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INSIGHTS INTO THE PREVALENCE AND TRANSMISSION DYNAMICS OF *INFLUENZA D VIRUS* AMONG MAMMALS: A MINI REVIEW

Influenza D Virus [IDV], a recently recognized member of the *Orthomyxoviridae* family, has attracted substantial scientific scrutiny due to its extensive host tropism, pronounced genetic heterogeneity, and potential zoonotic ramifications. Initially isolated from bovines, *IDV* has subsequently been identified in a diverse array of mammalian species, raising pivotal concerns regarding its epidemiological footprint, adaptive molecular evolution, and cross-species transmissibility. This mini-review aims to delineate the epidemiological distribution of *IDV* across mammalian hosts, elucidate its transmission dynamics, and evaluate its broader implications for both veterinary and public health sectors. A comprehensive examination of the extant literature was undertaken, with a focus on molecular epidemiology, host range plasticity, viral phylogenetics, and interspecies transmission modalities. The findings reveal that *IDV* predominantly circulates within cattle populations, with sporadic detections in swine, small ruminants, camelids, and, occasionally, humans. The primary modes of transmission include direct exposure to respiratory secretions, aerosolized dissemination, and fomite-mediated indirect spread, with environmental stability enhancing viral persistence. Although *IDV* exhibits relatively low pathogenicity in livestock, concurrent infections with other respiratory pathogens exacerbate clinical manifestations, resulting in significant economic repercussions, particularly within intensive livestock production systems. This review highlights the critical need for enhanced genomic surveillance and epidemiological monitoring, particularly in regions characterized by high-density animal husbandry and frequent interspecies interactions. A One Health paradigm is indispensable for assessing *IDV's* zoonotic potential and devising strategic interventions to mitigate its risks to global health security. By synthesizing current insights into *IDV's* epidemiology, evolutionary dynamics, and transmission networks, this work contributes to a more profound understanding of its ecological niche within the virosphere and provides a foundation for future investigations in virology, epidemiology, and infectious disease mitigation strategies.

Key words: Influenza D Virus, mammals, prevalence, transmission, epidemiology, zoonotic potential.

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Сүтқоректілер арасындағы Influenza D вирусының таралуы мен берілу динамикасына шолу: қысқаша шолу

Influenza D вирусы [IDV], жақында *Orthomyxoviridae* тұқымдасының мүшесі ретінде танылған, кең ауқымды иелерінің болуы, айқын генетикалық әртүрлілігі және ықтимал зооноздық салдарлары себепті ғылыми қауымдастықтың назарын аудартуда. Бастапқыда ірі қара малдан бөлініп алынған *IDV* кейіннен әртүрлі сүтқоректілерден анықталып, оның эпидемиологиялық әсері, молекулалық бейімделу эволюциясы және түр аралық берілуі туралы маңызды сұрақтарды туындатты. Бұл қысқаша шолу *IDV*-ның сүтқоректілер арасында эпидемиологиялық таралуын сипаттауға, оның берілу динамикасын түсіндіруге және мал шаруашылығы мен қоғамдық денсаулық салаларындағы ықтимал салдарларын бағалауға бағытталған. Қолданыстағы әдебиеттерге жан-жақты талдау жасалып, молекулалық эпидемиология, иелердің бейімделгіштігі, вирус филогенетикасы және түр аралық берілу механизмдері қарастырылды. Зерттеу нәтижелері *IDV* негізінен ірі қара мал

ірі қара мал арасында таралғанын, сондай-ақ шошқалар, ұсақ күйіс қайыратын жануарлар, түйелер және сирек жағдайларда адамдар арасында анықталғанын көрсетеді. Берілуінің негізгі жолдарына тыныс алу секрецияларымен тікелей байланыс, аэрозоль арқылы таралу және ластанған заттар арқылы жанама жұқтыру жатады, сонымен қатар қоршаған ортада тұрақтылығы вирустың ұзақ сақталуына ықпал етеді. *IDV* мал арасында салыстырмалы түрде төмен патогенділікке ие болғанымен, басқа респираторлық патогендермен қатар инфекция кезінде клиникалық белгілер күшейіп, бұл әсіресе қарқынды мал шаруашылығында елеулі экономикалық шығындарға әкеледі. Бұл шолу *IDV*-ның геномдық қадағалауы мен эпидемиологиялық мониторингін күшейту қажеттілігін атап көрсетеді, әсіресе жоғары тығыздықтағы мал шаруашылығы және түр аралық өзара әрекеттестік жиі кездесетін аймақтарда. *IDV*-ның зооноздық әлеуетін бағалау және оның жаһандық денсаулық қауіпсіздігіне тигізетін ықтимал қатерін азайту үшін «Бір денсаулық» қағидатын қолдану маңызды. Бұл жұмыс *IDV*-ның эпидемиологиясы, эволюциялық динамикасы және таралу желілері туралы қазіргі көзқарастарды біріктіре отырып, оны виросферадағы экологиялық орны туралы тереңірек түсінік қалыптастыруға және болашақ вирология, эпидемиология және инфекциялық аурулардың алдын алу стратегияларына негіз қалауға ықпал етеді.

Түйін сөздер: *Influenza D вирусы*, сүтқоректілер, таралу жиілігі, берілу механизмі, эпидемиология, зооноздық әлеует.

