



Canine morbillivirus (CDV): a review on current status, emergence and the diagnostics

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Abstract The increasing host range of canine morbillivirus (CDV) affecting important wildlife species such as Lions, Leopard, and Red Pandas has raised the concern. Canine distemper is a pathogen of dogs affecting the respiratory, gastrointestinal, and nervous systems. Seventeen lineages of CDV are reported, and the eighteenth lineage was proposed in 2019 from India. Marked genomic differences in the genome of wild-type virus and vaccine strain are also reported. The variations at the epitope level can be differentiated using specific monoclonal antibodies in neutralization tests. Keeping in mind the current status of the emergence of CDV, genetic and molecular study of circulating strains of the specific geographical region are the essential components of the disease control strategy. New target-based diagnostics and vaccines are in need to counter the effects of the emerging virus population. Control of CDV is necessary to save the endangered, vulnerable, and many other wildlife species to maintain balance in the ecological system. This review provides an overview on emergence reported in CDV, diagnostics developed till today, and a perspective on the disease control strategy, keeping wildlife in consideration.

Keywords Canine morbillivirus (CDV) · Emergence · Wildlife · Diagnosis · Monoclonal antibodies (mAb)

Introduction

Canine distemper (CD) is primarily a viral disease of dogs and can infect several wildlife species. The disease was first reported in Spain (1761) and from there is believed to spread across the world [16, 17]. Edward Jenner was the first person to mention the disease name “canine distemper” and Carre first studied its etiological agent in 1905 [4]. The important milestones in the CDV research timeline are presented in Fig. 1. The disease is caused by canine morbillivirus or canine distemper virus (CDV), a member of the genus Morbillivirus and the family Paramyxoviridae [49]. The other members of genus like Rinderpest virus (RPV) and Measles virus (MV) are known to cause devastating diseases in both animals and humans from ages [132]. The host range of CDV includes members of Canidae, Procyonidae, Mustelidae, Ursidae, Viverridae, Felidae, Ailruidae, Ursidae, Hyaenidae, Tayassuidae, Cercopithecidae, and so on [72, 73]. Collectively, more than 20 families of Carnivores and non-carnivores are reported to be affected [34]. CD is a multisystemic disease that affects the respiratory, gastrointestinal, and nervous systems of the animal [81]. The incubation period varies from 1 to 4 weeks and the disease manifests as acute systemic and chronic encephalitic forms [101]. Virions are highly contagious, transmitted through aerosolized nasal, oral, and ocular fluid [4]. Real-time reverse-transcription polymerase chain reaction (RT-qPCR) based kinetics study demonstrated the virus shedding from the rectum (4 to 20th days post-infection/dpi), nose (2 to 20th dpi), blood (2 to 12th dpi), with the peak of virus titre at 10th, 12th, and 6th dpi respectively [110]. Infected animals shed virus in urine up to 60–90 days after recovery from the acute phase of the disease [42]. The virus causes severe immunosuppression and the affected animals show the clinical signs as biphasic fever, cough, conjunctivitis, diarrhea, and anorexia. The

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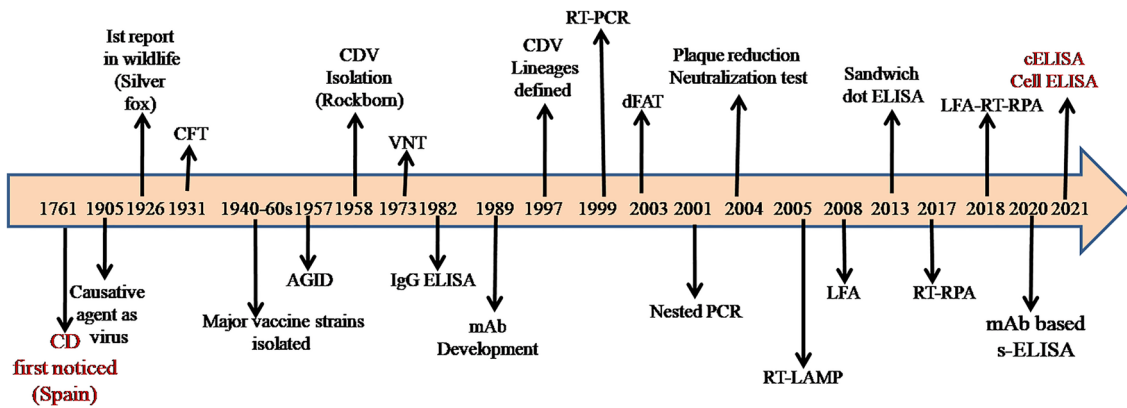


Fig. 1 The important milestones in the CDV research timeline

first peak of fever is seen after infection, followed by the second peak, after 6–9 days [95]. In some cases, the chronic stage of the disease occurs, manifested as seizures, tremors, twitching movements, and hard pads, referred to as “Old dog Encephalitis” [135].

