An Overview on Infectious Laryngotracheitis (ILT): A Serious Threat to Chicken Intensive Production System

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Abstract. *Infectious laryngotracheitis (ILT) is a respiratory viral infection, particularly common in adult chickens. The disease widely distributed in several countries causes severe economic losses. ILT virus (ILTV) is a double-stranded DNA which belongs to Alphaherpesvirinae subfamily of Herpesviridae family. Infected and latently carrier chickens are sources of ILTV infection, while the aerosol is the main route of the virus transmission. The acute epizootic form of ILT is characterized by a sudden onset, a rapid spread, and a high mortality rate with severe conjunctivitis, dyspnoea, gasping, coughing, expectoration of blood mixed with mucus, and drop in egg production. However, chickens in the mild enzootic form show less signs with a morbidity rate up to 5% and a mortality rate between 0.1% and 2%. The most characteristic post-mortem lesions are haemorrhagic tracheitis with the presence of a yellow cheesy plug in the respiratory tract. Despite diagnostics of signs and lesions, the confirmation of ILTV infection occurs via conventional isolation, detection of the virus in the affected tissues, as well as using recent molecular techniques. Prevention of ILTV infection depends on some key lines, including biosecurity measures and vaccination. Both live attenuated and recombinant vaccines are used for the prevention and control of ILTV infection. Therefore, the present review focuses on susceptibility, transmission, clinical picture, diagnosis, differential diagnosis, immune response, and prevention and control.*

Introduction

Infectious laryngotracheitis (ILT) is a highly contagious respiratory viral disease of chickens caused by the herpes virus (Garcia et al., 2013). The disease is associated with severe production losses as a result of mortality, decrease in the weight gain and egg production, the expenses of vaccination, biosecurity measures, and treatment of secondary infections by other avian pathogens (Guy and Garcia, 2008; Jones, 2010; Garcia et al., 2013; Parra et al., 2016). ILT shows a serious infection and causes huge economic losses particularly in high-density poultry-producing intensive production systems (Yan et al., 2016; Zorman Rojs et al., 2021). The disease was initially named as "avian diphtheria", but the name "ILT" was adopted by the Committee of Poultry Diseases of American Veterinary Medical Association by the year 1931 (Guy and Garcia, 2008). The high flock density, rearing of multiage and multipurpose chickens within the same area, short production cycles, and improper vaccination and biosecurity measures have contributed to the increased outbreaks of ILT in many countries all over the world (Blakey et al., 2019; Mishra et al., 2020; Tsiouris et al., 2021; Dodovski et al., 2022; Pajić et al., 2022; Gamal and Soliman, 2023). ILT remains a serious threat and has negative effects on the poultry industry worldwide since its first report in the mid-1920s. The disease was first described in the United States of America (USA) (May and Thittsler, 1925) and then it has been distributed in North and South America, Europe, Southeast Asia, and Australia. ILT is endemic in some countries as some regions in the same country or even multiple-age production sites (backyard flocks) are highly susceptible. Moreover, serious outbreaks are periodically observed when the strains of ILT virus (ILTV) transmit from chronically infected chickens to non-vaccinated flocks. ILTV belongs to *Alphaherpesvirinae* subfamily of *Herpesviridae* family, which has a double-stranded DNA genome of approximately 155 kb size. ILTV has a narrow host range as the main natural host is chicken. Moreover, chickens of all ages are susceptible and birds older than 4 weeks are mostly infected with ILTV (Aras et al., 2018; Tamilmaran et al., 2020). The virus shows lifelong infection by latency in the trigeminal ganglia. However, stress conditions such as transportation or reaching the peak of egg production can reactivate the latent virus to replicate and excrete (Coppo et al., 2013). Horizontal transmission of ILTV through the respiratory tract is the main route of the virus infection; however, the vertical transmission has not yet been reported (Wolfrum, 2020).