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Анализ распространенности и динамики передачи вируса гриппа D среди млекопитающих: мини-обзор

Вирус гриппа D [IDV], недавно признанный член семейства *Orthomyxoviridae*, привлек значительное внимание научного сообщества благодаря его широкому кругу хозяев, выраженной генетической гетерогенности и потенциальным зоонозным последствиям. Первоначально выделенный у крупного рогатого скота, *IDV* впоследствии был обнаружен у различных видов млекопитающих, что вызвало серьезные опасения относительно его эпидемиологического распространения, молекулярной адаптации и межвидовой передачи. Этот краткий обзор направлен на описание эпидемиологического распределения *IDV* среди млекопитающих, анализ его динамики передачи и оценку его более широкого влияния на ветеринарную и общественную систему здравоохранения. Проведен всесторонний анализ существующей литературы с акцентом на молекулярную эпидемиологию, пластичность диапазона хозяев, вирусную филогенетику и механизмы межвидовой передачи. Результаты показывают, что *IDV* преимущественно циркулирует среди крупного рогатого скота, с редкими случаями обнаружения у свиней, мелкого рогатого скота, верблюдов и, в отдельных случаях, у людей. Основные пути передачи включают прямой контакт с респираторными выделениями, аэрозольное распространение и непрямую передачу через загрязненные предметы, причем высокая устойчивость в окружающей среде способствует долговременному сохранению вируса. Несмотря на относительно низкую патогенность *IDV* для сельскохозяйственных животных, одновременные инфекции с другими респираторными патогенами усугубляют клинические проявления, что приводит к значительным экономическим потерям, особенно в условиях интенсивного животноводства. Этот обзор подчеркивает необходимость усиленного геномного мониторинга и эпидемиологического наблюдения, особенно в регионах с высокой плотностью животноводческих хозяйств и частыми межвидовыми контактами. Концепция «Единое здоровье» (One Health) является ключевой для оценки зоонозного потенциала *IDV* и разработки стратегических мер по снижению его рисков для глобальной безопасности здравоохранения. Обобщая современные данные о эпидемиологии *IDV*, его эволюционной динамике и путях передачи, данный обзор способствует более глубокому пониманию его экологической ниши в вирусной среде и закладывает основу для дальнейших исследований в области вирусологии, эпидемиологии и стратегии борьбы с инфекционными заболеваниями.

Ключевые слова: *вирус гриппа D*, млекопитающие, распространенность, передача, эпидемиология, зоонозный потенциал.

Introduction

Influenza D Virus [IDV], belonging to the *Orthomyxoviridae* family, was initially discovered in 2011 and later designated as a separate genus within the family. This classification was warranted due to its pronounced genetic and antigenic divergence from influenza A, B, and C viruses [1, 2, 3, 4]. In contrast to influenza A and B, which primarily afflict humans, *IDV* predominantly infects cattle and has been identified in various mammalian hosts, including swine, small ruminants, camels, and horses Figure, Table 1 [5, 6]. Research shows that this virus exists worldwide since scientists have confirmed its presence throughout North America, Europe, Asia and Africa within livestock herds [7, 8]. The virus is capable of persisting in cattle populations, where it plays a role in the bovine respiratory disease complex [BRDC], a significant cause of economic losses in the cattle industry [9, 8]. Furthermore, serological studies have detected *IDV* antibodies in individuals with occupational exposure to livestock, raising concerns about its zoonotic potential [10, 11].

Moreover, Serological data indicating prior exposure to *Influenza D Virus* in humans has been substantiated through three independent investigations. The initial study identified a low seroprevalence of *IDV* within the general population, whereas the second study, which concentrated on individuals with occupational exposure-specifically cattle-exposed farmers in Florida-reported an exceptionally high seroprevalence of 97%. The third study unveiled a temporal association between peak *IDV* prevalence in humans and concurrent outbreaks in domestic swine populations in Italy, suggesting potential interspecies transmission dynamics [12, 13]. *Influenza D Virus* exists in swine and ruminants but cattle maintain the status as its primary host and storage point. This virus produces mild to moderate sickness by invading respiratory systems from the upper to the lower portions whereas transmission occurs by physical contact and airborne droplets. The infection of *IDV* within the lower respiratory tract leads to the development of both bronchopneumonia and interstitial pneumonia which cause moderate disease severity. After inoculation *IDV* activates an immune response that relies on IgG1 antibodies because it stimulates both Th1 and Th2 cellular pathways. Pathogen recognition receptors alongside chemokines show increased activity during *IDV* infections of calves thus indicating potential *IDV* characteristics of moderate virulence and high transmissibility. [14].