CDV is a non-segmented negative-sense RNA virus of 15,960 nucleotides, wrapped over by a lipoprotein envelope. The genome comprises six structural proteins viz. nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), haemagglutinin protein (H), and the large protein (L) [80]. Non-structural protein (C) is encoded from the gene sequence of P protein by an overlapping open reading frame [118]. The study of detailed genetic sequence and the identification of conserved regions help to find targets for the specific identification of any pathogen. With the advancement in molecular studies after the 1990s, different genetic lineages of MeV [133], RPV [21], PPRV [113], and CDV [19] were identified, which are now one of the criteria for characterizing viral isolates based on their geographic origin. Till 2014 nine genetic lineages were reported based on H protein sequence identity (more than 95%) [107]. The number of genetic lineages has reached seventeen, namely America 1 to America 5, Asia 1 to Asia 4, Europe/ South America 1, South America 2 and 3, Europe wildlife, Arctic, Rockborn-like, Africa 1 and Africa 2 [33, 57]. In 2019, the eighteenth lineage was proposed (India-1/Asia-5) by our

laboratory, which represents the strains circulating in India [13].

Vaccines are the most important component of a viral disease control programs. Formalin-inactivated virus vaccine strains were used earlier to provide active immunity to dogs. The inactivated vaccine induces less antibody titre and is found to be less efficacious [4]. Ferret-passaged and egg-based vaccines of CDV have also been used for vaccination. The cell-culture attenuated strains, Onderstepoort, Synder Hill, Lederle, Convac, and Rockborn are widely used as live vaccines [25]. These vaccine strains provide effective immunity up to 4.4 years in dogs [50]. Rockborn strain was found to possess the residual virulence causing post-vaccination encephalitis, therefore its use was withdrawn in the mid-1990s [74]. The details of well-known strains of CDV are compiled in Table 1. Canarypoxvirus and Equine Herpesvirus type-1 (EHV-1) viral vector-based CDV vaccines are also found to protect dogs as well as wildlife species [91, 104, 144]. Many CDV strains have emerged in past few decades with different pathogenic characteristics and out of them apathogenic/naturally attenuated as a vaccine candidate is also reported [131].

This review provides a piece of comprehensive information on the emergence of CDV resulting in expansion of its host range, the current status of the disease, diagnostic tools developed till today, concluding with a perspective on

Table 1 Important (well-characterized) strains of CDV

Viral strain	Lineage	Available gene sequences	Accession no	Reference
Convac	America-1	H gene	Z35493	[63]
Onderstepoort	America-1	Complete genome	AF014953	[122]
SynderHill	America-1	H gene	AF259552	[45]
Lederle	America-1	H gene	EF418782	Not available
Rockborn	America-1	H gene	GU810819	[74]
Dog/Bly/Ind/2018	India-1/ Asia 5	H gene	MF964178	[13]

strategic advancement needed for effective prevention and control of the disease.

Current status and the emergence of the disease

CD is an endemic disease with a high frequency of outbreaks reported from all parts of the world. The serological survey has shown the high prevalence of the virus in the free-ranging dog population in many countries [23, 66, 119]. In India, several reports on isolation and characterization of CDV in dogs as well as wildlife from different geographical regions are present [10, 52, 62, 75, 128]. The dogs are the most common source of transmission of CDV to wildlife. Infection in endangered species like Siberian tigers, Ethiopian wolves, Red Panda [154], and other vulnerable wildlife species like Cheetah and Lions [5, 79, 117] shows the severe impact of CDV. From the very first report in silver fox [4], the list of wild animals is continuously increasing with the increased surveys, for example, *Tamandua tetradactyla* [73], mesocarnivores like Mink, Skunk, Raccoon [83]. Cheetah, domestic cats, and Asian Elephants are reported to be infected with the virus as indicated by the presence of specific antibodies but do not show any clinical signs [80]. The Phocine distemper virus (PDV) is also considered to be derived from CDV as a result of species jumping, selection pressure, and host adaptation [58]. CDV is now an emerging viral risk