ILT is caused by a DNA virus that mostly infects the upper respiratory tract, conjunctiva, and the tracheal mucosa (Ahaduzzaman et al., 2020) causing conjunctivitis, coughing, dyspnoea, panting and stretching of the head and neck with an open beak "hunger for air", expectoration of bloody stained mucus, swelling of infraorbital sinuses, and decreasing

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egg production with a mortality rate of 10–20% (Garcia et al., 2013; Wolfrum, 2020). On post-mortem examination, bloody exudate or diphtheric membrane could be observed in the trachea (Pajić et al., 2022). The most important characteristic microscopic picture of ILTV is the presence of intranuclear eosinophilic inclusion bodies (Ou and Giambrone, 2012). The laboratory diagnosis of ILTV is based on detection and isolation, serological monitoring, and using some molecular techniques such as polymerase chain reaction (PCR) (Guy and Bagust, 2020; Carnaccini et al., 2022).

The prevention and control of ILTV infection rely on inhibiting the contact between the virus and the hosts by application of biosecurity measures and vaccination (Dufour-Zavala, 2008; Maekawa et al., 2019). Live attenuated ILTV vaccines are prepared by attenuation in a chicken embryo or in tissue culture, while recombinant vaccines are prepared by using turkey herpes virus or pox virus as a vector (Samberg et al., 1971; Coppo et al., 2013; García, 2017; Maekawa et al., 2019). Both vaccines have been used commercially. ILT is one of the listed diseases that must be reported with adoption of strict biosecurity measures during outbreaks.

Therefore, the present review focuses on ILT with respect to its incidence and distribution, aetiology, susceptibility, transmission, clinical picture, diagnosis, differential diagnosis, immune response, and prevention and control.

Incidence and distribution

The first report of ILT was in the USA (May and Thittsler, 1925). Then it has been detected in the United Kingdom, Australia, and Europe (Cover, 1996). Nowadays, ILTV infections have been reported as important worldwide threats. The infections with ILTV were reported in more than 100 countries during the period of 2000–2013 (Menendez et al., 2014). The disease outbreaks have been detected in Canada (Ojkic et al., 2006), Europe (Neff et al., 2008), the USA (Dormitorio et al., 2013), China (Zhuang et al., 2014), Brazil (Preis et al., 2013; Parra et al., 2015, 2016), Netherlands (Dodovski et al., 2022), Greece (Tsiouris et al., 2021), India (Gowthaman et al., 2016; Mishra et al., 2020), Ontario (Alexander et al., 1998), Australia (Agnew-Crumpton et al., 2016), Egypt (Shehata et al., 2013; Abdo et al., 2017; Magouz et al., 2018; Bayoumi et al., 2020; ElSaied et al., 2021, 2022), Serbia (Orli´c et al., 2003; Pajić et al., 2022), Namibia (Molini et al., 2019), Algeria (Salhi et al., 2021), Iran (Razmyar et al., 2021), and Iraq (Alaraji et al., 2019). The increased incidence of ILT from time to time may be due to increasing the poultry production density, decreasing the downtime of production sites, poor biosecurity, and vaccination failure.

