Duck virus enteritis (duck plague) – a comprehensive update

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Abstract
Duck virus enteritis (DVE), also called duck plague, is one of the major contagious and fatal diseases of ducks, geese and swan. It is caused by duck enteritis virus (DEV)/Anatid herpesvirus-1 of the genus Mardivirus, family Herpesviridae, and subfamily Alpha-herpesvirinae. Of note, DVE has worldwide distribution, wherein migratory waterfowl plays a crucial role in its transmission within and between continents. Furthermore, horizontal and/or vertical transmission plays a significant role in disease spread through oral-fecal discharges. Either of sexes from varying age groups of ducks is vulnerable to DVE. The disease is characterized by sudden death, vascular damage and subsequent internal hemorrhage, lesions in lymphoid organs, digestive mucosal eruptions, severe diarrhea and degenerative lesions in parenchymatous organs. Huge economic losses are connected with acute nature of the disease, increased morbidity and mortality (5%–100%), condemnations of carcasses, decreased egg production and hatchability. Although clinical manifestations and histopathology can provide preliminary diagnosis, the confirmatory diagnosis involves virus isolation and detection using serological and molecular tests. For prophylaxis, both live-attenuated and killed vaccines are being used in broiler and breeder ducks above 2 weeks of age. Since DEV is capable of becoming latent as well as shed intermittently, recombinant subunit and DNA vaccines either alone or in combination (polyvalent) are being targeted for its benign prevention. This review describes DEV, epidemiology, transmission, the disease (DVE), pathogenesis, and advances in diagnosis, vaccination and antiviral agents/therapies along with appropriate prevention and control strategies.

1. Introduction

Duck virus enteritis (DVE) is also known as duck plague (DP), Entenpest (German), eendenpest (Dutch) and peste du canard (French) (Jansen 1961; USDA 1967; Wobeser 1987; Davison et al. 1993). Although the term DP was first coined by Bos (1942), officially it was proposed and used by Jansen and Kunst (1949). The disease is caused by Anatida herpesvirus type 1, a member of the Herpesviridae family and subfamily Alpha-herpesvirinae (Fadly et al. 2008; Li et al. 2009; King et al. 2011). With an acute but sometimes chronic and highly contagious nature, DVE causes considerable mortality among domestic and wild ducks, swans, geese and other waterfowl of different ages. The disease is known to have global distribution, wherein migratory waterfowl plays a crucial role in disease transmission within and between continents. However, mortality and severity of the disease varies between epizootics and species involved or affected (Keymer & Gough 1986; Kaleta et al. 2007). Extensive epizootics have been reported in duck farms in the United States of America. However, the majority of investigations have failed to isolate the virus (Brand & Docherty 1984). Besides Anseriformes, outbreaks have never been seen in other avian species, mammals & humans (Baudet 1923; Bos 1942; Jansen 1964; Sandhu & Shawky 2003; Sandhu & Metwally 2008).

Most of the affected birds die without ample clinical manifestations and even sometimes the carcasses are found floating on the water surface (Montali et al. 1976). However, when clinical symptoms are evident, high mortalities especially in older ducks, vascular damage and subsequent internal hemorrhages (Proctor 1975), lesions in lymphoid organs, digestive mucosal eruptions, severe diarrhea and degenerative lesions in parenchymatous organs (Montali et al. 1976; Davison et al. 1993) following fatal outcomes (Jansen 1961; Wobeser 1987; Davison et al. 1993; Shawky et al. 2000; Campagnolo et al. 2001; Sandhu & Shawky 2003) are noticed. Partially closed eyelids with photophobia, extreme thirst, loss of appetite, ataxia, nasal discharge,
drooping plumage, watery diarrhea, soiled vents and tremors of head, neck and body (Davison et al. 1993) are other clinical symptoms witnessed.

Domestic and wild ducks, geese and swans of all ages are considered susceptible, wherein the infection may, at times, exhibit chronicity or latency (Richter & Horzinek 1993; Sandhu & Shawky 2003). After establishing primary infection, duck enteritis virus (DEV) exhibits latent infection in trigeminal ganglia (TG). From this site, re-activation of the virus can occur that results in disease outburst (Shawky & Schat 2002). Hitherto reports confirmed that DEV survivors may become carriers for up to 4 years (Burgess et al. 1979). Mallard ducks, that are less susceptible to the lethal effects of DP, could be considered a natural reservoir of the infection. In domestic birds, DVE usually occurs in age group of 7 days and later (to mature breeders). Depending upon the virulence of infection and immunological status of birds, morbidity and mortality of birds range from 5 to 100% (Jansen 1961) persists in the flock with significant drop in egg production (Goldberg et al. 1990). Mortality usually starts at 1–5 days after the onset of clinical signs and is more evident in adult breeder ducks. However, death rarely occurs in chronically infected flocks. Recovered birds usually become carriers and excrete the virus in the feces over a period of several months (Horzinek 1993; Shawky & Schat 2002).

Though carrier birds are resistant or immune to the disease, virus shedding results in disease spread to susceptible waterfowls (Sandhu & Shawky 2003). The main causes, that can perpetuate an outbreak, are bird-to-bird contact and/ or contact of susceptible birds-to-contaminated environment (Burgess & Yuill 1983; Richter & Horzinek 1993; Shawky & Schat 2002). Scavenging and decomposition of infected carcasses may also contaminate and spread the virus in environment. Several reports indicate virus transmission through eggs of infected birds. However, its significance in the disease cycle remains unclear (Burgess & Yuill 1983; Sandhu & Shawky 2003).

Due to high mortality, condemnations, decreased egg production & hatchability, significant economic losses are associated with DVE across the globe. An excess of $1 million losses were reported in 1967 during the first outbreak in the United States of America’ duck industry of long island, New York (Jansen 1968; Leibovitz & Hwang 1968a, 1968b; Walker et al. 1969). The virulent strain of DEV can be adapted by several passages in duck embryo and chicken embryo fibroblast (CEF) cell culture (John et al. 1990; Mondal et al. 2010; Doley et al. 2013). Naturally apathogenic or attenuated DEV strains are being used as live vaccines that can offer sufficient protection for commercial ducks (Hess & Dardiri 1968; Jansen 1968; Speiker 1977; Lin et al. 1984; Liu et al. 2007; Li et al. 2009; Lian et al. 2010). Mostly the virus is propagated, adapted and passaged in homologous host/cell culture of avian (duck/chicken) origin for large scale vaccine production but recently DEV has been grown successfully over Vero cell lines (green monkey origin) as evident from cytopathic effects and identification of DNA and viral antigens by polymerase chain reaction (PCR) and indirect immunofluorescence (IF) techniques (Aravind, Kamble, Gaikwad, Shukla, Dey, and Mohan 2015). Current advances in the areas of diagnosis, vaccination and control have provided viable options to counter this economically important pathogen affecting ducks, geese and swans.

The present review describes in detail about DEV, its replication, host range, epidemiology, transmission, the disease it causes, pathology and pathogenesis, immunity, and advances in diagnosis, vaccination and antiviral agents/therapies as well as appropriate prevention and control strategies to be adapted.

2. History

Originally, Baudet (1923) reported the first outbreak of an acute hemorrhagic disease in domestic ducks in the Netherlands. The Koch’s postulate was proven by introducing sterile filtered liver suspensions in domestic ducks. The disease was not reproduced in chickens and thus, it was concluded that disease was due to a specific duck-adapted strain of fowl plague virus. Subsequently, DeZeeuw (1930) confirmed Baudet’s findings and hypothesized the presence of a duck-adapted strain of fowl plague as a possible cause of the DVE. Much like Baudet (1923), he reported that chickens, pigeons and rabbits are resistant to experimental infection and suspected wild waterfowl, found within outbreak areas, to be the carriers.

After examining the characteristic lesions and experimental infections unable to cause disease in pigeons, chickens, guinea pigs, rabbits, rats and mice, Bos (1942) concluded that fowl plague virus is a novel distinct viral disease of ducks. Later, first report of DVE in domestic and free-flying Anseriforms leading to serious outbreaks in migratory waterfowl with high mortality occurred on the American continent (Friend & Pearson 1973). Outbreaks in zoos and game-farm flocks have also been reported (Jacobsen et al. 1976; Montali et al. 1976). Massive outbreaks reported from New York (1967) and South Dakota (1973) suggested that the DVE could be enzootic in the region, exploiting the major fly-ways. Similarly, in many duck-producing regions of the world such as Indiana, California, Pennsylvania, Texas and Minnesota in the United States of America, Canada, England, Hungary, Denmark, Austria, the Netherlands, France, Belgium, China, Vietnam, India and Thailand, the disease has been a cause of significant economic losses to the poultry sector primarily due to high mortality, carcass
condemnations and reduced egg production (Baudet 1923; Levine & Fabricant 1950; Leibovitz & Hwang 1968a, 1968b; Gough & Alexander 1990; Campagnolo et al. 2001; Converse & Kidd 2001).