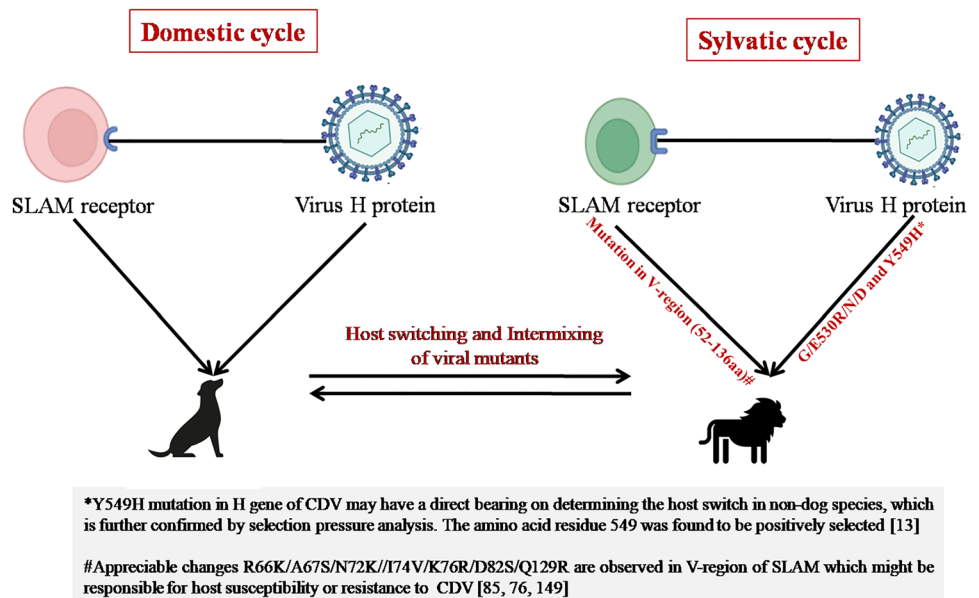
for several wildlife species [111], some of which are given in Table 2.

The H protein of the virus is immunodominant and is responsible for interacting with host cellular receptors—SLAM (Signaling lymphocytic activation molecule) and nectin-4. The H protein possesses a high percentage of mutations which undergoes positive selection to adapt to its new host. Therefore, the H protein is considered to be main force behind virus affinity towards different cells and acquiring the ability to infect a new host [34]. The interaction of H protein with SLAM and nectin-4 receptors has been depicted in Fig. 2. From the study of host cell receptors, the SLAM and nectin-4 receptors of dogs, felids, and small ruminants show some conserved residues and motifs which represent the specificity to particular morbillivirus [108, 145]. Nectin-4 receptor is comparatively conserved and is responsible for cell-to-cell spread within the host [76, 149]. SLAM receptor is the entry receptor for the virus and possesses mutations at several amino acid residues among the different hosts. Along with many other amino acids, the 76th position of the SLAM receptor plays a key role in host cell recognition and virus binding [85]. Based on the computational analysis, it was revealed that the Histidine residues at 28th position of N-terminal of SLAM receptors of *Macaca* are responsible for the stable interaction with H protein of CDV [150]. In our one of the unpublished data, most of the cases of wildlife population outbreaks showed changes at residue 549