The aetiology

ILTV is taxonomically identified as Gallid herpesvirus 1 of the family *Herpesviridae* in the sub-family *Alphaherpesvirinae* and genus *Iltovirus* (Roizman, 1982; Davison et al., 2009). The hexagonal nucleocapsid of ILTV is of icosahedral symmetry and is composed of 162 elongated hollow capsomeres (Watrach et al., 1963). The viral capsid is about 100 nm in diameter, while the whole viral particle size ranges from 200 to 350 nm (Granzow et al., 2001). The genome of ILTV contains 80 open reading frames (ORFs), of which 65, 9, and 6 are located in the UL, US, and IR regions, respectively (Lee et al., 2011). Besides, the virus envelope contains glycoprotein spikes or projections that surround the nucleocapsid (195–250 nm in diameter). The molecular weights of ILTV glycoproteins have been first reported as 205, 160, 115, 90, and 60 kD (York et al., 1987). The glycoproteins of ILTV envelop are able to stimulate both the humoral and cell mediate immune responses of the host (York and Fahey, 1990). Moreover, the antigens of glycoproteins gB, gC, gD, gE, gG, gH, gI, gJ, gK, gL, and gM are key factors for the virus attachment, entry, and replication in the target cell of the host (Helferich et al., 2007; Goraya et al., 2017; Gowthaman et al., 2020). For example, gG glycoprotein of ILTV can facilitate the virus entry (Tran et al., 2000) and cell-to-cell spread (Nakamichi et al., 2002) as well as may act as a broad-spectrum viral chemokine binding protein. Moreover, glycoproteins such as gB, gC, gD, gE, gG, gH, gI, gJ, gK, gL, and gM are encoded by highly conserved ORFs viz. UL27, UL44, US6, US8, US4, UL22, US7, US5, UL53, UL1 and UL10, respectively (Piccirillo et al., 2016). The surface gpB antigen showed a high conservancy between the different ILTV isolates in Egypt (Ali et al., 2019; Maha et al., 2020). These glycoproteins are important for the stimulation of both cell mediated and humoral immunity. Two clusters of *Iltovirus* specific genes have been identified; one is located between UL45 and UL22 which encodes 5 ORFs (ORF A-E), while the other is located between UL-1 and ICP4 and encodes UL-0 and UL-1 (Fuchs and Mettenleiter, 1996). ILTV is a linear and double stranded segmented DNA (Lieb et al., 1987). The complete genome sequence of ILTV comprises 148 kb nucleotides encoding long, short, and two inverted repeat sequences (Morales Ruiz et al., 2018). The guanine–cytosine content of ILTV is 48.2% (Lee et al., 2011).

The results of immunofluorescence, virus-neutralization, and cross-protection tests indicated that all ILTV strains are antigenically similar (Shibley et al., 1962), but they differ in their virulence in chicken embryos or in tissue culture (Izuchi and Hasegawa, 1982; Russell and Turner, 1983). Strains of ILTV vary in their virulence from highly virulent wild-type strains which cause high morbidity and mortality rates in a susceptible host to strains of low

virulence that produce mild or sub-clinical infections (Pulsford, 1963; Jordan, 1966). Many techniques, including chicken embryos inoculation (Izuchi and Hasagawa, 1982), restriction endonuclease analyses (Kotiw et al., 1982; Lieb et al., 1987; Guy et al., 1989), and DNA hybridization assays (Kotiw et al., 1986), have been adopted to differentiate ILT viruses with different virulence.

Resistance and sensitivity of the virus

The ILTV survives in deep litter for 3–20 days at 11–24.5°C, in the droppings of battery cages for 3 days at 11–19.5°C, and at least for 3 weeks in buried carcasses. It can survive for several months during storage at 4°C in diluents. Besides, the virus may remain viable for 10 days to 3 months at 13–23°C. The ILTV infectivity remains for months during storage at 4°C in enrichment media such as nutrient and glycerol broths. Moreover, the virus survives at 13–23°C in the tracheal exudate and chicken carcasses for days and months and at –20°C to –60°C for months and years.

On the other hand, the presence of the envelope on ILTV facilitates its inactivation by heat, organic solvents or lipolytic agents such as chloroform and ether, as well as oxidizing agents like H_2O_2 (Meulemans and Halen, 1978; Neighbour et al., 1994; Ou and Giambrone, 2012). ILTV may be destroyed after exposure to 55°C for 15 minutes or to 38°C for 48 hours (Jordan, 1966). Exposure to 3% cresol, 5% phenol, or 1% sodium hydroxide solution can inactivate ILTV in less than one minute (Meulemans and Halen, 1978). The complete inactivation of ILTV in contaminated poultry house equipment could be achieved via fumigation with 5% hydrogen peroxide mist (Neighbour et al., 1994). Besides, the viability of the virus in the litter could be decreased by heating at 38°C for 24 hours (Giambrone et al., 2008).