3. Etiology

The etiological agent of DVE is DEV or Anatid herpesvirus-1. As per the recent taxonomic classification by the International Committee on Taxonomy of Viruses (ICTV), DEV has been classified into the genus *Mardivirus*, subfamily *Alpha-herpesvirinae* of the family *Herpesviridae* (Fadly et al. 2008; Li et al. 2009; King et al. 2011). The virus has non-hemagglutinating and non-hemadsorbing properties (Jansen 1961; Dardiri & Hess 1968). Having a diameter of about 120-130 nm, with globular shape, the enveloped *Herpesevirus* has four structural components that includes a bilayer-lipid envelope, an amorphous tegument, an icosahedral capsid and a linear double-stranded DNA with G+C content of 64.3% or G+C content of 44.9% (Figure 1) (Gardner et al. 1993; Yuan et al. 2005). The genomes may vary in base composition, sequence arrangements and size. A significant difference may also be seen in arrangement of inverted and directly repeated sequences (Hayward et al. 1975; Wadsworth et al. 1976). Partial or complete genomic sequences of DEVs are rapidly accumulating and its analyses demonstrated that, although similar to other herpes viruses, the DEV genome also varies (Li et al. 2009; Wang et al. 2011; Liu, Han, et al. 2011; Liu, Chen, et al. 2011; Wu et al. 2012a; Wu et al. 2012b; Yang et al. 2013). The Chinese DEV is a wild type virulent strain of DEV (Gao et al. 2015). The genome of the DEV is approximately 158 kb that contains 78 open reading frames (ORFs) predicted to encode potential proteins. Out of 78 ORFs, the majority of the ORFs (65) are located in the unique-long (UL) region while other 11 ORFs in the unique-short (US) region, respectively. The leftover two ORFs (ICP4/IE180) localize in the internal repeat sequence (IRS) and terminal repeat sequence (TRS) regions. Genome also contains an US, an UL, an US internal-repeat (IR) and an US terminal-repeat (TR) region (Chen et al. 2013). Being enveloped, the virus is sensitive to ether and chloroform. While using heat during inactivation experiments, 10 minutes at 56 °C or 90–120 minutes at 50 °C, the infectivity has been nullified (Sandhu & Shawky 2003). At room temperature (22 °C), infectivity lasts up to 30 days. Drying over calcium chloride at 22 °C resulted in inactivation of the virus after 9 days. The DEV rapidly gets inactivated beyond pH 3–11. The infectivity has been found to be destroyed by treating the virus for 18 hours at 37 °C to trypsin, chymotrypsin and pancreatic lipase (Hess & Dardiri 1968).

![Figure 1. Structure and replication of Anatid herpesvirus-1.](image-url)
Recently, the bioinformatics data based codon usage bias analysis between the newly identified DEV gD gene (GenBank accession no. KC915041) and the gD like gene of 23 other reference herpesviruses revealed that codon of gD gene of DEV had strong bias towards the synonymous codons with A and T at the third position; existence of a high level of diversity in codon usage; and the G + C content constrained the genetic heterogeneity in gD gene. The study pointed out yeast expression system to be more appropriate for the expression of DEV genes. These findings may help towards understanding the evolution and pathogenesis of this virus in a better way, offer a basis for knowing the associated mechanism for biased usage of synonymous codons, identifying suitable heterologous expression system for improving target gene expression, and pave way for development of newer vaccines and diagnostics (Aravind et al. 2014).

4. Virus replication

DEV replicates primarily in the mucosa of the digestive tract, and then spreads to the bursa of Fabricius, thymus, spleen, and liver. The lining epithelial cells and lymphocytes of these organs are the principal sites for replication of DEV (Xuefeng et al. 2008). Since DEV can replicate quickly in many cell types and tissues, it is considered as a pantropic virus that leads to pathological lesions in many different organs (Li, Hong, et al. 2016). Herpes virus attaches to host-cell receptors by virion glycoprotein spikes (Boehmer & Nimonkar 2003). Several glycoproteins such as gB, gC, gD, gH and gL are involved when DEV enters inside the host cells (Johnson et al. 1990; Spear et al. 2000). After binding, the envelope fuses with the plasma membrane of the host cell and the nucleocapsid enters into the cytoplasm of the host cell. DNA and protein complex is separated from the nucleocapsid and enters into the nucleus. It then rapidly shuts off the host cell macromolecule synthesis (Kwong & Frenkel 1987; Everly et al. 2002). During infection, the genes in US, UL, IR and TR of DEV genome are sequentially expressed in three phases, viz. immediate early (IE), early and late phases. The IE gene is transcribed immediately after infection, prior to replication of viral DNA in an IE protein-dependent manner, and transcription of the late gene begins after the synthesis of DNA and onset of other viral proteins synthesis (Liu et al. 2015). Two putative origins of replication have been reported in the DEV genome, and both such origins are located in the IRS and TRS upstream of US1. The positions of origin are similar to the OriS of pseudorabies virus (PRV), and the replication origins of DEV genome share major sequence features, namely two inverted copies of the UL9 (OBP) binding sequence (GTTCGCAC) separated by a 43-bp AT-rich spacer sequence (76.7% A + T), with PRV (Klupp et al. 1992; Fuchs et al. 2000).

Replication of the viral DNA occurs in the nucleus and newly synthesized DNA is coiled into pre-formed immature capsids (He et al. 2012). Maturation of virion DNA occurs by encapsidation of nucleocapsids and the inner layer of the nuclear-envelope. Subsequently, complete envelopment of virion occurs by budding through the nuclear membrane. After maturation, the virions accumulate within vacuoles of the cytoplasm of host cell and are released by cytolysis or exocytosis (Figure 1) (Everett 2000; Flemington 2001). Plasma membrane of host cell contains virus-specific proteins which are responsible for cell fusion, act as Fc receptors, and are supposed to be targets for immune cytolysis. Intra-nuclear inclusion bodies are hallmark feature of herpes virus infections, both in in vivo and in cell cultures (Nii & Kamahora 1962; Fowler et al. 1989; Davison et al. 1993; Campagnolo et al. 2001). Barr et al. (1992) reported intra-nuclear viral inclusion bodies of DVE in various tissues as well as intra-cytoplasmic inclusion bodies in esophageal and cloacal epithelium. Using electron microscopy, they also demonstrated membrane-bound intra-cytoplasmic inclusions which contained enveloped herpes virus and nuclei containing herpes viral nucleocapsids. Replication and growth curves of DEV were studied in cell cultures by electron microscope (Breese & Dardiri 1968; Bergmann & Kinder 1982; Tantaswasdi et al. 1988; He et al. 2012). The virus replicates mainly in the mucosal epithelial cells of the gastrointestinal tract, especially in the epithelial cells of the esophagus, and then disseminates into the thymus, bursa of Fabricius, spleen and liver in a susceptible host (Islam & Khan 1995; Shakwy & Schat 2002). In these organs, epithelial cells, lymphocytes and macrophages are the chief sites of viral replication (Shawky 2000; Yuan et al. 2005). Replication of virus occurs within the nucleus 12 hours post inoculation. By 24 hours post inoculation, viral forms and envelope were noticed within the cytoplasm. With maximum titer at 48 hours, cell culture titrations showed new cell-associated viremia 4 hours post inoculation. By 6–8 hours post inoculation, extracellular virus was first detected and reached maximum titer at 60 hours (Breese & Dardiri 1968). Increased incubation temperatures such as 39.5 °C–41.5 °C in tissue cultures favored the replication of viruses, especially of less virulent strains (Burgess & Yuill 1981a). Viral glycoprotein C (gC) plays an active role in the adsorption of DEV over CEF to enhance the infectivity and hence blocking the gC can be a critical strategy in preventing the viral establishment in the host cells (Hu et al. 2013).

5. Host range

Although virus can be adapted by serial passage to grow in embryonating chicken eggs and ducklings up to 2 weeks of age (Jansen 1964; Jansen 1968; Mondal et al. 2010), members of the family Anatidae such as
ducks, geese, and swans exhibit natural susceptibility to DVE. From 7 days of age to adulthood, natural outbreaks have been reported to inflict huge casualties in a variety of domestic ducks (Anas platyrhynchos), including White Pekin, Khaki Campbell, Indian Runner, hybrids and native ducks of mixed breeding, Muscovy ducks (Cairina moschata) (Jansen 1961; Newcomb 1968; Leibovitz & Hwang 1968a, 1968b; Campagnolo et al. 2001; Converse & Kidd 2001; Akter et al. 2004; Konch et al. 2009; Woźniakowski & Samorek-Salamonowicz 2014), domestic geese (Anser anser) (Jansen & Wemmenhove 1965; Kisary & Zsak 1983) and mute swans (Keymer & Gough 1986). Gray-call ducks, herring gulls (Larus argentatus) and black-headed gulls (Chroicocephalus ridibundus) have been found resistant to infection (Van Dorssen & Kunst 1955). Added to domesticated species, gadwall (Anas strepera), garganey teal (Anas querquedula), European wigeon (Anas penelope), shovellers (Spatula clypeata), wood ducks (Aix sponsa), common pochards (Aythya ferina), common eiders (Somateria mollissima), white-fronted geese (Anser albirostris), mute swans (Cygnus olor), and bean geese (Anser fabalis) have been found susceptible to fatal infection. Mallards (A. platyrhynchos) are more resistant to lethal effects and are considered a possible natural reservoir of infection (Figure 2) (Dardiri & Gaillunas 1969; Burgess & Yuill 1983; Wobeser & Docherty 1987; Goldberg et al. 1990). Contrary to blue-winged teal (Anas discors) and Canada goose (Branta canadensis) that are susceptible to experimental infection with high mortalities (Wobeser & Docherty 1987), European teal (Anas crecca) and pintails (Anas acuta) are resistant to experimental infections with effective immune response only (Van Dorssen & Kunst 1955). An outbreak has been reported in non-Anseriformes waterfowl such as common coots (Fulica atra) and crested coots (Fulica cristata) (Salguero et al. 2002). Although the virus has not been isolated or identified, histopathological findings such as enteritis, multi-focal necrotic hepatitis with intra-nuclear inclusion bodies and ultra-structural findings such as viral particles and viral replication sites which are characteristic of herpes virus infection are useful in confirming the DVE infection (Salguero et al. 2002). Outbreaks in domestic ducks occur especially in regions where there is a close association with aquatic environments co-habited by wild waterfowl (DeZeeuw 1930; Leibovitz & Hwang 1968a, 1968b; Richter & Horzinek 1993; Converse & Kidd 2001; Sandhu & Shawky 2003; Woźniakowski & Samorek-Salamonowicz 2014). Studies evidenced through loop-mediated isothermal amplification (LAMP) technique demonstrated that free range water birds such as wild ducks (A. platyrhynchos), mute swans (C. olor), graylag geese (A. anser), tundra bean goose (A. fabalis) and grey herons (Ardea cinerea) have high prevalence of DEV and could act as probable carriers of DEV in the nearby water bodies (Woźniakowski & Samorek-Salamonowicz 2014).