Table 2 Host range of CDV

Family	Affected animals	Scientific names	Reference
Canidae	Silver fox	<i>Vulpes vulpes</i>	[4]
	Ethiopian wolf	<i>Canis simensis</i>	[41]
	Coyotes	<i>Canis latrans</i>	[44]
	Jackal	<i>Canis aureus</i>	[4]
Ursidae	Giant pandas	<i>Ailuropoda melanoleuca</i>	[36, 98]
	Black bears	<i>Ursus Americana</i>	[26]
Ailuridae	Red Panda	<i>Ailurus fulgens</i>	[20, 154]
Felidae	Lion	<i>Panthera leo</i>	[93]
	Leopard	<i>Panthera pardus</i>	[8]
	Siberian tiger (Amur tiger)	<i>Panthera tigrisaltaica</i>	[99]
Cercopitheidae	Rhesus monkey	<i>Macaca mulata</i>	[29, 97]
	Cynomologus Macaques	<i>Macaca fascicularis</i>	[105, 127]
	Japanese Monkey	<i>Macaca fusata</i>	[152]
Procyonidae	Racoons	<i>Procyon lotor</i>	[4]
Hyaenidae	Hyaena	<i>Crocuta crocuta</i>	[45]
Mustelidae	Ferrets	<i>Mustela putorius furo</i>	[122]
	Minks	<i>Neovison vison</i>	[4]
Viveridae	Civets	<i>Pagumalarvata</i>	[4]
Myrmecophagidae	Collared anteater	<i>Tamandua tetradactyla</i>	[73]
	Giant anteater	<i>Myrmecophaga tridactyla</i>	[30]
Elephantidae	Asian Elephant	<i>Elephas maximus</i>	[86]

Fig. 2 CDV tropism vis-à-vis receptor fidelity in domestic and wildlife animal population



of viral H protein. It was further confirmed that the Y549H mutation was positively selected by selection pressure. And the mutation at this particular residue might be a key determinant in adaption of virus in wildlife population. Also the mutation Y549H in H protein has been reported to be involved in the interaction of virus with the V domain of mink SLAM receptors [38].

With the ability of the virus to infect primates and adapt to the new host, few in-vitro studies were conducted manipulating human cell receptors (SLAM) and the H protein of the CDV [106]. These studies showed that the CDV has the fair possibility to emerge as a human pathogen with few mutations [16, 130]. As MeV shows cross-protective immunity with CDV, only the unimmunized population for MeV might be susceptible to new CDV [98]. The CDV isolates are classified as old CDV (vaccine strains) and new CDV based on the differences in their antigenic characteristic in neutralization tests [78]. Even different biotypes of different physiological properties and pathogenic patterns are reported [87, 126]. This variation is reflected in increasing cases of outbreaks of CD in vaccinated populations [2, 102, 136]. The widely used vaccine strains belong to the America-1 lineage, which possesses significant genetic variation from the circulating CDV strains of other lineages in different geographical areas [13].

Co-circulation of different lineages may result in homologous recombination and the emergence of viral variants or sub-lineages [46, 39, 94, 153]. The possibility of recombination of old vaccine strains with new viral variants has been suggested as the reason for the evolution of CDV and disease in vaccinated animals [28]. These are anticipated explanations, as the evolutionary analysis and emergence of CDV is not clearly studied and described yet. Being a pathogen

of such a wide host range and the significance of wildlife in ecological balance, the monitoring and research of CDV require utmost priority without any critical gaps.

Available diagnostic tools for CDV

Ferrets were used as an experimental animal for diagnosis in earlier days [32]. Later, virus isolation started as a common laboratory practice for diagnosis using ferret kidney cells, dog alveolar macrophage culture, and Vero cells [4]. Primarily, the diagnosis is done based on the history of animals and the clinical signs indicating multi-systemic affection. Tissue samples like the external epithelium of affected linings viz. hard pad, urothelium, uvea contain the persistent virus [54]. The sign and symptoms of the disease are not very noticeable at the early stage, especially in wildlife. Therefore, the correct and rapid diagnosis is the key to the management and control of the disease. Today's requirement of an in-depth genetic study of pathogens puts forth the demand for highly sensitive and specific diagnostic assays. There are several diagnostic tests with varied sensitivity, specificity, required time, and different levels of skills to perform the test [106]. The diagnostic tools developed for CDV detection are included in Table 3.

Virus detection

Virus isolation

Virus isolation is the "gold standard" test for the diagnosis of viral diseases. CDV presents a low success rate in