Susceptibility

Host

Despite the fact that chicken is considered as the primary host for ILTV infection (Bagust, 1986), other host species including peafowls, peacocks, pheasants, guinea fowl, and turkeys are also susceptible to the natural infections (Crawshaw and Boycott, 1982; Hanson and Bagust, 1991; Bautista, 2003; Guy and Bagust, 2003). Ducks are refractory to the infection and act as carriers (Yamada et al., 1980). Pigeons, quail, sparrows, crows, doves, and starlings are resistant to ILTV (Guy and Garcia, 2008). Regarding breeds, rare cases of ILTV infections may occur in hobby/show/game chickens, broilers, heavy breeders, and commercial leghorn hens. Despite vaccination against ILTV, sporadic cases of infections were reported in heavy breeders and leghorns due to errors in the vaccine application or adoption of improper biosecurity measures. It has been reported that a high environmental temperature (35°C) could induce a higher mortality in heavy adult breeds compared with light adult breeds that have ILTV infection (Fahey et al., 1983).

Age

All ages of chicken (8 days to 4 years) are susceptible to ILTV infection (Kingsbury and Jungherr, 1958; Jordan, 1966; Linares et al., 1994). Chickens more than 3 weeks of age are highly susceptible (Dufour-Zavala, 2008). Despite the fact that the disease is common in adult layer chicken flocks (Aras et al., 2018; Tamilmaran et al., 2020), it has been also recognized in 3-week-old broiler chickens (Crespo et al., 2007; Guy et al., 1990; Timurkaan et al., 2003; Sellers et al., 2004; Moreno et al., 2010; Dormitorio et al., 2013; Pitesky et al., 2014).

Infection and transmission

The routes of ILTV entry are the nasal, conjunctiva, oral, and infra orbital sinus of chickens. The active viral replication usually occurs in the epithelium of the trachea and larynx. So, the main routes of ILTV infection are the respiratory tract and eyes (Williams et al., 1992). Oral infection is also possible, but exposure of nasal epithelium should be present following ingestion (Robertson and Egerton, 1981). Wind-borne transmission of ILTV has been demonstrated between commercial poultry operations (Johnson et al., 2005).

The sources of ILTV include clinically infected or latently carrier chickens as well as contaminated fomites, feed and water, bedding, and equipment. Unwashed or disinfected slaughterhouses are rendering vehicles (Pajić et al., 2022).

Despite the spread of ILTV to the non-respiratory sites via leucocytes, no viremia has been detected during infection (Oldoni et al., 2009). The transmission of ILTV frequently occurs through the direct contact between acute or chronic carrier infected chickens and the susceptible ones. Birds surviving from previous outbreaks act as a chronic carrier source of ILTV infection to healthy birds. Infected birds can also shed the virus in their respiratory secretions for 10 days post-infection (Williams et al., 1992). The ILTV-infected birds may transmit the virus via oral secretions (Hughes et al., 1987). The virus may persist in the respiratory tract of sub-clinical or latent infected chickens for up to 6–8 days (Bagust et al., 1986). The long-term tracheal carriers (approximately 2%) have been detected among convalescent birds (Hanson and Hanson, 1984). ILTV can remain latent in the trigeminal ganglia, while stress factors such as egg production or transportation may reactivate it. The reactivated virus could be transmitted from one bird to another causing an increase in its virulence (Dufour-Zavala, 2008; García, 2017). Hence, live attenuated ILTV vaccines are used only in endemic areas to avoid the direct contact between vaccinated or infected chickens or non-vaccinated birds (Ou

and Giambrone, 2012). The latent ILTV infection is usually detected either via isolation on the tracheal organ culture or application of PCR (Bagust, 1986).

It has been found that ILTV may withstand in biofilms of drinking water systems and spread to susceptible birds (Ou et al., 2011). The mixing of vaccinated and non-vaccinated chickens is also important for the direct transmission. Airflow between flocks also helps in spreading ILTV (Ou and Giambrone, 2012). No vertical transmission has been reported (Wolfrum, 2020).