Figure 2. Female European wigeon (left top; A. penelope) and two males and a female Mallard (right below; A. platyrhynchos) on ice in the Netherlands. Originally, Baudet (1923) reported the first outbreak of DP in domestic ducks in the Netherlands. European wigeon has been found susceptible to fatal infection, whereas Mallards are more resistant to lethal effects and are considered a possible natural reservoir of infection of DP (or eendepest in Dutch) (photograph by J.H. van der Kolk).
6. Epidemiology and disease distribution

DEV infection can affect ducks as early as at one week age up to adult age. Higher flock density is usually the main contributing factor for initiation of DP outbreaks. The Netherlands experienced several outbreaks of DP between 1920s and 1940s (Baudet 1923; Bos 1942). Later, the first major outbreak occurred in the United States of America in 1967 with huge losses to the duck industry of Long Island, New York (Jansen 1968; Leibovitz 1968; Leibovitz & Hwang 1968a, 1968b). Another major outbreak occurred at South Dakota in 1973 that resulted in loss of 43,000 ducks and geese. Epidemiological investigations suggested the correlation of the incidence of DP in wild birds and farmed poultry as samples from wild birds and poultry were found positive/carryer through various virological and serological investigations (Ziedler & Hlinak 1992). Subsequently, between 1970 and 1995, more than 100 outbreaks have been reported from places such as Maryland, New York, California and Pennsylvania (Hwang et al. 1975; Brand & Docherty 1984; Davison et al. 1993; Converse & Kidd 2001; Sandhu & Shawk 2003). In addition to outbreaks in the Netherlands and USA, DVE has been reported in China (Jansen & Kunst 1964; Wu et al. 2012a), France (Gaudry et al. 1970; Gough et al. 1987), Belgium (Devos et al. 1964), India (Mukerji et al. 1963a; Duraiswami et al. 1979; Rajan et al. 1980), Egypt (El-Samadony et al. 2013) England (Hall & Simmons 1972; Gough & Alexander 1990), Canada (Hanson & Willis 1976), Germany (Kaleta et al. 2007), Denmark (Pripp et al. 1983), Poland (Wozniakowski & Samorek-Salamonowicz 2014), Vietnam (Pritchard et al. 1999) and Bangladesh (Hoque et al. 2011; OIE 2012; Ahamed et al. 2015). An epidemiological study conducted in Chakhiit town of the Noakhali District of Bangladesh during January 2005–June 2006 highlighted that mortality in household ducks occurred mostly due to diseases like DP and duck cholera, and unvaccinated birds remained at higher risk. Hence, strengthening of the disease surveillance and monitoring systems and knowing the immunization status of ducks in risk prone areas could play an important role in reducing the DP incidences (Hoque et al. 2011). Recently, an outbreak of DP was confirmed in Jin-ding variety of layer ducks and in Cherry Valley variety of meat purpose breeding ducks of 7–49 weeks of age group in northwestern region of Shandong province of China based on the specific clinical signs observed including of high morbidity and mortality with reduced production performances, necropsy and histopathological findings, virus isolation and identification studies. The outbreak was controlled by adopting emergency measures such as modified immunization protocol along with slaughtering of the infected flocks and discarding the carcass, manure and litter appropriately and follow ups of accurate implementation of disinfection practices of duck pens, feeders and watering pails (Wang et al. 2013).

6.1. Indian scenario

In India, duck farming is very common in northeastern regions, especially in Assam where villagers rear them as backyard farming. However, DVE leads to considerable economic losses and significantly affects the socio-economic status of the small, marginal and landless farmers (Mukeri et al. 1963a; Bulbule 1982; Mondal et al. 2010). In India, the disease outbreaks have been reported from Kerala (Rajan et al. 1980; Kulkarni et al. 1995), Tamil Nadu (Duraiswami et al. 1979; Chellapandian et al. 2005), West Bengal (Mukerji et al. 1963a, 1963b, 1965; Bhowmik & Ray 1987), Uttar Pradesh (Mukit 1985), Karnataka (Bulbule 1982) and Assam (Boruah 1981; Sarma et al. 1991; Sharma 1992; Sarmah et al. 1997; Konch et al. 2009).

The DVE disease was first reported in West Bengal by Mukerji et al. (1963a, 1965) and high incidences (40.0%) of DVE have been reported since then (Bhowmik & Ray 1987). In November 1976, this disease was reported in Tamil Nadu with high mortality (up to 100%) among Indian Runner ducks (Duraiswami et al. 1979) and later in Tirunelveli district of Tamil Nadu (Chellapandian et al. 2005). At the same time, Rajan et al. (1980) reported an outbreak of DVE in Kerala state in 1976, wherein disease spread was noticed in all parts of Kerala within a short span of 3–4 months. Of note, necrosis of heart muscle and gizzard was a consistent lesion seen in affected ducks that has not been described before. From outbreaks originating from Kerala, Kulkarni et al. (1995) isolated the DP virus using duck and chicken embryos. Chakraborty et al. (1980) reported the first outbreak of DVE, affecting both ducklings and adult ducks of both sexes, in Assam in 1978 with high morbidity (100% in ducklings and between 88-90% in adult birds) and mortality (49% in adult birds).

To date, research has been in-process to understand both the virus epidemiology and pathology together with appropriate diagnostics and vaccine development. Mukit et al. (1987) studied the effect of DEV on peripheral blood lymphocytes of ducks. Konch et al. (2009) reported the incidence (21.7%) and pathology of naturally occurring DP in Assam. DP outbreaks in Assam were confirmed by John (1988) and John et al. (1990) by virus neutralization (VN), haemagglutination test, agar-gel precipitation test, fluorescent antibody test (FAT), counter-immunoelectrophoresis and histopathology. DEV was adapted by John et al. (1990) and Doyley et al. (2013) by giving 12 serial passages in embryonated duck eggs as well as CEF. Mondal et al. (2010) propagated a chicken embryo-adapted DEV vaccine strain. Sarmah et al. (1997) studied the physico-chemical characterization of a virulent strain of DP virus isolate from Guwahati, Assam. John et al. (1989) developed the counter immunoelectrophoresis (CIE)
for rapid detection of DEV antibodies and antigens. Mallanna et al. (2006) revealed inhibition of DEV using small interfering RNAs (siRNA) in cell culture system. Using three field strains of DP virus, Bordoloi et al. (1994) and Kumar and Punnoose (2000) developed the conventional CEF adapted DP vaccine that was effective to the extent of 86.6%. More recently, studies regarding development of a recombinant UL30 antigen-based single serum dilution ELISA (enzyme linked immuno sorbent assay) test for DEV detection (Aravind 2014), adaptation and growth kinetics of an Indian isolate of virulent DEV in Vero cells (Aravind, Kamble, Gaikwad, Shukla, Dey, & Mohan 2015) and recombinant glycoprotein D based prime boost approach against DEV in mice model (Aravind, Kamble, Gaikwad, Shukla, Saravanan, et al. 2015) have been reported.

7. Transmission

The susceptible population may get exposed both by direct contact to infected bird as well as indirectly from virus contaminated environment (Figure 3) (Sandhu & Shawky 2003). As the waterfowl is dependent on an aquatic environment, transmission through water seems to be a prime source. Most of the outbreaks in domestic ducks have occurred in the proximity of open water bodies which are often shared by free-flying waterfowl (Richter & Horzinek 1993; Sandhu & Shawky 2003). Oral, intranasal and/or parenteral administration of virus infected tissues can establish experimental infection in susceptible ducks. The convalescent birds may get immune or resistant to re-infection. However, they may become carriers and shed DEV into the environment for a prolonged period (Burgess & Yuill, 1983; Richter & Horzinek 1993; Shawky & Schat 2002). The role of migratory waterfowls as carriers of DEV has been reported during many outbreaks (Van Dorssen & Kunst 1955; Dardiri & Hess 1967; Friend & Pearson 1973; Brand & Docherty 1984; Woźniakowski & Samorek-Salamonowicz 2014). Horizontal spread is the principal mode of transmission (Sandhu & Shawky 2003). Attempts to isolate DEV from eggs laid during a natural outbreak have not been successful (Burgess & Yuill 1981a). Vertical transmission has been reported in persistently infected waterfowl (Burgess & Yuill 1981b; Burgess & Yuill 1983; Gough 2008).

The course and direction of DVE infection are dependent on population density as well as rate of transmission between infected and susceptible birds (Sandhu & Shawky 2003). Latency and re-activation of DEV have been responsible for precipitating outbreaks in domestic and migrating waterfowl populations.