Table 3 Diagnostic tools for routine diagnosis of CDV in laboratory and field

	Diagnostic tool	Target	Application	References
1. Virus detection	(MDCK, Vero cells-SLAM B95a, etc) Virus	Virus	Gold standard test	[7]
a. Virus isolation			Highly sensitive, helpful for generating virus repository (Require live virus titre, specific cell line and cell culture facilities)	[107] [120]
b. Antigen detection	Direct ELISA	CDV antigen	Detects antigen in serum	[119]
	Sandwich ELISA	H protein	High specificity Detection and quantitation	[91]
		F protein	Efficient in field application with fecal and serum samples	[148]
	Sandwich dot ELISA	Virus	Epidemiological surveillance	[65]
	LFA	F protein	Practically applicable in the field for quick diagnosis	[1]
c. Nucleic acid detection	RT-PCR	N gene	Standard laboratory test	[39]
	One-step nested-RT-PCR	N gene	100-fold sensitivity than RT-PCR and nested PCR	[56]
	Double step real time-RT-PCR	N gene	Highly sensitive and specific Quantitate viral load in clinical samples	[34]
	One-step real-time RT-PCR	--	To study viral replication and kinetics of viral RNA load in infection	[105]
	RT-LAMP assay	H gene	100-times sensitive than RT-PCR	[66]
2. Virus-specific antibody detection	ELISA	IgG/Antibody	Only 1 hour reaction Detect within 6 days of infection Sensitive as SNT	[11]
	Dot blot assay	N-protein specific IgM	Detecting recent infections	[10, 17]
	Capture sandwich ELISA	N-protein specific IgG & IgM Antibody	No Cross-reactivity with other Morbilliviruses	[131, 60, 61]

*Diagnostic sensitivity (Dsn), Diagnostic specificity (Dsp)

NA –Information not available

virus isolation due to its high sensitivity of virus to light and temperature [4]. CDV isolation often requires supplementation with canine or ferret pulmonary macrophages [7], co-cultivation with mitogen-stimulated lymphocytes derived from healthy dogs' and ferret's blood. Stable expression of canine SLAM receptors (CD150) on Vero cells results in enhanced isolation of field isolates of CDV, especially from dogs [112]. A virulent CDV was first isolated and adapted in dog kidney cells by Rockborn [103]. MDCK (Madin-Darby canine kidney), MV1 Lu (Mink lung epithelial cells), and Vero cells are commonly used for the primary isolation of CDV, but with a low success rate [67]. B95a, a marmoset lymphoblastoid cell line is efficient in CDV isolation similar to other morbilliviruses—RPV and PPRV [53, 61, 125].

After several blind passages, the virus adapts to the cell line and shows the visible changes appreciated under the light microscope. Cytopathic effect for CDV is similar to other morbilliviruses, especially measles virus, characterized by degenerated cells, granular appearance, vacuolization, and multi-nucleated giant cells (syncytia) [67]. The onset of CPE usually varies with strain of the virus, type of cell line used, incubation, and media condition for cells. The vaccine and wild-type strains can be differentiated by the type of CPE, as the level of attenuation of the strain is directly proportional to the fusion efficiency of H protein [139]. The CPE of attenuated strains is differentiated by the size of syncytia i.e. large patches of fused cells visible under the light microscope.

Nucleic acid detection

The antigen and nucleic acid detection do not require the live virus in the samples, as required in virus isolation. Molecular assays present the advantage of sensitive and specific detection in both the antemortem and post-mortem samples. RT-PCR is the widely used molecular diagnostic test and detects CDV in whole blood, serum, and cerebrospinal fluid [40]. Nested PCR combined with conventional RT-PCR gives comparatively high specificity [60]. Also, nested-PCR is more sensitive than RT-PCR and Immunofluorescence

assay for CDV diagnosis of clinical samples like urine, blood, and saliva [51, 116]. RT-qPCR using the TaqMan probe based on CDV-N and P genes is highly sensitive and specific over other tests [35, 109]. For rapid identification, the sequencing of the whole genome by nanopore technology is used [92].

Many commonly used molecular tests are modified to differentiate wild-type and vaccine strains based on the variations in their genomic sequences (Table 4). For example, firstly the conserved sequences are targeted to amplify the both, followed by primer specific to either wild-type or vaccine strains. Also, the RFLP results in different number of fragments in both the strains. These significant variations might be responsible for the outbreaks in vaccinated populations as well.

Monoclonal antibodies in CD diagnosis

Orvell et al. first developed the mAbs against N, F, H, and P protein of CDV [89]. The mAbs hold the potential to be used in immunodiagnosics as well as immunotherapy of CDV [14, 15, 48]. Recently, two different studies show the role of mAbs in identifying the linear B-cell epitopes on P and H protein [68, 115]. Sandwich ELISA based on monoclonal antibodies (mAb) against H protein can detect the CDV in conjunctiva, nasal swab, and lungs [96]. mAb-based sandwich dot ELISA is rapid in detecting the CDV for epidemiological surveillance [69]. A sandwich ELISA using two mAbs against different epitopes of F protein was also developed to detect CDV in serum and fecal samples [155]. Monoclonal antibodies provide high specificity to the diagnostic assays [1, 96]. MABs developed against H and N proteins of PPRV has been proved to be irreplaceable components of c-ELISA and s-ELISA, respectively [120, 121]. These diagnostic assays have contributed significantly to the PPRV diagnosis and its control program in India. The learnings from research in PPRV, the sibling member of CDV, can guide future research of CDV diagnostics and vaccines in many ways.

