus types, whereas Influenza D virus exhibits the second most extensive host range, surpassed only by Influenza A virus.

is essential to evaluate the potential risks posed by Chinese IDVs to both animal and human health. Ultimately, IDV infections are associated with mild to moderate respiratory diseases in animals and play a significant role in the BRD complex [124].

Approaches for Controlling IDV Infections and Addressing Future Risks. Influenza viruses have caused significant mortality through annual epidemics and pandemics, prompting advancements in public health infrastructure and surveillance. Recent studies have developed effective diagnostics for the Influenza D virus (IDV), including a sensitive real-time RT-PCR assay and a multiplex assay that detects multiple respiratory pathogens. Additionally, bioaerosol surveillance has shown promise for monitoring IDV in public areas. Innovative vaccine strategies, such as a DNA vaccine targeting IDV lineages and an inactivated virus vaccine, have demonstrated protective efficacy in animal models. These vaccines resulted in significant antibody responses and reduced viral titers. While progress has been made in managing IDV infections, further research is essential to evaluate and enhance antiviral strategies to prevent future outbreaks and zoonotic transmission to humans [25, 159, 38].

Conclusions

The antigenic switch potential of the Influenza D virus represents a critical area of investigation in virology, underscoring the virus's ability to adapt and evade host immune responses. Through this review, we have elucidated the mechanisms by which Influenza D may undergo antigenic variation, primarily through genetic re-assortment and mutations, akin to its closely related counterparts in the Influenza A and B virus families. This capacity for antigenic shift not only facilitates viral persistence within diverse hosts but also poses significant challenges for public health initiatives aimed at controlling outbreaks. Understanding the antigenic landscape of Influenza D is essential for predicting its evolutionary trajectory and the emergence of novel strains that may cross species barriers, potentially leading to zoonotic transmission. Moreover, the implications of antigenic variability extend to vaccine development, highlighting the necessity for continuous surveillance and the formulation of adaptive immunization strategies. As we advance our understanding of the antigenic properties of Influenza D, it becomes increasingly vital to integrate genomic surveillance with epidemiological studies to better inform preventive measures. In conclusion, the antigenic switch potential of the Influenza D virus is a multifaceted phenomenon that necessitates further exploration.

Continued research in this domain is imperative to unravel the complexities of the virus's antigenic behavior and to develop robust frameworks for the mitigation of its impact on public health. Antiviral targets often become the major therapeutic task, however the efficiency of chosen tasks could be different from the purposed aim, once was effective in inhibition viral replication, next time the antiviral potency could be decreased significantly due to antiviral drug intolerance development.

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Ethics approval

No applicable.

Data availability

The data will be available upon request.

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Authors' contribution

Abdul Bari Hejran undertook the responsibilities of data collection and analysis, as well as the initial drafting of the manuscript and the meticulous review of the methodology. Khaidarov Saken spearheaded the conceptualization and design of the study, orchestrated the research activities, contributed to the drafting and revision of the manuscript, and granted approval for the final version prior to submission. Parwiz Niazi executed a comprehensive literature review, facilitated data interpretation, and contributed to the formulation of specific sections of the manuscript. Rahmatullah Afghan rendered assistance with statistical analysis, enriched the interpretation of findings, and provided critical revisions to the manuscript content. Each author played a pivotal role in ensuring the meticulousness and rigor of the study from its inception to final submission.

Competing interests

None.

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