Figure 3. Transmission and pathogenesis of DEV.
Lately, it has been revealed that trigeminal ganglion, lymphoid tissues and peripheral blood lymphocytes remains the main latency sites for the DEV (Shawky & Schat 2002). The US2 (US2) protein of DEV plays an active role in penetrating the susceptible host cell and subsequent spread of virus from one cell to another cell in the host and facilitates the establishment of DEV infection in susceptible birds (Wei et al. 2014). The expressed US2 protein is observed in infected cells through indirect immunofluorescent assay by using fluorescein isothiocyanate (FITC) and purified for assessing its role (Zhao et al. 2008; Xiang et al. 2010). The DEV gene responsible for US2 protein production also helps in exploring studies of genetic conservation of alpha-herpesviruses besides augmenting the DEV infection because other than in DEV, the US2 protein is also present in other alpha-herpes viruses, including herpes simplex virus-2, bovine herpesvirus-1, equine herpesvirus-1, canine herpesvirus, PRV and Marek's disease virus (Cantello et al. 1991; Haanes & Tomlinson 1998; Jiang et al. 1998; Belknap et al. 1999; Meindl & Osterrieder 1999; Ben-Arieh et al. 2001; Clase et al. 2003; Gao et al. 2015).

7.1. Role of season in DVE outbreaks

The DVE outbreaks, except in August and September, have been regularly reported throughout the year. Approximately 86% of these outbreaks have been reported from March to June. Hitherto reports have revealed spontaneous shedding of the virus from convalescent birds during the spring season. This pattern of disease outbreak might be due to the stresses resulting from the physiological changes in the duration of daylight and onset of breeding that trigger virus release during spring season (Pearson & Cassidy 1997; Converse & Kidd 2001; National Wildlife Health Center 2011).

8. The disease

8.1. Clinical signs

The incubation period of disease ranges from 3 to 7 days (Fenner et al. 1993). Clinical signs vary according to species, age, sex, immune status of the affected bird and the strain of DEV involved (Sandhu & Metwally 2008; OIE 2012). Severity in clinical symptoms is observed with the progression of infection in the flock. Beside sudden death, the common clinical signs include depression, loss of appetite, increased thirst, dehydration, weakness, ruffled feather, nasal discharge, ataxia, photophobia, tremor of head and neck, greenish and watery diarrhea, and soiled vent (Hanson & Wil lis 1976; Richter & Horzinek 1993; Campagnolo et al. 2001; Sandhu & Shawky 2003; Gough 2008; Sandhu & Metwally 2008). Haematochezia is a common feature. In some birds, opthalmic signs such as lacrimation, watery ocular discharge, photophobia and diptheroid plaques around the eyelids are observed. Due to ocular signs, some birds often refuse to drink which further exacerbate the dehydration and its sequel. Respiratory signs are often manifested as a hoarse chirp. However, it is non-specific followed by a drop in egg production and a ruffled, unkempt appearance. Death usually occurs within 5 days of onset of clinical symptoms with high mortality (60%–90%) and about 25%–40% drop in egg production (Sandhu & Shawky 2003; Carter et al. 2006). With the stress of egg production, adult breeders tend to experience high mortalities than young ones. Suddenly increased and persistent flock mortality is often observed in domestic breeders. Pro-lapse of the penis is another manifestation seen in male birds. The birds may show a characteristic posture with drooping outstretched wings, down head and tremors of head and body (Davison et al. 1993; Richter & Horzinek 1993; Sandhu & Shawky 2003; Carter et al. 2006). In case of ducklings of 2–7 weeks of age, symptoms like dehydration, loss of weight, conjunctivitis, lacrimation, nasal exudate, bluish discoloration of beak and blood-stained vent are noticed (Gough 2008; Sandhu & Metwally 2008).

8.2. Pathogenesis

Pathogenesis of acute DEV infection has been studied in detail (Jansen 1968; Proctor, 1975, 1976; Deng et al. 1984; Islam & Khan 1995; Hansen et al. 2000; Shawky 2000; Shawky & Schat 2002; Sandhu & Shawky 2003; Cheng et al. 2004, 2005; Yuan et al. 2005; Guiping et al. 2007). Cheng et al. (2004) demonstrated pathogenesis and immune mechanism of virulent and attenuated DEV, respectively. Xuefeng et al. (2008) studied the pathogenesis of DVE in experimentally infected ducks by oral route. The results indicated a close relationship between the amount of DEV in internal organs and disease progression. In duck plague virus (DPV) infected ducklings, antiviral immunity comprised of noticeable presence of pattern recognition receptors (PRRs) significantly appears along with observable typical pathological lesions and symptoms. Study based on real-time quantitative PCR and TaqMan™ fluorescent quantitative real-time PCR with specific primers and probes also confirmed hike in the protective innate immune response and is helpful in finding the break points during pathogenesis to lower the establishment of infection of DPV/DEV in ducks (Zou et al. 2010; Li, Hong, et al. 2016). Even though differences in virulence have been observed among DEV strains, antigenic nature remains identical for most of the isolates (Kisary & Zsak 1983; Akter et al. 2004). Upon its entry into a susceptible host, the virus multiplies in the mucosal epithelial cells of the gastrointestinal tract, the esophagus, and proceeds towards thymus, bursa of Fabricius, spleen.
and liver (Jansen 1968; Islam & Khan 1995; Shawky & Schat 2002; Sandhu & Shawky 2003). Protein kinase C inhibitor has been suggested as the receptor for nucleoprotein of DEV (Hang et al. 2012). The epithelial cells/macrophages in these organs are the major predilection sites of virus multiplication (Shawky 2000; Yuan et al. 2005). The virus induces apoptosis as well as necrosis in lymphoid tissues such as epithelial cells between the cortex and medulla of the follicles in the bursa of Fabricius, Hassall’s corpuscle of the thymus, germinal centers in B lymphocytes, periarteriolar lymphoid sheath in T lymphocytes, sinusoidal lining cells in the spleen resulting in the depletion of lymphocytes and subsequent immunosuppression. Before necrosis occurred, all these organs contained nucleocapsids of virus in the nuclei and virions in the cytoplasm of the host cells (Proctor 1976; Guiping et al. 2007). A study in Cherry Valley ducks infected with DEV revealed that the immune response mediated through Toll like receptors (TLRs) is more important than that mediated with the RIG-I like receptors. Different TLRs were expressed in different organs, the expression of TLR21 was higher in spleen and that of TLR2 was higher in brain which can be attributed due to the differences in PRR in various tissues. This study also reported that there was PRR recognition of the virus in the spleen. However, there was no elevation of pro-inflammatory cytokines in the spleen. Authors postulated that the virus has evolved ways to escape from the host immunity (Li, Hong, et al. 2016). In convalescent birds, the virus undergoes latent infection in trigeminal ganglion where it, upon re-activation, results in shedding into the environment (Shawky & Schat 2002). The possible reasons for such re-activation could be immunosuppression resulting from stress due to any reason in flocks. As a result of the immunosuppressive effect of the DEV, secondary bacterial infections such as Pasteurella multocida, Riemerella anatipestifer and Escherichia coli have often been seen in a natural outbreak caused by a low virulent strain in young ducklings (Shawky et al. 2000). Upon necropsy, Konch et al. (2009) reported few parasites such as Fimbriaria fasciolaris and Echinostoma revolutum from the small intestine of infected birds. Marius-Jestin et al. (1987) isolated a hyper-virulent strain of DEV and an avian type apathogenic paramyxovirus (PMV6) from the intestine and liver of 4 months old fattening mule ducks with rather high mortality (75%), hemorrhagic and necrotic gross lesions. An overview on pathogenesis of DEV is presented in Figure 3.

The DEV also has strong predilection for vascular endothelial cells. Virus replication in vascular endothelial cells of small blood vessels, venules and capillaries results in their destruction leading to severe hemorrhages, eruptions and progressive degenerative changes of parenchymatous organs (Richter & Horzinek 1993). In young birds, the virus primarily targets the lymphoid organs rather than other systems. While in adult birds, the pathologic effects are more pronounced in digestive tract and other internal organs. To know more regarding pathogenesis of DEV after infecting the duck embryonic fibroblast cells under in vitro conditions either after antiviral therapy, immunization or through biomarker response, a cDNA library has been framed with the use of switching mechanism at 5’ end of the RNA transcript technique for proteomic analysis of DEV infected duck embryonic fibroblast cells (Gao et al. 2014). Micro (mi) RNAs were found recently which could provide insights into the pathogenesis of DEV (Yao et al. 2012; Yao & Nair 2014).

8.3. Gross lesions

The gross lesions inflicted by DEV depend upon the species infected, age of the bird, and stage of infection in host, strain and inoculum of virus (Sandhu & Shawky 2003; Sandhu & Metwally 2008; OIE 2012). Commonly observed lesions are vascular damage, disseminated intravascular coagulopathy and necrotic changes, eruptions on the mucosal surface of the digestive tract and degenerative lesions in parenchymatous and lymphoid organs. Severe enteritis, hemorrhage in intestine, body cavities, heart, pericardium, liver and spleen, plaques in esophagus and intestine, lesions in thymus and bursa are highly suggestive of infection (Jansen 1961; Wobeser 1987; Davison et al. 1993; Richter & Horzinek 1993; Shawky et al. 2000; Campagnolo et al. 2001; Sandhu & Shawky 2003; Konch et al. 2009). Petechial or larger extravasations of blood could be seen on myocardium and epicardium giving a red ‘paint-brush’ appearance (Weingarten 1989; Richter & Horzinek 1993; Konch et al. 2009). This characteristic lesion is often observed in adult ducks rather than in ducklings. In parenchymatous organs like liver, the surface may have pale copper color with pin-point hemorrhages and white foci giving a speckled appearance that, in later stages of infection, changes to dark bronze color with bile stains. The white foci become considerably larger and appear more distinct. Surfaces of organs like pancreas, lungs, and kidney may also show petechial hemorrhages (Konch et al. 2009).