Backyard avian species act as a vital source of ILTV infection for commercial poultry flocks due to viral latency (Ojkic et al., 2006; Neff et al., 2008). Darkling beetles and mealworms are mechanical carriers and living ILTV has been found in them for 42 days following a disease outbreak (Ou and Giambrone, 2012). Direct and indirect contact with respiratory exudates in contaminated litter, equipment, vehicles, feed bags, feathers, dust, footwear, and clothes as well as movement of people are also other routes of ILTV infection (Kingsbury and Jungherr, 1958; Zellen et al., 1984). Dogs and cats fed on infected dead carcasses also help in the spread of the virus (Kingsbury and Jungherr, 1958).

Once ILTV enters the host via its natural portals, it rapidly replicates in the epithelium of the eye, sinuses, and larynx until it reaches the maximum virus titre on days 4 to 6 post-infection and then remains in tracheal secretions between days 6 to 10 post-infection (Hitchner et al., 1977; Robertson and Egerton, 1981; Bagust, 1986; Guy and Bagust, 2003). The virus could be detected in the trigeminal ganglion from two of cytolytic infections onwards (Bagust, 1986; Oldoni et al., 2009) causing severe damage and haemorrhages in the epithelial lining of the respiratory organs (Guy and Bagust, 2003). The replication of ILTV leads to the up-regulation of some genes which are responsible for cell growth and proliferation. With the help of up-regulated cellular proteases, the virus attaches the underlying tracheal lamina propria (Reddy et al., 2014) and then systematically disseminates to the liver, caecal tonsils, and cloaca (Oldoni et al., 2009; Coppo et al., 2013). The production of some cytokines and inflammatory mediators by the infected cells results in intensive oedema with lymphocyte infiltration (Guy and Garcia, 2008; Devlin et al., 2010). The latency of ILTV in the trigeminal ganglion depends on the induction of an effective adaptive immunity (Williams et al., 1992), while the viral reactivation is mediated by thymidine kinase and polypeptide 4 production (Schnitzlein et al., 1995; Han et al., 2002).

Incubation period

Under natural infection conditions, the incubation period of ILTV varies within 6–13 days (Seddon and Hart, 1935), while the intra-tracheal inoculation of the virus results in induction of signs within 4 days (Davison et al., 1989).

Clinical picture

The severity of the clinical signs of ILTV infection varies according to the virulence of the virus, presence of other infections, stress conditions, and the age and immune status of infected birds (Kirkpatrick et al., 2006; Gowthaman et al., 2016). Sporadic cases of ILTV infections in vaccinated flocks have been reported due to vaccination failure or improper application of biosecurity measures (Hidalgo, 2003). Following the acute infection, the virus may remain latent in the trigeminal ganglion of the central nervous system (Hughes et al., 1991; Williams et al., 1992). However, stressors such as laying, shifting, and mixing of flocks can reactivate the virus and stimulate its replication in the tracheal epithelium (Hughes et al., 1989) with a subsequent shedding and transmission to susceptible birds. The clinical course of ILTV infection ranges from 11 days to 6 weeks depending on the clinical form of the disease.

The morbidity and mortality rates of ILT are variable and depend on the virulence and load of the circulating field virus (Devlin et al., 2006; Oldoni et al., 2009), age of the flock, period of the production cycle, vaccination history, as well as concomitant other respiratory infections (Guy and Garcia, 2008) such as mycoplasmosis, colibacillosis, infectious coryza, salmonellosis, Newcastle disease, fowl pox, and other immunosuppressive diseases such as mycotoxicosis, Marek's disease, chicken infectious anaemia, and reticuloendotheliosis (Mohamed et al., 1969; Couto et al., 2016; Abdo et al., 2017; Beltran et al., 2017; Razmyar et al., 2021; Zorman Rojs et al., 2021; Pajić et al., 2022).