Table 4 Molecular tests developed to differentiate wild-type and vaccine CDV strains

Test	Target	References
Multiplexed RT-nested PCR	H gene	[117]
RT-PCR	H gene	[151]
RT-qPCR	M protein and M-F intergenic region	[145]
duplex RT-PCR	N gene	[31]
RT-PCR–RFLP	N gene BamHI restriction enzyme (RE) digestion	[140]
	N gene MspI RE digestion	[37]
RT-LAMP	H gene	[71]

CDV—antibody detection

Dogs show lifelong protection from the disease through induction of high titre neutralizing antibodies (1:100) after infection, which usually achieves a peak in 2–3 weeks [6]. Most of the studies have reported that antibody titre of 1:32 is indicative of borderline protective titre against CDV infection [9], while some found it to be in the range of 1:80 to 1:160 [129]. An increase in IgG titer greater than fourfold within 14 days indicates infection in even recently vaccinated animals [55]. Although the virus neutralization test (VNT) is the gold standard and OIE accepted test, it is time-taking and requires conventional virology skills to perform the test and the handling of live viruses. This makes it less preferable over other immunological assays like ELISA, IFT, etc. ELISA is widely used to detect IgM and IgG antibodies till three months of infection in both dogs and non-dog hosts [43] as well as gives consistent specificity and sensitivity as serum neutralization test (SNT) [84]. The plaque reduction neutralization test is also used to evaluate the pre and post-vaccination status of the animal [90]. Immunoperoxidase plaque staining for CDV detection is another specific and sensitive technique for serological study [123].

There are cross-reactive epitopes among CDV, MV, PPRV, and RPV and should be considered while testing serological samples [114]. M protein shares the highest number of cross-reactive epitopes among CDV and MV [88]. F protein also shares the homology in the cleavage site (six amino acids) for furin protease and is replaceable between CDV and MV [134, 138]. F protein shares the high heterotypic cross-reactive epitopes among all structural proteins of the genus, showing the evolutionary relationship [116]. Therefore, the recombinant F protein-based vaccines provide heterotypic but incomplete protection. Recent antigenic profiling of morbilliviruses (CDV, PPRV & MV) from our laboratory using a panel of in-house developed six mAbs has indicated that PPRV possesses a more close antigenic relationship to CDV as compared to MV (unpublished information).

Point of care diagnostic tests for CDV

Field diagnostic tests are the need of the hour to detect the infection on-site and control the spread of disease. RT-loop-mediated isothermal amplification (RT-LAMP) has been developed with high sensitivity (100%), specificity (93.3%), and 100 fold lower detection limits as compared to conventional RT-PCR [24, 148]. RT-recombinase polymerase assay (RT-RPA) having a portable, user-friendly tube scanner has been developed [142]. A Microfluidic paper-based test device has also been developed using nanoparticle-coated polyclonal antibodies raised in rabbits. The test also presents a potential for field diagnostic tests as suggested by studying

clinical data [77]. An incubation-free LFA-RT-RPA assay is also developed for CDV detection using a gold particle-conjugated anti-FAM antibody but presents the limitation of nucleic acid extraction requirement [143]. One-tube reverse transcription-insulated isothermal polymerase chain reaction has also been developed as another point-of-care diagnostic which presents comparable results with real time RT-PCR [146].

Point-of-care diagnostic test should be simple enough to be easily performed by a layman with mere instructions; hence the lateral flow assay (LFA) holds the advantage over all other tests. Also, the problem of sample collection in wildlife and the transport-related damage raises the need for specific, easy, and on-site diagnostic assays like LFA to diagnose the disease at an early stage. CDV-LFA was developed in the sandwich assay format using two monoclonal antibodies (mAbs) of IgG1 isotype against two different epitopes of F protein viz. 9D3 as a bio label and 7B2 in the ‘test’ line, resulting in sensitive and specific detection [1]. Different commercial LFA kits are also available from different countries like Rapigen Inc. CDV Antigen test, LilifTM CDV Rapid Antigen kit, etc. Recently, a mAb based LFA is developed in our laboratory for CDV antigen detection in sandwich mode (unpublished) and antibody detection in competitive mode [56].