Hence, Bovine respiratory disease [BRD] represents a formidable ailment in juvenile cattle, precipitated by a complex interplay of pathogenic agents and environmental stressors. Concurrent infection with *influenza D virus* and *Mycoplasma bovis* exacerbates the condition, intensifying pulmonary lesions. *IDV* primarily establishes itself within the lower respiratory tract, instigating heightened leukocyte infiltration. Moreover, the virus modulates immune gene expression, with interferon-gamma (IFN-γ) exhibiting the most pronounced upregulation. This immunomodulatory effect amplifies both disease severity and the innate immune response, further complicating the pathological landscape [15]. According the **"Saegerman et al. (2022)"** investigated the role of *IDV* in bovine respiratory disease by analyzing 883 nasal and nasopharyngeal swabs from symptomatic cattle in Québec, Canada (2017–2020), reporting an *IDV* prevalence of 5.32%. *IDV* was significantly associated with bovine respiratory syncytial virus and *Mycoplasma bovis*. Phylogenetic analysis identified most strains within clade D/660, with evidence of reassortment between clades D/660 and D/OK in samples from 2018–2020. The study highlighted *IDV's* epidemiological significance in Canadian dairy cattle and confirmed genomic reassortment through whole-genome sequencing [16, 17]. And *IDV* has three major lineages: globally distributed D/OK, USA-specific D/660, and Japan-restricted D/Japan. Since 2014, two distinct lineages have co-circulated in the USA, undergoing reassortment and forming at least seven genotypes [18, 19, 20, 21]. Although specific receptor preferences exist *IDV* shows wide-ranging ability to infect domesticated animals and wild species in the environment. Scientific records show that *IDV* exists in water buffalo along with Asian elephants and hedgehogs while demonstrating abilities for continued transmission between domesticated species and species of wild origin. Auxiliary receptors needed for *IDV* attachment are not present in wild Cervidae or Suidae nor in tigers. Tissue microarray analysis demonstrated that tigers together with Cervidae and Suidae have no receptors for viral binding while dromedaries, springboks, water buffalo, Asian elephants and hedgehogs confirm the presence of receptors. The virus demonstrates the ability to cross between species according to its potential spread across agricultural and ecological environments [22]. This mini-review evaluates modern studies about *Influenza D Virus's* wild host distributions while exploring transmission pathways and how different mammalian groups accept the virus. Additionally it considers *IDV's* epidemiological

track and its potential to jump species. The evaluation of viral interspecies transmission patterns and evolutionary adaptation ability comes from thorough research on serological and molecular surveillance data. The review will evaluate substantial information gaps and analyze widespread effects of *IDV* on veterinary medicine and public health and lay out essential steps to advance detection systems and detection techniques and disease control approaches that combine veterinary medicine with public health practice under the One Health framework.

Table 1 – Epidemiology, Dissemination Pathways, and Pathophysiological Consequences of Influenza D Virus in Bovine and Porcine Populations across Diverse Geographical Regions

No	*Samples*	*Mammals*	*Prevalence*	*Transmission Dynamics*	*Effects*	*Presentation*	*Future Prospective*	*Reference*
1	369 samples	Cattle, Swine	High seroprevalence in bulls in Argentina	Airborne and direct contact transmission	Respiratory symptoms, mild fever	Subclinical infections common	Need for continuous monitoring	23
2	500 samples	Swine, Cattle	*IDV* detected in Italian cattle and swine	Potential cross-species transmission	Respiratory disease in young animals	Mild to moderate respiratory distress	Surveillance and genetic analysis required	24
3	800 samples	Cattle, Swine	Widespread across Europe	Airborne and direct contact transmission	Increased respiratory disease	Asymptomatic to mild respiratory symptoms	Improved diagnostic methods needed	25
4	600 samples	Cattle, Swine	Found in multiple regions in the U.S.	Seroprevalence in livestock	No severe clinical impact	Subclinical to mild infections	Potential zoonotic implications	26
5	450 samples	Cattle	Novel genetic clusters identified in Italy	Emerging virus with evolving transmission routes	Mild respiratory illness	Self-limiting symptoms in cattle	More research on evolution and spread needed	18
6	300 samples	Swine	Detected in U.S. feral swine populations	Wildlife reservoirs may contribute to spread	Potential spillover risk	Limited clinical data available	Risk assessment in wild populations needed	27
7	650 samples	Cattle	High prevalence among French cattle	Zoonotic potential remains unclear	Respiratory infection	Asymptomatic or mild disease	Zoonotic risk assessment required	28
8	550 samples	Cattle, Swine	Detected in China	Increasing in livestock populations	Mild respiratory disease	Clinical signs are inconsistent	Global surveillance recommended	29
9	750 samples	Cattle	Evidence of antigenic drift	Reassortment events possible	Respiratory symptoms	Mostly subclinical infections	Vaccine development necessary	30
10	400 samples	Cattle, Swine	Found in multiple continents	Serological studies indicate wide distribution	No major outbreaks reported	Minor respiratory impact	Potential for mutation and adaptation	31