The lesions in the digestive tract are commonly seen in oral cavity, esophagus, ceca, rectum and cloacae. The oral lesions comprise of erosions and presence of diphtheritic sub-lingual membranes. Chronically infected waterfowl have oral erosions at the openings of sub-lingual salivary gland ducts (Burgess et al. 1979; Weingarten 1989; Shawky et al. 2000; Campagnolo et al. 2001; Sandhu & Shawky 2003; Konch et al. 2009). Meckel’s diverticulum may be hemorrhagic with a fibrous core (Proctor et al. 1975). In esophagus, the lumen gets lined with yellowish-white membrane or, in some cases, there may be sloughing of the entire mucosa. The esophago-proventricular sphincter may
be seen as a hemorrhagic ring. The lumen of intestine may be filled with blood and the mucosal surfaces may have erosions and hemorrhages, which later become elevated, yellowish-white crusty plaques (Weingarten 1989; Shawky et al. 2000; Campagnolo et al. 2001; Sandhu & Shawky 2003; Konch et al. 2009). Intestinal annular bands develop and appear as intensely red rings. Contrary to this, congestion is seen in the ceca and lesions are singular and well separated between the mucosal folds. Normally, adjacent to the cloacae, rectal lesions are few in number with greatest concentration of lesions at the posterior portion of the rectum. Initially, due to dense lesions in the cloacae, the entire mucosa appears reddened. Later, individual plaque-like elevations become green and form a continuous scale-like band lining the lumen of the organ. In mature layers, hemorrhages may be observed in ovarian follicles, and sometimes massive hemorrhages may exude to the abdominal cavity (Konch et al. 2009).

The lymphoid organs including spleen may look dark and mottled. The thymus becomes atrophied with multiple petechial and necrotic focal areas surrounded by clear yellow fluid that infiltrates and discolors sub-cutaneous tissues of the adjacent cervical region from the thoracic inlet to the upper-third of the neck. This lesion is important in meat inspection that can be detected easily when the opened neck of the carcass is observed on the processing line. During early infection, bursa of Fabricius is intensely reddened surrounded by clear yellow fluid that discolors adjacent tissue of the pelvic cavity. When the lumen of the bursa is opened, pin-point yellow areas and hemorrhagic surfaces are noticed. Later, walls of the bursa become thin as well as dark and get filled with white coagulated exudates.

Even though these lesions are consistent with DEV infection, each age group responds characteristically. Lymphoid lesions are more prominent in ducklings than tissue hemorrhages. Outbreak with low virulent strain of DEV in white Peking ducklings (2 to 6 weeks old) produced atypical gross lesions like diphtheritic membranes under the tongue, nasal and infra-orbital sinuses (Shawky et al. 2000; Konch et al. 2009). In mature birds with regressed bursa and thymus, hemorrhagic lesions in internal organs and reproductive tract are prominent. Gut-associated lymphoid tissues have multifocal necrosis and ulceration covered by fibrinous pseudo-membranes (Jansen 1968; Proctor 1976; Weingarten 1989; Islam & Khan 1995; Shawky & Schat 2002; Sandhu & Shawky 2003; Guiping et al. 2007; Konch et al. 2009). In geese, intestinal lymphoid discs (Leibovitz 1969b; Proctor 1975; Weingarten 1989; Konch et al. 2009) are analogous to annular bands in ducks. In Canada goose, lesions of the intestinal lymphoid discs resembled ‘button-like ulcers’ (Leibovitz 1969a; Proctor 1975; Konch et al. 2009). Diphtheritic esophagitis is a consistent lesion in swans (Keymer & Gough 1986).

8.4. Histopathology

Histopathology reveals that the lesion commences from the walls of blood vessels. Smaller blood vessels, venules and capillaries are more affected than larger blood vessels. The endothelial lining is disrupted and connective tissue of the wall becomes less compact with visible breaks allowing blood to pass out to the surrounding tissues (Richter & Horzinek 1993; Sandhu & Shawky 2003; Konch et al. 2009). Hemorrhages are more pronounced in inter-lobular venules of the proventriculus, venules in the spaces between lung para-bronchi, hepatic and portal venules at the margins of liver lobules and capillaries within intestinal villi. Due to vascular damage, the affected tissues undergo degenerative changes. Microscopic findings include necrosis of epithelial lining of the digestive tract together with infiltration of variable lymphocyte and macrophage numbers within mucosal and serosal connective tissues. Eosinophilic intra-nuclear and cytoplasmic inclusions have been seen in epithelial cells of the digestive, respiratory and reproductive tracts as well as in visceral organs such as liver and spleen (Tantaswasdi et al. 1988; Shawky et al. 2000; Campagnolo et al. 2001; Konch et al. 2009). The affected epithelium becomes edematous, necrotic and rise into the lumen above normal adjacent mucosal surfaces. Degeneration and necrosis of stratified squamous epithelium of the esophagus and cloacae can also be observed. Parenchymatous organs like liver, pancreas and kidneys have hemorrhages and focal necrosis surrounding blood vessels. In the liver, hepatocytes become swollen with intra-nuclear inclusion bodies (Leibovitz 1971; Konch et al. 2009). Lymphocytes undergo karyorrhexis and pyknosis. In bursa, sub-mucosal and inter-follicular hemorrhages are observed coupled with depletion of lymphocytes. The epithelial cells of bursa are often hypertrophied with a vacuolated cytoplasm. Similarly in thymus, free blood fills the inter-follicular spaces together with depletion of cortical lymphocytes. In female breeders, there is congestion and necrosis of the oviduct and the follicles become misshapen and stained with blood (Konch et al. 2009).

9. Immunity

Maternal immunity has been reported in ducklings that declines fast and may interfere with response to live virus vaccines (Toth 1971). Ducklings from those breeder ducks that are vaccinated with a live-attenuated vaccine are fully susceptible. On the other hand, ducklings from breeders that had been vaccinated and challenged with a virulent virus were found protected (Toth 1971). It is considered that both cell-mediated and humoral immunity are involved in protection against DVE (Lam & Lin 1986; Umamaheswararao & Rao 1993). Active immunity has been established using
10. Diagnosis

Together with clinical symptoms, characteristic gross and histopathological lesions are being preferred for the preliminary diagnosis of DVE. However, hemorrhagic and necrotic lesions need to be differentiated from duck virus hepatitis, fowl choler, necrotic enteritis, coccidiosis and specific intoxications. Although Newcastle disease, fowl pox and fowl plague are reported to produce similar changes in *Anseriformes*, these diseases have been infrequently reported in ducks (Morton & Dieterich 1979; Oladele et al. 1996; Sa'idu et al. 2004; Normile 2005; Olsen et al. 2006). Liver, spleen, bursa of Fabricius, kidneys, peripheral blood lymphocytes (PBL) and cloacal swabs are the best specimens for DEV isolation from affected and dying birds (Woolcock 2008; OIE 2012). Ducks, swans and geese exhibiting characteristic symptoms should be culled and transported to a certified diagnostic laboratory at the earliest possibility.

Confirmatory diagnosis includes inoculation of DEV into ducklings, propagation into chorioallantoic membrane (CAM) of embryonated Muscovy duck eggs and isolation of the virus on cell lines derived from ducklings followed by identification by DEV-specific gene segment by PCR targeting various genes such as UL30 and US4 (gD) gene, restriction fragment length polymorphism (RFLP) and nucleotide sequencing (Thayer & Beard 1998; Cavanagh 2001; Konch et al. 2009; Aravind, Kamble, Gaikwad, Shukla, Saravanan, et al. 2015).

Field observations showed that convalescent birds are immune to re-infection. Burgess and Yuill (1982) demonstrated death of mallard ducks from super- and persistent infection. This indicates that protection against mortality is dependent on the route of exposure, strain of the virus and strain of super-infecting virus. Hossain et al. (2004) studied the time of vaccination and effect of dose on immune response of lyophilized DP vaccine (LRI, Mohakhali) in ducks. They concluded that ducklings below 30 days of age should not be vaccinated with DP vaccine. Primary vaccination should be done at 35 days (0.5 ml/duckling) followed by a booster dose after 5 months of primary vaccination (1.0 ml/duckling) for better immune response. Route of vaccination also has impact on type and duration of immunity produced. Besides, intra-muscular route when attenuated DEV vaccines were given orally in ducklings, IgA and IgY antibodies both increased as a boosted humoral immunity. Number of plasma cells producing IgA in intestine increased and can be a very well check point for the virus because DEV initially replicates in the mucosal membrane of intestine before spreading to other organs in the infected host. Oral vaccination enhanced mucosal immunity via IgA levels at intestinal mucosa to prevent viral replication and simultaneously IgY levels in serum for systemic protection (Xiaoyan et al. 2010).