Differential diagnosis

The clinical signs of CD are similar to other viral diseases caused by Canine parvovirus (CPV), Canine coronavirus (CCoV), canine adenovirus (CAV), Rabies virus, influenza virus, and some bacterial and parasitic diseases [59]. According to a study conducted in selected areas of Madhya Pradesh (India) CDV, CPV and CAV are more prevalent than Rabies but are comparatively less in focus due to unnoticeable signs in dogs and zoonotic unimportance [23, 100]. Feral dogs harbor the CDV, CPV, and CAV very often [47, 82]. Even in serological surveys, other wild carnivores have reported the presence of antibodies against CDV and CPV altogether [132]. Therefore, there is also a need for diagnostic tests for differential detection of the virus and virus-specific antibodies. Important to today’s scenario, one-step duplex PCR was also developed for identification and differential diagnosis between CDV and Canine Coronavirus (CCoV) targeting the CDV-H gene and CCoV-M gene [141]. Similarly, a one-step triplex PCR detecting CDV, CPV, and Canine Kobu virus was developed, for differential diagnosis as well as surveillance [70].

Conclusion

CD is an endemic disease of dogs and was under control until some time ago due to the availability of effective vaccines. The strains Onderstepoort, Convac, Synder Hill, Rockborn, were isolated and came in use around 1960s. In the past few decades, a large number of new cases are constantly reported in the vaccinated population of dogs and a large number of wildlife species, which has raised the concern towards disease control and wildlife protection. Some constant mutations have been found in H protein like Y549H which are responsible for the host range expansion of the virus. The difference in circulating strains and the emergence of new lineages confirms the continuous mutations in virus isolates. Yet more studies on recombination and evolution of CDV are required.

Control of CDV needs specific diagnostics, vaccines improvement to make it effective in dog population as well as wildlife, and proper serological surveillance to prevent unexpected outbreaks. Therefore, there is a need for novel targets, for both the modified diagnostics as well as vaccines to counteract the effect of circulating virus. Our laboratory isolated “CDV (Dog)/Bly/Ind/2018”, which represents the currently circulating CDV strains of India [13]. This strain of the virus has been extensively characterized and has been proposed as an attenuated vaccine candidate (Indian Patent application number 202011057169, dated 30/12/2020). A panel of monoclonal antibodies to this strain has been developed and characterized (unpublished information). Conventional virology techniques like virus isolation and virus neutralization test are still in use for laboratory diagnostics because of their high specificity. Molecular assays like RT-PCR, RT-qPCR, and LAMP are used when the rapid diagnosis is required. For the serological study, ELISA based on IgM and IgG antibodies are commonly used to detect recent infection and later phases of the disease, respectively. Point-of-care diagnostics are easy to perform and give a quick accurate diagnosis, hold an important place in disease diagnosis and management plan.

Widely used conventional cell culture adapted vaccines sometimes do not provide complete protection and presents residual virulence/retained pathogenicity, especially in cross-species vaccination in wildlife. To overcome the disadvantages presented by attenuated vaccines, recombinant, and other new-generation vaccines can be developed [22]. Looking at the wide host range and poor accessibility to the affected wildlife species, a focus on the development of an oral vaccine against canine morbillivirus may provide some solution. Control of disease needs to be planned at the root level i.e. control in feral dogs and strictly defined boundaries of protected areas to block the dog-wildlife interface and prevent spillover of disease to wildlife. Apart from dogs, ferrets, minks, and raccoons also serve as a reservoir

of CDV and are responsible for transmission and co-circulation of different lineages of overlapping geographical regions between dogs and wildlife [3, 148]. Therefore, vaccination of these species is another important component for the control of CDV [50, 147]. Keeping in mind the role of dogs in virus transmission to wildlife, immediate mitigation strategies, and their execution is the need of the hour [27]. The broad host range of CD makes it difficult to eradicate, but with strategic research and applicability at the field level, the increasing cases and outbreaks can be controlled.

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Declarations

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