Acute epizootic form

It is characterized by a sudden onset, a rapid spread, and a high mortality rate (OIE, 2014). Sudden death has been reported in chickens with a good body condition before the appearance of any clinical disease (Preis et al., 2013). Death usually occurs within 3 days of ILTV infection (Cover, 1996).

Affected chickens with acute ILT show anorexia and severe respiratory distress in the form of dyspnoea, gasping, or rattling (Guy and Bagust, 2003). The most characteristic signs are coughing and expectoration of blood mixed with mucus due to tracheal obstruction with clotted blood and exudates. Therefore, affected chickens show long drawn-out gasps with open-mouthed breathing, high-pitched squawk, extended head and neck, and moist rales (Kernohan, 1931; Jordan, 1958). The clotted blood is found on walls of a farm as well as in cages, feed turfs, and on the floor of poultry houses. Swollen eye lids with oedema, lacrimation, and eye congestion are also common in ILTV infection. Laying chicken flocks may show a drop in egg production or even experience complete cessation of egg production, which may recover to the

normal level (Lohr, 1977). This form of the disease is characterized by a high morbidity rate (90–100%) and a sudden increase in the average daily mortality rate (5% to 70%) with an average of 10–30% for up to 15 days (Seddon and Hart, 1935; Aziz, 2010).

Mild enzootic or chronic form

The silence of ILT is a synonym for a milder form of the disease (Sellers et al., 2004; Garcia et al., 2013). Mild or chronic ILT is similar to other respiratory infections. It is characterized by general unthriftiness, rales, coughing, head shaking, conjunctivitis, sinusitis, drop in egg production up to 10%, and decreasing body weight gain (Hinshaw et al., 1931; Ou et al., 2012). The morbidity rate may go up to 5% and the mortality rate usually ranges between 0.1 and 2% (Bagust et al., 2000; Ou and Giambrone, 2012).

Post-mortem lesions

The most characteristic gross lesion of acute ILT is haemorrhagic tracheitis (Barhoom and Dalab, 2012). The tracheal mucosa and larynx could be congested or cyanotic (Zhao et al., 2013). A yellow cheesy plug of caseous material could also be observed on the larynx, syrinx, and tracheal mucosa (Gowthaman et al., 2014; OIE, 2014). Mucoid tracheitis with or without diphtheritic exudates may be noticed in the tracheal lumen of chronic or mild ILTV infected chickens (Abdo et al., 2017). A pseudo-membrane of fibrino-necrotic exudates can be observed in the upper respiratory tract (Yavuz et al., 2018). Conjunctivitis with almond-shaped eyes (Kirkpatrick et al., 2006; Ou and Giambrone, 2012) and sinusitis (Parra et al., 2016) may also be observed. The lungs and air sac lesions in ILTV infected cases are rare. Nevertheless, lung congestion and caseous air sacculitis have been noticed (Aziz, 2010). Concomitant infections of ILTV with other respiratory pathogens may result in mucoid rhinitis and sinusitis, facial swelling, and muco-fibrinous tracheitis of infected chickens (Couto et al., 2015). Rare cases have shown severe erosive esophagitis and pharyngitis as an atypical ILTV infection in backyard chickens (Sary et al., 2017).

Histopathologic examination

Microscopic lesions of ILTV infection in the trachea have been described as infiltration of epithelia mucosa with lymphocytes, histiocytes, and plasma cells, enlargement of cells, as well as loss of goblet cells and cilia, followed by cell destruction, necrosis, and desquamation (Timurkaan et al., 2003). Haemorrhages may be seen in the necrotic epithelium due to rupture of blood capillaries (Sary et al., 2017). Intranuclear eosinophilic inclusion bodies could be observed in epithelial cells on days 1–5 post-infection and then disappear later due to the denudation of epithelial cells (Guy et al., 1992; VanderKop, 1993; Srinivasan et al., 2012). Inclusions are clusters of viral particles, proteins, and genomes (Preis et al., 2013). Six days post-infection, regeneration with proliferation of the remaining lining epithelium could be detected in surviving chickens during the acute phase (Bagust et al., 2000). The histopathological findings in the bronchi are characterized by epithelium necrosis and degeneration as well as infiltration with mononuclear cells (Preis et al., 2013).