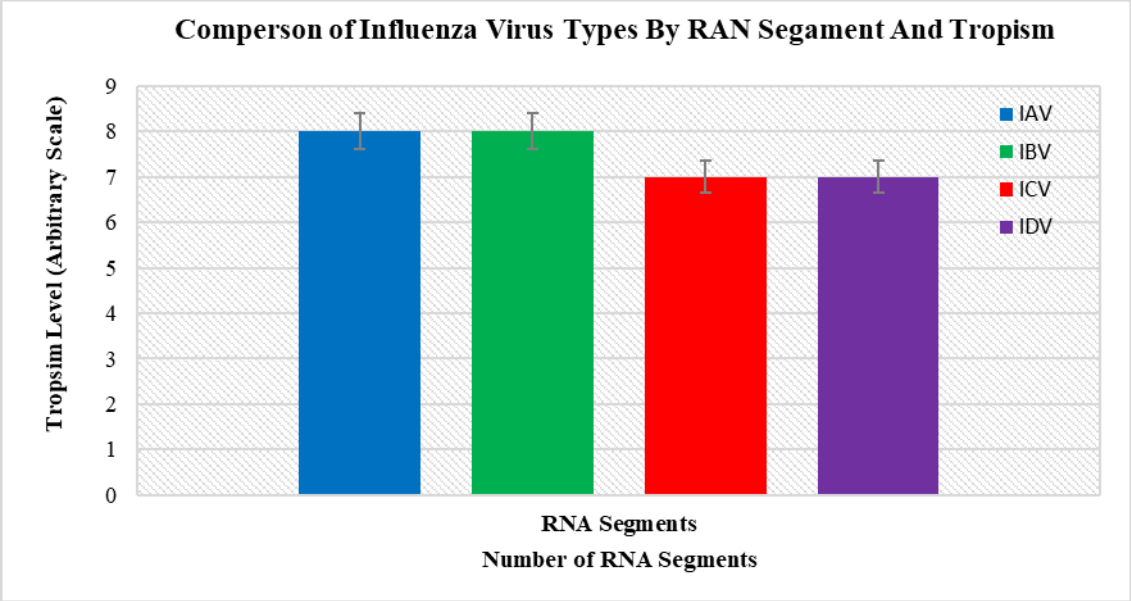

Figure 1 – Depicts the biological and evolutionary attributes of *Influenza D Virus* in relation to other influenza viruses. It underscores *IDV's* distinctive genomic architecture, comprising seven RNA segments, and its reliance on the HEF glycoprotein for receptor binding, fusion, and entry. Furthermore, the figure highlights *IDV's* extensive cell tropism, exceptional acid stability, and high-affinity interaction with both human and non-human sialic acids. The virus's accelerated evolutionary rate (~1.68×10^{-3} substitutions per site per year) further signifies its capacity for interspecies transmission and adaptive evolution [12, 32, 33, 34, 35].

Results and Discussion

Host Range and Prevalence of Influenza D Virus

In bovines, *Influenza D Virus* has been implicated in the etiology of bovine respiratory disease [36, 37]. Epidemiological investigations have documented an 8.0% prevalence of *IDV* among cattle afflicted with BRD, whereas a lower incidence of 3.4% has been observed in asymptomatic cattle. Notably, in 62.5% of *IDV*-positive BRD cases, *IDV* was identified as the sole viral pathogen present [38]. In swine, seroprevalence rates fluctuate between 9.5% and 11.7%, signifying active viral circulation within domestic pig populations [39, 40]. Moreover, a markedly elevated prevalence exceeding 30% has been detected in pigs and goats in specific geographic regions, potentially attributable to inadequate biosecurity protocols and intensified livestock stocking densities [41]. For instance, Between September 2003 and May 2004, a total of 15,402 bovine serum samples were procured from 73 beef cattle farms across Nebraska. To assess the prevalence of *Influenza D virus,* 40 farms were randomly selected from this dataset, and 293 serum samples underwent serological analysis for *IDV* antibodies. Findings revealed that 235 out of 293 samples (80.2%) tested seropositive for the D/13N strain, while 237 out of 293 samples (80.9%) exhibited seropositivity for the D/46N strain. Additionally, the study examined the contemporary epidemiological status of *IDV* in Nebraska cattle by collecting serum samples from 242 calves on a single farm during the spring of 2014, where seropositivity rates among herds ranged between 91% and 100% Table 2 [42]. Although *Influenza D Virus* predominantly infects animals, emerging evidence suggests a potential for zoonotic transmission [12]. Serological investigations have identified the presence of *IDV*-specific antibodies in individuals with occupational exposure to cattle, implying the possibility of human infection [39]. Nevertheless, the implications of *IDV* for human health remain ambiguous, necessitating further research to elucidate its pathogenic potential and clinical significance in human populations [12].

Table 2 – Comparative analysis of Hemagglutination Inhibition (HI) and Microneutralization (MN) assay outcomes for Influenza D Virus in a cohort of 200 bovine serum samples from Morocco* [43, 44]

HI assay	MN assay		Total no.
	No. positive	No. negative	
No. positive	66	4	70
No. negative	31	99	130
Total no.	97	103	200
Comparison	Sensitivity, 68% (95% CI 57.8%–77.2%)	Specificity, 96% (95% CI 90.4%–98.9%)	

*By using D/bovine/France/5920/2014 as antigen. Titers ≥10 were considered positive. HI, hemagglutination inhibition; MN, microneutralization. For HI as compared with MN.

Cattle:- Cattle serve as the principal reservoir for *IDV*, exhibiting extensive seroprevalence globally, with notably high rates in North America (77.5%), Europe (up to 94.6%), and Asia (5.9%–71%).

Swine:- While *IDV* is documented in swine, its prevalence remains comparatively lower than in cattle, displaying variable seropositivity across Europe, North America, and China (peaking at 36.8%).

Camels:- Camels exhibit an exceptionally high *IDV* seroprevalence, reaching near-universal levels (99-100%) in regions such as Kenya, Ethiopia, and Mongolia; however, potential serological cross-reactivity with ICV complicates interpretation.

Small Ruminants:- Sheep and goats demonstrate relatively low *IDV* seroprevalence compared to cattle or camels, with reported positivity rates not exceeding 8.8%.

Horses:- Equines exhibit minimal seropositivity for *IDV*, with detection rates of 11-12% in the United States and below 1.4% in the United Kingdom, while experimental infections suggest limited viral replication without clinical manifestations.

Wild Animals:- *IDV* has been identified in wild suids, with seroprevalence reaching 42.7% in feral pigs in the United States and 0.5% in wild boars in France, indicating restricted transmission dynamics in wildlife populations Table 3 [36, 45, 46, 47].