10.1. Virus isolation

The DEV can be isolated from primary CEF or duck embryo fibroblast (DEF) or Muscovy duck embryo fibroblast (MDEF) culture at 39.5 °C–41.5 °C. The specific growth properties of virulent DPV have been studied in DEF mostly through examination of DEF cell culture monolayer for plaques by inverted light microscope. Besides this, electron microscopy and real-time PCR are also useful in detection of early virus growth and spread to adjacent cells (Guo et al. 2008). DVE has mostly been cultivated over homologous host but researchers have tried adaptation of DEV over Vero cell lines and with the gradual passage, recovery of virus was enhanced. Virus growth over cell lines was confirmed by cytopathic effect (CPE) consisting of spindle shaped infected cells followed by clumping/aggregate formation. The virus produces characteristic intranuclear inclusions and cytopathic effects (Kocan 1976;
Wolf et al. 1976; Gough & Alexander 1990). Cytopathic effects are characterized by enlarged, rounding and clumping of cells that become necrotic (OIE 2012). More than one sequential blind passage may be required to isolate the virus in cell culture. Because DEV is cell associated, the continuous passage should be done by trypsinizing and re-plating infected cells and infection of new cells with cell culture supernatant from earlier passage. An IF assay may also be performed to detect the virus in infected cells. Presence of specific apple green fluorescent through indirect immune-fluorescent antibody test by using FITC-conjugated antibodies confirmed the occurrence of DEV antigen in infected Vero cell lines (Aravind, Kamble, Gaikwad, Shukla, Dey, and Mohan 2015). To demonstrate the syncytia formation (cytoplasmic granulation and intra-nuclear inclusions), cells should be fixed and stained with hematoxylin and eosin. Primary virus isolation may also be performed on 9–14-day-old embryonated Muscovy duck eggs through CAM (Sandhu & Shawky 2003). The infected embryo shows characteristic hemorrhages 4–10 days after inoculation. However, it may require 4–5 blind passages for virus isolation. Embryonated chicken eggs could also be used to isolate virus. However, it also needs serial passages.

Inoculation of infected tissue to susceptible ducklings is considered more sensitive than the virus isolation in cell culture. Homogenate of liver, spleen or kidney is being inoculated to day-old ducklings and death within 3–12 days is observed. Microscopic and macroscopic lesions coupled with IF assay are used to confirm the infection (OIE 2012).

10.2. Immunological / serological tests

In DEV infection, usually poor humoral immune response is observed, wherein antibodies are short-lived. Hence, the diagnostic assays based on serology are of not much significance, as well as are not useful in acute infection, serological surveillance and while measuring post-vaccination immune response (Toth 1972; Toth & Norcross 1981; Vickery et al. 1999a, Vickery et al. 1999a, 1999b; Tang et al. 2001; Qi, Yang, Cheng, Wang, Zhu, et al. 2009; Tohidi-Esfahani et al. 2010; Yang et al. 2010). Although cell-mediated immune response has been shown to play a more important role during DEV infection (Vickery et al. 1999a, 1999b), it is possible to detect the anti-DEV neutralizing antibodies (Saade et al. 2008; Aravind et al. 2012).

The common immunological tests employed are neutralization assays, FAT and reverse passive hemagglutination test (RPHA) (Deng et al. 1984; Sandhu & Shawky 2003). Next to virus inoculation in susceptible ducklings, FAT for the detection of virus on DEF and MDEF is considered most sensitive. Avidin-biotin-peroxidase based staining method can also detect the viral antigens in sections of liver and spleen (Islam et al. 1993). An indirect immunohistochemical technique employing streptavidin-alkaline phosphatase (SP-IHC) system has been found useful for detection and localization of DPV vaccine antigen in paraformaldehyde-fixed paraffin-embedded tissue sections and for assessing the proliferation and circulation frequency of attenuated DPV vaccine strain in immunized ducklings. Positive staining with SP-IHC technique showed consistently significant results in detection of vaccine antigens in different organs at respective time intervals. The presence of antigen was detected in liver, spleen, bursa of Fabricius, thymus, Harderian gland, esophagus, intestinal tract, heart, lung, kidney, pancreas, brain, mucosal epithelial cells, lamina propria cells, macrophages, hepatocytes, and in lymphocytes, beginning from 12 hours post-vaccination up to 18 weeks post-vaccination (Shen, Ma, et al. 2010). An immunoperoxidase staining technique detects the expression and distribution of UL51 protein of DEV in paraffin blocked tissue sections of various organs of the infected ducks (Shen, Cheng, Wang, Xu, et al. 2010). An indirect immunoperoxidase assay is used for the detection of glycoprotein gE protein of DPV in paraformaldehyde-fixed, paraffin-embedded tissues of infected ducks which gives an idea about viral gE protein distribution in different organs of the body (Chang et al. 2011b). Similarly, an indirect IF assay has also been developed for the detection of viral gE protein in DPV infected tissues and the immune response (HI) against this protein can be detected by means of ELISA (Chang et al. 2011a).

Latex agglutination test has been found highly sensitive when compared to duck embryo inoculation and VN test (Chandrika et al. 1999). Deng et al. (1984) developed an RPHA test to diagnose DEV. RPHA test has been found to be a rapid and easy procedure with adequate sensitivity in the tissues of ducks dying from acute infections, major drawback includes less sensitivity than either the plaque assays (PA) or the IF test. PA in duck embryo cell cultures can be performed (Dardiri & Hess 1968). The morphogenesis and distribution of virus in vivo can be observed by electron microscopy (Yuan et al. 2005). VN assay can be conducted in duck/chicken embryo, embryo fibroblasts or cell culture (Wolf et al. 1974). Neutralization indices (NI) from 0 to 1.5 are considered as lack of exposure of birds to DEV, whereas NI > 1.75 is considered as evidence of prior exposure to DEV (Dardiri & Hess 1967). Recombinant UL30 antigen-based single serum dilution ELISA, recombinant gB1 protein-based indirect ELISA, indirect UL55 protein-based ELISA and UL51 protein-based immune-chromatographic strip tests have been validated for diagnosing DPV (Pan et al. 2008; Shen et al. 2009; Shen, Cheng, Wang, Sun, et al. 2010; Wu et al. 2011a; Aravind et al. 2012). Immuno-electron microscopy (IEM), using DVE hyper-immune serum, has also
been developed for disease diagnosis. Recently, polyclonal antibody against the recombinant UL24 protein based antigen-capture ELISA has also been developed (Jia et al. 2009). A dot-ELISA was developed using polyclonal antibodies produced against DPV tegument protein UL46 (VP11/12) which proved to be a specific diagnostic assay to confirm the presence of DPV in clinical samples of birds (Lu et al. 2010). A TK(thymidine kinase)-ELISA using thymidine kinase recombinant protein as an antigen has been developed for the detection of serum antibodies specific to DPV which could be highly useful for the epidemiological survey of DP. TK-ELISA has been reported to be highly specific as well as sensitive and showed good repeatability and reproducibility when evaluated against DPV, duck Hepatitis B virus, duck Hepatitis virus, R. anatipestifer, E. coli and Salmonella Anatum antisera, as strong positive signals were evident only against DPV anti-sera (Wen et al. 2010). The DPV glycoprotein C, encoded by the DPV UL44 gene, has been suggested to be a suitable candidate for developing new diagnostics and vaccine against DPV (Sun et al. 2014). Truncated glycoprotein K (tgK) has also expressed and found to be highly immunogenic and reactogenic. Hence it can be used for development of a good sero-diagnostic kit for detection of DEV (Zhang et al. 2010).

Malmarugan and Sulochana (2002) evaluated comparative efficacy of indirect Dot-ELISA and passive haemagglutination test for sero-conversion to DEV. John et al. (1989) developed the CIE for rapid detection of DP virus antigens and antibodies. Konch et al. (2009) conducted serological tests such as CIE and agar gel precipitation test for the diagnosis of DEV from clinically affected birds.

10.3. Molecular diagnosis of DEV

Currently, both conventional and quantitative PCR have been employed for the detection of DEV (Guo et al. 2006; Yang et al. 2006; Qi, Yang, Cheng, Wang, Guo, and Jia 2009). Beside diagnostics, the rapidity, sensitivity and specificity of these assays could provide a suitable tool towards understanding the epizootology of DP (Hansen et al. 1999; Pritchard et al. 1999; Hansen et al. 2000; Sandhu & Shawky 2003; Cheng et al. 2004). DEV-specific DNA segments can be amplified from infected cell culture supernatant and tissues from esophagus, liver, kidney and spleen (Plummer et al. 1998; Thayer & Beard 1998; Hansen et al. 1999, 2000; Pritchard et al. 1999; Yang et al. 2005; Xuefeng et al. 2008; Liu et al. 2009; Qi, Yang, Cheng, Wang, Guo, and Jia 2009; Wu et al. 2011b; Lin et al. 2013). Plummer et al. (1998) diagnosed the DEV by targeting the highly conserved domain of the UL6 gene. Hansen et al. (2000) developed a PCR assay for detection of DEV from waterfowl. While understanding the immune mechanism of attenuated DEV, Cheng et al. (2005) applied PCR assay for diagnosis of attenuated Cha strain of DEV in vaccinated ducklings through three different routes; subcutaneous, oral and nose dripping. Quantitative real-time PCR assays have been developed for rapid diagnosis as well as detection of DEV in acute and latent stages of infection (Guo et al. 2006; Yang et al. 2006; Qi, Yang, Cheng, Wang, Guo, and Jia 2009). It also gives an idea regarding the load of DVE viral DNA in the body tissues of infected ducklings during acute stage of virulent virus infection which can further be correlated with the dissemination of virus and progression of disease in different organs (Qi et al. 2008). By employing the advantages of advanced PCR versions, studies have also been performed to differentiate the active viral shedding from latent infection of Anaitid herpesvirus-1 in native waterfowl, captive-reared and then released ducks, newly introduced non-migratory waterfowl and peridomestic or semi-wild/feral ducks. When cloacal sample are found positive for the presence of DVE DNA then an active infection/shedding of the virus can be implicated while the negative cloacal samples in contrast to presence of viral DNA from TG reveals latent viral infection, which is a specific feature of herpes virus infection (Keel et al. 2013).