The conjunctiva epithelium of ILTV infected chickens could show swelling, hyperaemia, and infiltration with inflammatory cells, and could be followed by epithelial damage, sloughing, and accumulation of inflammatory exudates containing inflammatory cells and fibrinocellular debris (Aziz, 2010).

It is important to note that the histopathological findings can not differentiate between the lesions caused by ILTV field strains and those caused by the virus vaccine strains which reverted to their virulence.

Diagnosis

The characteristic coughing of bloody mucus, open mouth, gasping, dyspnoea, extended head respiration, conjunctivitis, haemorrhagic tracheitis, and fibrinopurulent membrane in the larynx and trachea are very suggestive for ILT. The confirmation of infection is done by conventional isolation, detection of the virus in the affected tissues, and adoption of recent molecular techniques (Humberd et al., 2002).

Conventional isolation and detection

Tracheal scraping or exudate is the best sample for ILTV isolation (Tripathy & Garcia, 1998). Both cell lines and egg inoculation are used for the primary isolation of ILTV; however, the cell culture cultivation is more rapid and economic than the egg inoculation method (Meulemans and Halen, 1978; Garcia and Riblet, 2001). There are different types of cell cultures that could be used for the primary isolation of ILTV such as chicken embryo liver, chicken embryo lung, and chicken kidney cell cultures (Schnitzlein et al., 1995). Other types of tissue culture including chicken embryo fibroblast, Vero cells, avian leukocyte cultures derived from a chickens' buffy coat (Chang et al., 1977), QT35 or IQ1A quail cells (Garcia et al., 2013), and Leghorn male hepatoma (Schnitzlein et al., 1995) have also been used for isolation of the virus. Both tracheal organ culture and conjunctival organ cultures have been used to study the host-pathogen interaction (Jones and Hennion, 2008). The propagation of ILTV on the tissue culture could be observed as swelling of cells, rounding of the nucleoli, and formation of syncytia. Moreover, the intranuclear inclusion bodies or syncytial cell formation could be detected following cell line inoculation (Hinshaw et al., 1931). The demonstration of specific inclusion bodies in the affected tissues has been shown to be significantly less sensitive than the virus isolation.

ILTV could also be isolated on the chorio-allantoic

membrane of embryonated chicken eggs. Two days post-inoculation, opaque plaques resulting from necrosis and proliferative tissue reactions as well as embryo's deaths could be observed.

The immunofluorescence, immuno-peroxidase, and immunohistochemistry-labeled monoclonal antibodies could be used for the detection of ILTV antigen in the affected tissues or in the trachea or conjunctiva stained smears using immunoprobes (Hitchner et al., 1977; Ide, 1978; Goodwin et al., 1991; Guy et al., 1992; Yavuz et al., 2018; Carnaccini et al., 2022). The immunohistochemistry could be useful in the detection of ILTV infection when classical histologic lesions are absent or inconclusive (Carnaccini et al., 2022). The direct electron microscopic examination has been used for the rapid detection of ILTV from the tracheal scrapings (Hughes and Jones, 1988). Monoclonal antibodies have also been applied to detect a high concentration of the virus in the tracheal scraping using enzyme-linked immunosorbent assay (ELISA) (York and Fahey, 1990).

Serological identification

The agar gel immunodiffusion, virus neutralization, indirect fluorescent, and ELISA tests are used for the demonstration of specific antibodies against ILTV with variable sensitivities (Adair et al., 1985; Bauer et al., 1999).