Table 3 – Synopsis of Serological Findings and Molecularly Confirmed Cases of Influenza D Infections, Categorized by Country, Year, Host Species, and Diagnostic Methodology [36, 48]

Country, Year	Animal Species	Method
EUROPE		
Belgium (BE), 2019	Deer	HI
Denmark (DK), 2019	Bovine	real-time PCR
France (FR), 2009–2018	swine and wild boar	HI and real-time PCR
France (FR), 2011–2018	bovine, small ruminants	HI
France (FR), 2019	hedgehogs	HI
Germany (DE), 2019	Deer	HI
Ireland (IE), 2014–2016	bovine, swine, and sheep	HI and real-time PCR
Italy (IT), 2012–2019	bovine and swine	PCR and real-time PCR
Luxembourg (LU), 2012–2016	bovine and swine	HI
Netherlands (NL), 2021	Swine	real-time PCR
Sweden (SE), 2019	bulk tank milk	ELISA

Continuation of the table

Country, Year	Animal Species	Method
Switzerland (CH), 2016	Bovine	real-time PCR
United Kingdoms (UK), 2017	Bovine	real-time PCR
AFRICA		
Benin (BJ), 2012–2014	Bovine	HI
Ethiopia (ET), 2019	Camels	HI
Kenya (KE), 2015	Camels	HI
Morocco (MA), 2015	Bovine	HI and MN
Namibia (NA), 2020	wildebeest and giraffe	real-time PCR
Nigeria (NG), 2021	Bovine	real-time PCR
Nigeria (NG), 2019	Camels	HI
Togo (TG), 2017–2019	Bovine	HI
ASIA		
Japan, Yamagata (JP-06), 2019	Bovine	real-time PCR
Japan, Hokkaido (JP-01), 2018	Bovine	real-time PCR
China, Guangdong (CN-44), 2016	bovine, swine, and caprine	real-time PCR
China, Shandong (CN-37), 2014	Bovine	real-time PCR
Malaysia (MY), 2018	Swine	real-time PCR
Mongolia (MN), 2019	Camels	HI
Republic of Korea (ROK), 2019	bovine and swine	HI and real-time PCR
Saudi Arabia (SA), 2019	Camels	HI
Turkey (TR), 2018	Bovine	Real-time PCR
SOUTH AMERICA		
Argentina (ARG), 2013	Bovine	ELISA
Brazil (BR), 2020	Bovine	real-time PCR
NORTH AMERICA		
USA, California (CA), 2018	Bovine	real-time PCR
USA, Hawaii (HI), North Carolina (NC), Oklahoma (OK), Texas (TX), 2012–2013	feral swine	HI
USA, Kansas (KS), 2010–2012	Bovine	real-time PCR
USA, Kentucky (KY), 2017	Swine	next generation sequencing
USA (samples collected across the country)/2014, 2015	Bovine	HI
USA, Mississippi (MS), Michigan (MI), Minnesota (MN), and Oklahoma (OK), 2011–2017	Deer	HI
USA, Mississippi (MS), 2004–2014	Bovine	real-time PCR, HI
USA, Nebraska (NE), 2003–2004, 2012–2014	Bovine	HI

Continuation of the table

Country, Year	Animal Species	Method
USA, Oklahoma (OK), 2011–2013	Swine	next generation sequencing
USA, 12 states, 2014	Bovine	real-time PCR
Canada, Quebec (QC), 2020	Bovine	real-time PCR
Mexico (MX), 2015	Bovine	real-time PCR
AUSTRALIA		
Australia—New South Wales (AU), 2019	Bovine	transcriptomics
Australia (AU), 2019	Camels	HI

Serological Prevalence of *Influenza D Virus* in Cattle, Sheep, Goats and Swine Populations

Hemagglutination Inhibition (HI) analysis confirmed the presence of anti-*IDV* antibodies across all four examined livestock species **(Table 4)**. Among the 3,381 serum samples analyzed, 232 (6.9%) tested positive for *IDV* antibodies. The highest seropositivity rate (20.9%) was recorded in Ugandan cattle, with swine seropositivity also detected exclusively in Uganda. In contrast, sheep and goats exhibited substantially lower seropositivity rates, ranging between 2% and 4.4%. HI titers in positive samples varied from 10 to 640, with the highest titers observed in cattle and swine sera. Notably, adjusting the threshold for positive sera from a titer of 10 to 20 yielded comparable results [49, 50].

Table 4 – Seroprevalence Rates of *Influenza D Virus* in Cattle, Sheep, Goats, and Swine across Four Countries in West and East Africa

Country	Sampling Period	Animal Species	Number of Tested Samples	Number of Positive Samples	Positivity Rate (%)	HI Titer Range
Benin	2017–2019	Cattle	332	13	3.9	20–80
Côte d'Ivoire	2019	Cattle	180	13	7.2	10–80
		Sheep	171	7	4.1	10–40
		Goat	163	6	3.7	10–40
Togo	2017–2020	Cattle	759	48	6.3	10–320
		Sheep	392	8	2	10–80
		Goat	817	36	4.4	20–160
		Swine	80	0	–	–
Uganda	2017–2019	Cattle	321	67	20.9	10–160
		Swine	166	34	20.5	10–640

Factors Influencing ***IDV*** Seropositivity

To identify determinants associated with *IDV* seropositivity, we analyzed various contributing factors. The statistically significant variables are summarized in Table 5. Cattle exhibited a higher likelihood of seropositivity compared to goats and sheep, with odds ratios (OR) of 0.48 and 0.30, respectively ($p < 0.001$). Conversely, swine demonstrated a 1.5-fold increased probability of *IDV* seropositivity compared to cattle (OR = 1.56, $p = 0.03$). Moreover, cattle in Uganda were at a significantly greater risk of *IDV* infection than those in other surveyed countries (OR = 5.33, $p < 0.001$).