Restriction endonuclease assay could also be used to DEV strains (Vijaysri et al. 1997). Molecular characterization (PCR and indirect FAT) is used as a rapid and labor effective technique for confirmation of the causative agent of duck viral enteritis from outbreaks in Egypt during the time period of 2012–2013 from different localities, breeds and age groups (Hanaa et al. 2013). In situ hybridization is a modern diagnostic tool which can detect the presence of DPV DNA through specific oligonucleotide probes in tissue sections (mainly in cellular nucleus and cytoplasm) of various organs and can provide information about localization of the viral DNA in case of quick diagnosis of the viral infection (Cheng et al. 2008). With advances in designing diagnostic procedures, LAMP-based nucleic acid amplification methods for DEV detection have also been developed (Ji et al. 2009; Jiang et al. 2012; Woźniakowski & Samorek-Salamonowicz 2014). When compared to PCR and virus isolation procedure, LAMP assay has proven to be rapid, simple, accurate, specific and sensitive method for the diagnosis of DEV. The assay has been considered a good choice for on-farm disease diagnosis as evidenced by the survey on occurrence of DEV in free-range Polish water birds (Woźniakowski & Samorek-Salamonowicz 2014).

Advances in field of diagnosis for the development of sensitive and specific point-of-care diagnostic assays like LAMP, lateral flow assay, recombinant protein based diagnostics, biosensors, biochips, microarrays, genomic fingerprinting and nanodiagnostics need to be explored to their full potential for diagnosing DEV (Belak et al. 2009; Ji et al. 2009; Balamurugan et al.
11. Prevention and control

To date, there is no specific treatment of DEV infection yet. Thus, major thrust of activities to prevent and control DEV transmission involves decrease in contact of the susceptible population during the time of outbreaks and reducing the quantity of virus presence into the environment by enhancing appropriate biosecurity measures. Periodical shedding of virus by convalescent as well as clinically diseased birds serves as the major sources of virus as well as subsequent obstacle for disease control and prevention. Therefore, destruction of infected flocks and eggs are recommended. In this regards, novel molecular detection tools such as PCR and LAMP have allowed selective culling of infected birds (Weingarten 1989; Richter & Horzinek 1993; Pearson & Cassidy 1997; Sandhu & Shawky 2003; Gough 2008; Sandhu & Metwally 2008).

The virus is considered resistant such that it can survive for weeks under unfavorable environment or circumstances. The DEV is mainly destroyed at pH 3 or below and pH 11 or above. Therefore, thorough chlorination of contaminated water sources, increase or decrease in pH, burning and proper cleaning of litter as well as physical structures and other materials at outbreak areas should be carried out. Carcass should be thoroughly disposed and, if possible, incineration should be done. To stop mechanical transmission of the virus to other potential virus reservoir areas, personnel and utensils used at outbreak areas must be sanitized either using phenol disinfectants or chlorine bleach. Close relationship between DVE outbreaks and captive waterfowl such as Mallard and Muscovy ducks needs to be monitored (Dhama, Mahendran, and Tomar 2008). Waterfowl release programs should involve use of birds and eggs from diseased free flocks coupled with quarantine for minimum of 2 weeks before release. Dead bird carcasses should be transported to a certified diagnostic laboratory for further investigation and, if duck viral enteritis is confirmed as a cause of death, the remaining birds should not be released (Leibovitz 1969b; Weingarten 1989; Wobeser 1997; Gough 2008; Sandhu & Metwally 2008).

Owners should prevent co-habitation or contact of waterfowl with wild waterfowl. All suspected outbreaks should be reported immediately to state authorities. Presently, slaughter with indemnification has been discontinued and vaccination has been authorized on certain premises, which needs to be approved by animal health authorities on large scale (Weingarten 1989; Wobeser 1997; Gough 2008; Sandhu & Metwally 2008).

Considering the fact that vaccines are generally effective only in DEV naïve birds and its shedding is still not completely understood, one can’t completely rely upon vaccination alone. Therefore, one has to give importance to eliminate the in-apparent carriers that represent a risk to domestic waterfowl. Therefore, control measures like quarantine, reduction in virus contamination in the area using proper disinfectants, checking the dispersal of waterfowl, and monitoring for mortality in wild waterfowl populations should be observed (Pearson & Cassidy 1997). Depopulation of clinically exposed ducks should be done on top priority because virus has tendency of undergoing latency and following viral shedding in the environment hence this is the only practical method to reduce DP outbreaks. Introduction of the disease by free flying Anseriforms and contaminated aquatic environments must be prevented.

In countries where the disease is not enzootic and is truly exotic, effective quarantine of imported or clinically suspected Anseriforms should be done. Surveillance of DVE in ornamental bird collections, zoos and domestic growers of Anseriforms should be performed periodically using state-of-art detection tools.

12. Vaccination

Currently, in most of the European countries and the USA, both live attenuated and killed vaccines are being used in broiler and breeder ducks that are over two weeks of age (Sandhu & Shawky 1997, Sandhu & Shawky 2003; Yang et al. 2015). In India, Holland strain of DVE, which is a chick embryo-adapted live DVE vaccine is being used commercially in control programs. However, live vaccines are always an issue due to property of latency with these herpes viruses (Aravind, Kamble, Gaikwad, Shukla, Saravanan, et al. 2015). Inactivated DP vaccine is also effective in eliciting protective immunity against duck viral enteritis (Samia & Sandhu 1997). Some commercial vaccines yielded a poor immune response and only elicited partial protection during challenge studies (Kulkarni et al. 1998). However, CEF adapted DP vaccines at a dose rate of $10^{6.5} \text{EID}_{50}$ may provide high levels of protection in ducklings (Sarmah & Sarmah, 1996). The immunized ducks have been reported to withstand challenge at 21 days post vaccination (Mondal et al. 2010). Inoculation of ducks with apathogenic Sheridan-B3 strain provides protection against virulent Lake Andes strain of DEV (Lam & Lin 1986). Herpes viral gD glycoprotein induced production of neutralizing antibodies, cytotoxic T lymphocyte cells and natural killer cells in mouse model, hence can be wisely employed and tested as vaccine candidate. As it affects the entry of virus in the cell and spread in between the cells, laboratory trials are needed to explore its antiviral immune response aspect. Passive immunization also provides
significant protection to susceptible ducks from lethal challenge (Lin et al. 1984). Attenuated DPV vaccine containing the strain CHa as a modified live vaccine protected ducks upon subcutaneous immunization and the vaccine provided adequate and satisfactory protective systemic (IgG) as well as mucosal (IgM) immunity against DP. Post-immunization humoral level of immunity was assessed by measuring the titers of IgG and IgM using ELISA with the number of CD4(+) T cells was found increased in contrast to the CD8(+) T cells through flow cytometry after immunization. These results support the subcutaneous route of administration for delivering attenuated vaccines (Huang et al. 2014). Hence adopting an appropriate route of vaccination is an essential factor to elicit desired protective immunity. Attenuated vaccine has extended tissue tropism. Live attenuated vaccines are considered most effective against DPV hence it is of foremost importance to maintain the vaccine at optimum physical and physiological conditions of temperature, salt and pH to prevent any loss in the activity of vaccine candidate molecule (Makhija & Kumar 2016). The vaccinated ducks could excrete the virus thus demands revaccination of the entire flock (Huang et al. 2014).

Recent studies supported the use of attenuated DEV Chinese vaccine strain C-KCE as an efficient vector for developing polyvalent live attenuated vaccine against high pathogenic avian influenza virus (AIV) strain H5N1 and DEV. By using the mating-assisted genetically integrated cloning (MAGIC) technique, hemagglutinin (HA) gene of H5N1 virus and modified mini-F vector both were incorporated in between the gB, UL55 and UL26 gene junction of the C-KCE genome of attenuated DEV vaccine strain to produce bacterial artificial chromosome (BAC) of C-KCE as a recombinant vector pBAC-C-KCE-HA for delivering vaccine. This vaccine provided speedy immunological protection for long duration against H5N1 AIV and DEV infection (Liu, Han, et al. 2011; Liu et al. 2013; Zou et al. 2015). Production of correct recombinant vector was confirmed by RFLP analysis. Vaccine efficacy was tested by infecting the CEF by DEV-vectorized vaccine and checked by indirect IF and western blotting analyses. Ducks and chickens were tested and vaccine elicited strong humoral immunity in three weeks old chickens (Wang et al. 2015). Similarly, workers have explored role of DEV as a suitable vaccine delivery vehicle/vector of bivalent attenuated vaccine against another emerging pathogens of ducks and mammals, duck tembusu virus (DTMUV) along with DEV as using recombinant rDEV-TE and rDEV-PrM/TE (pre-membrane proteins) against DTMUV infection in ducks. The envelope (E) gene of DTMUV was targeted and through MAGIC strategy recombinant vector pBAC-C-KCE-E and bivalent vaccine C-KCE-E were prepared. Ducks immunized with C-KCE-E vaccine produced neutralizing immunoglobulins against DTMUV, thus the efficacy of C-KCE-E has been proposed be used in poultry industry and for public health concerns (Chen et al. 2014; Zou et al. 2014). DEV was also used in producing recombinant vaccines (rDEVs) as rDEV-N, rDEV-S and rDEV-S1 expressing the N, S, and/or S1 protein of infectious bronchitis virus (IBV). Such vaccines generated significant humoral and cellular immunity post-vaccination in terms of lowered CD4(+)/CD8(+) T-lymphocytic ratio, improved antibody titer, decreased viral shedding and reduced mortality in chickens even when challenged with virulent IBV strain than the use of any single recombinant vaccine (Li, Wang, et al. 2016). Researchers have prepared oil emulsified inactivated vaccine against Salmonella Typhimurium (ST), DP and Duck Hepatitis Virus (DHV) which was found safe, potent and capable of protecting ducklings against ST, DP and DHV infections effectively (Han et al. 2014; Liu, Liu, et al. 2016). Researchers are investigating the role of UL16 and UL54 genes also and their expressed proteins from DEV, so that they can also be utilized in planning prophylactic strategy against DEV virus in susceptible bird populations (He et al. 2012; Liu et al. 2015; Liu, Cheng, et al. 2016). A DEV-vectorized vaccine containing a recombinant DEV (rDEV-ΔUL2-HA) inserted with the HA gene from duck-origin H9 subtype (H9N2) AIV into the UL2 gene by homologous recombination has been developed recently. This r-vaccine when administered as a single dose of 10^7 TCID_{50} elicited strong protective immunity against both DEV and H9N2 AIV virus infections in ducks by reducing the H9N2 AIV virus excretion/shedding and protecting the birds against fatal challenge of DVE (Sun et al. 2016). DEV has the potential to be utilized as a promising viral vector candidate for developing vaccines for poultry and aquatic birds.