Table 5 – Determinants of Anti-IDV Seropositivity Rates among Cattle, Sheep, Goats, and Swine across Four Countries in West and East Africa

Variable	Categories (N)	n(%)	OR	95% (CI)	*P*
Species	Cattle (1592)	141 (8.9)	RF		
	Goat (980)	42 (4.3)	0.48	0.34–0.69	<0.001
	Sheep (563)	15 (2.7)	0.30	0.18–0.52	<0.001
	Swine (246)	34 (13.6)	1.56	1.05–2.32	0.03
Countries*	Benin (332)	13 (3.9)	RF		
	Côte d'Ivoire (180)	13 (7.2)	–	–	0.1
	Togo (759)	48 (6.3)	–	–	0.1
	Uganda (321)	67 (20.9)	5.33	2.89–9.84	<0.001
Sex	Male (1456)	90 (6.2)	RF		
	Female (1925)	142 (7.4)	–	–	0.2

N: number of samples tested; n: number of positive samples; %: proportion of positive samples; OR: odds ratios; CI: confidence interval; RF: reference factor; p values ≤ 0.05 are considered statistically significant;* For these countries, only cattle sera were considered.

Transmission Dynamics and Infection Pathways

Influenza D Virus demonstrates complex transmission dynamics and multifaceted infection mechanisms, affecting a broad spectrum of animal hosts with the potential for interspecies spillover, including human exposure.

Direct Transmission: Influenza D Virus propagates predominantly via respiratory droplets and close-contact interactions among susceptible hosts. Infected cattle and swine serve as primary vectors, enabling efficient viral dissemination within herd populations. Experimental investigations have substantiated *IDV's* ability to infect and spread among diverse mammalian species, including ferrets, mice, guinea pigs, and pigs, highlighting its robust potential for direct transmission [51].

Indirect Transmission: IDV may spread indirectly by persisting on contaminated surfaces, feed, and the environment. While data on its stability are limited, evidence from other influenza viruses suggests fomites could facilitate transmission.

Inter-Species Transmission: IDV exhibits a wide host adaptability, infecting both domestic and wild animal species. Cattle function as the principal reservoir; however, viral presence has been identified in swine, small ruminants, camels, horses, and feral pigs. This expansive host spectrum underscores the potential for cross-species transmission, including spillover events, particularly from cattle to swine [52, 53, 54].

Zoonotic Implications of IDV: Serological investigations in North America revealed an *IDV* seroprevalence of 1.3% in human sera collected in the USA and Canada in 2011, whereas Italian studies reported a sharp increase from 5.1% in 2005 to 46% by 2014. A study by Leible et al. evaluated *IDV* exposure among 31 workers on five large-scale dairy farms, detecting viral presence in the nasal washes of 67% of individuals at least once during a five-day period; however, no correlation was observed between viral presence and respiratory symptoms. Although serological findings suggest potential exposure, conclusive evidence confirming *IDV* as a human pathogen remains absent, with no documented cases of human infection to date. Nonetheless, research into *IDV* receptor-binding properties, its replication efficiency in human respiratory epithelial models, and the identification of viral genetic material in airport bioaerosols, hospital environments, and nasal swabs from a pig farmer imply that humans may possess a latent susceptibility to infection [36, 38, 55].

Additionally, Influenza viruses, encompassing influenza A (IAV), influenza B (IBV), influenza C (ICV), and *influenza D (IDV)*, are pivotal respiratory pathogens affecting both humans and animals. Unlike IAV, which exhibits a broad host range, IBV, ICV, and *IDV* **Table 6** demonstrate a more restricted spectrum of infectivity. Notably, swine serve as susceptible hosts for all four influenza genera. While IAV infection in pigs manifests as swine influenza-a well-documented zoonotic concern with substantial implications for human and animal health-the pathogenicity of IBV and *IDV* in pigs was evalu-

ated through intratracheal and intranasal inoculation of IAV-seropositive pigs, alongside exposure of naïve pigs to infected counterparts to assess viral transmission. Both IBV and *IDV* induced fever and pulmonary lesions and replicated within the lungs of infected pigs; however, only *IDV* demonstrated transmissibility to contact animals. Despite variations in viral replication within the respiratory tract, no significant differences in the pathogenic potential of IBV and *IDV* were observed Figure 2 [56, 57].

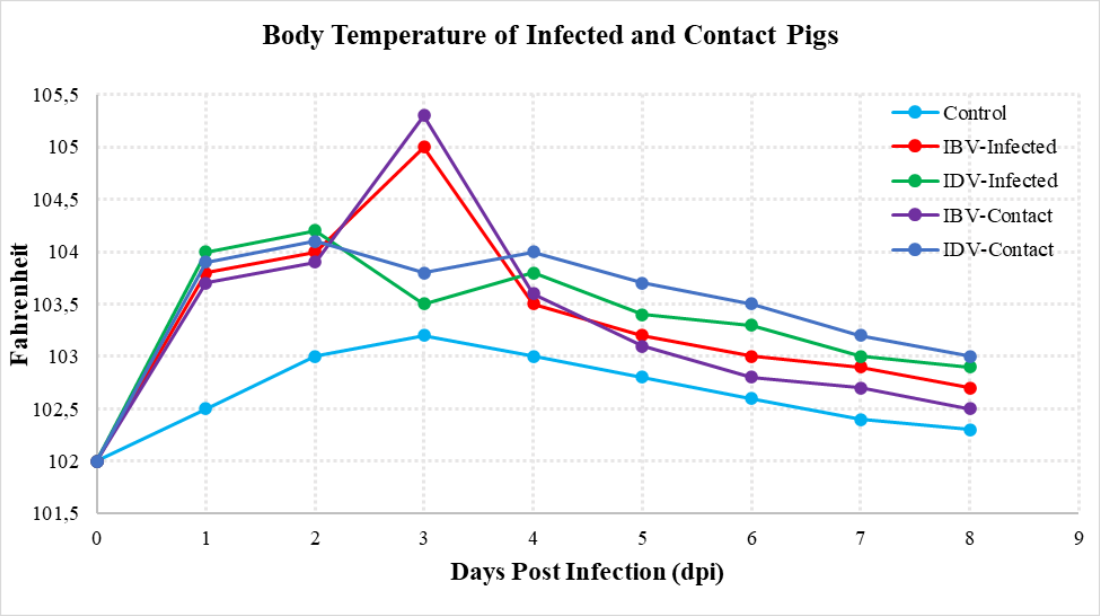

Figure 2 – Illustrates the body temperature variations in infected and contact pigs over eight days post-infection (dpi) with Influenza B Virus (IBV) and *Influenza D Virus (IDV)*, compared to a control group. Initially, all groups exhibited similar temperatures, but by 1 dpi, IBV- and *IDV*-infected pigs, as well as their respective contact groups, showed a notable temperature increase, peaking sharply at 3 dpi. *IDV*-contact pigs exhibited the highest fever, closely followed by IBV-infected and IBV-contact pigs, while the control group maintained a steady lower temperature. After 3 dpi, temperatures gradually declined, with infected and contact pigs still showing slightly elevated levels compared to controls. The data indicate that both IBV and *IDV* infections induce fever, with *IDV* possibly having a stronger transmission effect in contact pigs [56]

Table 6 – Genetic Composition and Protein Functions of Influenza Viruses: This table outlines the gene segments of influenza A (IAV), influenza B (IBV), influenza C (ICV), and *influenza D (IDV)* viruses. For each influenza species, the corresponding protein products and their respective biological functions are summarized [58]

Gene Segment	IAV	IBV	Viral Function
1	PB2	PB2	RNA-dependent RNA polymerase (RDRP) component
2	PB1	PB1	RDRP component
	PB1-F2 [1]		Inflammation, apoptosis, regulation of host immune responses
	PB1-N40 [1]		Regulates PB1 expression and activity
3	PA	PA	RDRP component
	PA-X [1]		Enhances viral gene expression, facilitates host mRNA degradation, regulation of cell-mediated host responses
	PA-N155 [1]		Functions unknown, likely involved with viral replication
	PA-N182 [1]		Functions unknown, likely involved with viral replication
4	HA	HA	Host receptor binding and membrane fusion
5	NP	NP	Packages viral RNA in vRNPs [2] with RDRP components

Continuation of the table

6	NA	NA	Sialidase; assists with release of new virions from host cell
		NB	Function unknown but highly conserved
7	M1	M1	Facilitates packing of vRNPs into new virions
	M2	BM2	Ion channel; assists in release of vRNPs into host cytoplasm
	M42 [1]		Alternate ion channel
8	NS1	NS1	Host immune response antagonism
	NS2/NEP	NS2/NEP	Nuclear export protein for newly synthesized vRNPs
Gene Segment	**ICV**	**IDV**	**Viral Function**
1	PB2	PB2	RNA-dependent RNA polymerase (RDRP) component
2	PB1	PB1	RDRP component
3	P3	P3	RDRP component
4	HEF	HEF	Host receptor binding, membrane fusion; esterase; assists release of new virions
5	NP	NP	Packages viral RNA in vRNPs with RDRP components
6	M1	M1	Facilitates packing of vRNPs into new virions
	CM2	DM2	Ion channel; assists in release of vRNPs into host cytoplasm
7	NS1	NS1	Host immune response antagonism
	NS2	NS2	Nuclear export protein for newly synthesized vRNPs

[1]Accessory protein; [2] vRNPs: viral ribonucleoproteins.

Pathogenesis and Clinical Implications of *IDV* in Mammals

Symptoms in Different Hosts:

Cattle: Infection with *Influenza D Virus* in cattle generally manifests as mild respiratory distress. Controlled experimental studies have demonstrated minimal clinical indicators, including sporadic episodes of dry coughing and intermittent nasal exudation [27]. For instance, *Influenza D virus* is a segmented RNA virus predominantly identified in cattle and implicated in mild to moderate respiratory manifestations. A comprehensive study conducted between 2017 and 2020 detected *IDV* in 883 nasal and nasopharyngeal swabs collected from Canadian cattle exhibiting respiratory symptoms. The virus demonstrated a prevalence rate of 5.32%, with a significant correlation to co-infections involving other respiratory pathogens. These findings underscore the necessity for enhanced global surveillance of *IDV* within cattle production systems to better understand its epidemiological impact and mitigate its potential influence on bovine health [16].

Swine: Although *Influenza D Virus* has been identified in pigs presenting with influenza-like symptoms, the precise clinical presentation in swine remains inadequately characterized [59].

Other Mammals: In species such as guinea pigs, *Influenza D Virus* infection has been detected without notable clinical manifestations, despite the virus actively replicating within respiratory tissues [60].