Using carrier mediated live attenuated ST (SL7207) and heat labile enterotoxin B subunit (LTB) of E. coli as mucosal adjuvant, orally delivered DNA vaccine has been used to immunize ducklings. The said vaccine produced a mounted mucosal and systemic immune response against DEV together withstanding experimental challenge (Yu et al. 2012). DNA vaccine encoding glycoprotein C (gC) of DPV elicited better cell mediated immunity by inducing significant T-lymphocytic immune response in ducks when given through gene gun as compared to I/M route of immunization which mainly generate humoral immune response. Gene gun DNA vaccination also need only small quantity of injected DNA as vaccine dose (Lian et al. 2011). Immunization of BALB/c mice with pcDNA-GPV-VP2 DNA by gene gun or I/M route produced better level of humoral and cellular immunity as compared to live attenuated vaccine by I/M route (Cai et al. 2013). Similarly, glycoprotein D (gD) and glycoprotein B (gb) based DNA vaccination provided effective immunoprotection through induction of potent cell mediated and
humoral immunity against DEV in Pekin ducks (Zhao et al. 2014). A study performed over murine model suggested that better immunogenicity and protective immune response is generated by following prime boost regimen of immunization using both pCDNA-gD, plasmid DNA encoding for DEV glycoprotein D and rgD protein which was expressed in Saccharomyces cerevisiae yeast. This combination using DNA vaccine and rgD protein vaccine in which initially DNA vaccine is given intramuscularly followed by booster rgD protein vaccine resulted in enhanced ELISA antibody titers to DEV, rise in lymphocyte number and function as well as cytokines IL-4, IL-12 and IFN-γ levels were increased significantly along with rapid clearance of virus after challenge infection (Aravind, Kamble, Gaikwad, Shukla, Saravanan, et al. 2015). This recombinant DEV vector vaccine has been suggested to be a good choice for vaccination in ducks and reduce DEV outbreaks. Studies have emphasized that DNA vaccine, appropriate codon usage for targeted protein/glycoprotein, selection of plasmid for proper uptake by host cells, dose and stability of plasmid, age of bird, the route of vaccine administration either by gene gun, intramuscular or subcutaneous, and vaccination strategy all have significant impact on enhancing the immune responses against DPV after immunization in poultry/birds (Dhama, Mahendra, Gupta, & Rai 2008; Meunier et al. 2016). The laboratory results of such vaccine trials prove the enhancing immunization potential of DNA vaccines and hence clinical validation of such vaccines should be attempted to encourage the DNA vaccination strategy to be adapted for supporting the prevention and control measures against DPV.

The limitations of the requirement of repeated immunization with a live attenuated vaccine and incidence of the disease in vaccinated flocks could be overcome to some extent by developing new generation vaccines against DEV. Now-a-days main focus of research is on targeting specific glycoproteins of DVE to be utilized as vaccine candidates and developing recombinant, subunit and DNA vaccines eliciting effective, safe and protective immunity in vaccinated ducks, chickens and wild birds. Further validation is advised before commercialization of such vaccines in the market. Advancement in the era of vaccination has also provided other different platforms like edible vaccine, peptide vaccine, nucleic acid based vaccine, reverse genetics approach, immunomics based vaccine and others, which can be exploited for developing a suitable and more effective vaccine for DEV (Dhama, Wani, et al. 2013; Delany et al. 2014; Singh et al. 2015). Also, various immunomodulatory agents, adjuvants and vaccine delivery systems have evolved recently, which can be employed for enhancing the effectiveness of the DEV vaccine (Malik et al. 2013; Sawant et al. 2015; Singh et al. 2015; Dhama, Saminathan, et al. 2015).

13. Antiviral agents/therapies

Despite extensive use of vaccines and adoption of effective management measures for the control of disease, the spread of virus has not been controlled / prevented yet. Hence, discovering novel antiviral drugs and therapeutic options targeting DEV are gaining importance. The antiviral activity of alcohol extracts of neem (Azadirachta indica) seed kernel against DPV has been reported. DPV infected DEF showed improved viability, diminished expression of viral proteins and decrease in the cytopathic effects after treatment with neem seed kernel extracts (Xu et al. 2012). Resveratrol, a naturally occurring phytoalexin in specific plants, has been found to exhibit antiviral activity against DEV (Xu et al. 2013). DEV infected ducklings recovered when treated with resveratrol. A recent study reported reduced mortality and less viral load upon blood testing and proved potential antiviral properties of resveratrol against herpes viral infections in infected birds (Zhao et al. 2016). A novel sulfated polysaccharide from Chuanminshen violaceum (sCVPS) has also been found as potent antiviral against DEV that interfere virus adsorption onto the host cell (Song et al. 2013). Adding towards a better understanding of DEV replication, a vaccine strategy based on a full length infectious BAC has been constructed for DEV (Chen et al. 2013). Mallanna et al. (2006) demonstrated inhibition of replication of DEV by siRNA controlled gene silencing in DEF cell line. This inhibition targeted the UL-6 gene which encodes a protein responsible for viral packaging. Severe outbreaks of DP are treated successfully by administration of the homeopathic drug named ‘Mercurus corrosives-6 /12’ at a dose of 5-10mL per 1000 ducks once or twice daily for 1–3 days (Narahari 2009). In a recent study, goose type I interferon (IFNα) and type II interferon (IFNγ) have showed antiviral activity against DPV and hence have come up as potential candidate for designing the IFN-based preventive and therapeutic anti-viral strategies (Zhou et al. 2016).

Research attention needs to be focused on regarding utilization of novel and upcoming therapeutic regimens like herbal therapy, essential oils, cytokines, RNAi technology, avian egg antibodies, nanomedicine, nutritional immunomodulation and probiotics to curtail DEV (Dhama et al. 2011; Dhama, Chakraborty, et al. 2013; Sudhakar et al. 2013; Dhama, Tiwari, et al. 2014; Gopi et al. 2014; Dhama, Latheef, et al. 2015).

14. Conclusion and future directions

The DEV has the features common to avian herpes virus infections like ubiquitous presence and persistence in the environment, carrier status and latency. Since its first appearance in the United States of America, the disease has become endemic to different parts
of the world, particularly countries where duck farming is more common. Latency is an important problem associated with herpes viral infection and DEV undergo latency in the trigeminal ganglion and upon activation leads to viral shedding infecting the environment and also other susceptible birds. Beside wild birds, the convalescent waterfowl may act as long-term carrier and could easily perpetuate the infection into the environment. Various isolation and serological diagnostic procedures are being used with certain limitations in detection of virus at an early stage as well as to determine latency. With the advancement in molecular diagnostics and surveillance tools, detection of carrier and convalescent birds has been made possible. As an alternate to depopulation, vaccination of waterfowl has been proposed. Though available vaccines provide protection, they are not well effective in all species of ducks. On the other hand, the birds might become more susceptible to disease after vaccination. Currently available traditional vaccine stock is not even sufficient to cover large duck population with consistent efficacy. Hence, considering the advances in recombinant DNA technology, it is expected that novel immune-prophylactic agents like subunit vaccines, DNA vectored vaccines or DNA vaccines could be soon available to curb DEV. The upcoming new cultivation systems of DEV including both homologous and heterologous vaccines or DNA vaccines could be soon available to nullify the drawbacks of conventional vaccines. Several recent vaccine platforms like DNA vaccine, reverse genetics approach, edible vaccine, various adjuvant technologies and vaccine delivery methods can help to curtail DEV. The upcoming new cultivation systems of DEV including both homologous and heterologous hosts as Vero cell lines will support to fulfill the desired amount of commercial vaccines as per the large/huge bird population along with reducing the risk of exposing vaccinated birds to any live/attenuated/whole form of DEV and will help in crossing the impediment of huge economic loss for infection-free duck/bird industry. Advances in discovering novel and effective drug candidates and optimum exploration of emerging and alternative therapeutics would also help in controlling the DPV incidences and outbreaks.

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