Co-infections:

Influenza D Virus frequently interacts with other respiratory pathogens, amplifying disease severity:

Bovine Respiratory Disease Complex (BRD): IDV is recognized as a contributory agent in BRD, a multifactorial respiratory syndrome in cattle. Concurrent infection with pathogens such as *Mycoplasma bovis* exacerbates the severity of respiratory illness, compounding its clinical impact [15].

Influenza A Virus: Although the interactions between *IDV* and Influenza A Virus in co-infections are not extensively characterized, their potential interplay remains plausible, necessitating further research to elucidate their combined impact on disease progression.

Impact on the Livestock Industry: The emergence of *Influenza D Virus* in livestock presents substantial economic and health challenges:

Economic Implications: Respiratory ailments in cattle, including those linked to *IDV*, contribute to considerable financial losses by reducing productivity and elevating veterinary expenditures [61].

Surveillance Strategies and Diagnostic Approaches of *IDV:* The surveillance and diagnostic assessment of *Influenza D virus* are paramount for

safeguarding animal health and curbing its potential zoonotic spillover.

Sampling and Detection Techniques:

Reverse Transcription Polymerase Chain Reaction (RT-PCR): This advanced molecular assay facilitates the identification of *IDV* RNA within respiratory specimens, including nasopharyngeal swabs and pulmonary tissues, ensuring exceptional sensitivity and specificity in pathogen detection [36].

Serological Assays: Identification of *IDV* serum antibodies happens through the use of virus neutralization tests (VNT) combined with hemagglutination inhibition (HI) assays. The validity of enzyme-linked immunosorbent assays (ELISA) towards viral protein detection allows researchers to distinguish between different *IDV* lineages by targeting proteins like hemagglutinin-esterase fusion (HEF) and nucleoprotein (NP).

Viral Isolation: Cultivating *IDV* in cell lines from clinical samples aids in isolating the virus, allowing for its detailed characterization and further investigation [36, 62, 63].

Challenges in Surveillance:

Underreporting: Insufficient awareness and the absence of routine diagnostics for *IDV* contribute to its underreporting, obstructing precise evaluations of its prevalence and geographical dispersion.

Scarcity of Comprehensive Research: The dearth of extensive investigations, particularly in specific regions, impairs the understanding of *IDV's* epidemiology and its implications for both animal and public health.

Serological Cross-Reactivity: Immunoassays may demonstrate cross-reactivity between *IDV* and other influenza viruses, complicating differential diagnosis. Advancements in assay development targeting distinctive *IDV* epitopes seek to alleviate this diagnostic challenge [64].

Future Perspectives and Research Gaps of *IDV*

IDV, identified in both domestic and wild animal populations, exhibits the potential for interspecies transmission; however, definitive evidence of human-to-human transmission or notable pathogenicity in humans remains absent.

Vaccination and Control Strategies: Advances and Constraints: Currently, no commercially available vaccines or targeted antiviral therapies exist for *IDV*. Experimental strategies, including a DNA vaccine encoding the consensus hemagglutinin-esterase fusion protein from two distinct *IDV* lineages Table 7, have demonstrated potential in animal models by inducing robust neutralizing antibody responses. Moreover, the development of recombinant temperature-sensitive *IDV* strains presents a promising avenue for vaccine innovation. However, despite these scientific advancements, the lack of approved prophylactic and therapeutic interventions underscores a critical gap in the effective control and management of *IDV* infections [65, 66, 67, 68, 69, 44].

Table 7 – Lineage-based allocation of the reference dataset [70]

Lineage	Reference Dataset	True Positive Dataset
D/OK	9	89
D/660	7	47
D/Yama2016	2	3
D/Yama2019	2	3
D/CA2019	2	1
D/France2012	1	0

One Health Paradigm: Synergizing Veterinary and Human Health Research: Embracing a One Health paradigm, which harmonizes veterinary and human health research, is imperative for a holistic approach to *IDV* surveillance and mitigation. This integrative framework underscores the intrinsic interdependence of human, animal, and environmental health, enabling a more efficacious response to emerging zoonotic threats. Notably, plant-based molecular farming has been proposed as an innovative platform for producing vaccines and therapeutics against diverse influenza viruses, aligning seamlessly with the One Health initiative. The implementation of such multidisciplinary strategies can significantly enhance our capacity to monitor, control, and curtail *IDV* transmission across species [71, 72, 73].

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Conclusion

Research studies demonstrate that *Influenza D virus [IDV]* spreads widely throughout different mammalian species and cattle maintain the primary virus reservoir. Molecular and serological testing supports the finding that interspecies transmission happens more frequently than previously thought thus creating major issues regarding the virus's potential to switch to humans. Epidemiological research stands urgent because scientists have discovered *IDV*-neutralizing antibodies within people who had occupational contact with infected animals despite no confirmed human infections. The virus shows remarkable capabilities to adapt and survive between varied ecological environments to the point that strict surveillance practices become essential. The combined use of enhanced genome surveillance techniques and complex DNA relationship tracking tools will serve as crucial components for studying viral evolutionary changes and identifying new threats. Health authorities need to direct future research toward complete host-range assessments and transmission models and investigations about possible re-assortment occurrences with additional influenza viruses. The research community must maintain unbroken awareness through combined international partnerships alongside inter-disciplinary studies. Early warning systems along with strengthened pandemic readiness systems constitute essential measures to prevent emerging public health threats related to *IDV*.

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