Molecular detection

The dot-blot hybridization assay and cloned DNA fragments labelled with digoxigenin are rapid techniques that could detect the ILTV DNA in acute and chronic latent infections (Keam et al., 1991; Key et al., 1994). Molecular techniques used for the detection of ILTV DNA are regarded as quick, accurate, and highly sensitive ways for the virus identification. They include dot-blot hybridization, PCR, nested PCR, real-time PCR, multiplex PCR, in situ hybridization (Nagy, 1992; Abbas et al., 1996; Clavijo & Nagy, 1997; Nielsen et al., 1998; Pang et al., 2002; Creelan et al., 2006; Ou et al., 2012), and PCR followed by restriction fragment length polymorphism (Chang et al., 1997; Kirkpatrick et al., 2006; Oldoni and Garcia, 2007; Oldoni et al., 2008). The sequencing analysis (alignment) and the phylogenetic tree of gpB, gpC, and gpG genes of the Egyptian ILTV isolates have revealed that they have a genetic stability and a high degree of identity with the wild-type viruses (Maha et al., 2020). The use of PCR method is recommended for the definitive diagnosis of ILTV infection, particularly in the absence of typical patho-morphological lesions (Shirley et al., 1990; Williams et al., 1994). The PCR is more sensitive than the virus isolation, and the real-time PCR method has been successfully used for the final diagnosis of the disease (Oldoni et al., 2008; Preis et al., 2013). Recently, a loop-mediated isothermal amplification has also been considered as a highly specific and sensitive method for the detection of ILTV DNA. This assay is suitable for the basic diagnostic laboratory detection in the field, while real-time PCR is used for further verification.

Differential diagnosis

ILT should be differentiated from other similar viral respiratory infections such as Newcastle disease, avian influenza, infectious bronchitis, adenovirus, and fowl pox using molecular techniques (Davidson et al., 2015). Some tests are used for differential diagnosis such as the agar gel immune diffusion technique using an ILTV hyper-immune serum.

The immune response

Following ILTV infection, different several types of immune responses could be evolved (Jordan, 1981). The neutralizing antibodies could be detected within 5–7 days post-infection, reach the peak at 21 days, and then decline to low levels over a year (Hitchner et al., 1958; York et al., 1989). In vaccinated chickens, a substantial increase in the number of immunoglobulin (Ig) A and Ig G-synthesizing cells could be detected in the trachea on day 3 post-vaccination with a significant increase in IgA-cells on day 7 (York et al., 1989). The secretory mucosal IgA protects the respiratory tract epithelium and elicits a local immune response.

The cell-mediated immune response to ILTV infection has also been demonstrated. Bursectomised chickens without specific antibodies were protected from ILTV challenge post-vaccination (Fahey et al., 1983) through the transfer of histocompatible immune lymphoid cell cells (Fahey et al., 1984). It has been reported that antibody titers against ILTV could not correlate with the resistance to the infection (Shibley et al., 1962; Jordan, 1981). Moreover, the principal mediator of ILVT resistance is the cell-mediated immunity in the trachea (Fahey and York, 1990).

The maternal derived antibodies against ILTV could not protect chicks against infection or even interfere with the vaccination (Fahey et al., 1983). Natural infection of chickens older than 2 weeks or vaccination may provide birds with a full protection against ILTV challenge (Hitchner, 1975).

Intervention strategies for prevention and control

ILT is an important viral respiratory disease which has been included within the list E of OIE. Once ILTV infection is confirmed in a certain area, strict measures should be adopted to prevent the spread of the virus in the infected and endangered areas. For the eradication of ILT, the implementation of a strict control programme and the cooperative effort of government agencies, laboratories, poultry producers and companies, and veterinarians are the must (Dufour-Zavala, 2008). The control measures

are mainly based on the definitive diagnosis, adoption of strict biosecurity measures, and vaccination (Mallinson et al., 1981; Guy and Garcia, 2008). The application of good biosecurity measures on farms can prevent ILT. A geographic information system can provide information about biosecurity plans, quarantines, vaccinations, and ILTV outbreak sites (Dufour-Zavala, 2008). Also, a vaccination strategy is essential to prevent the spread of ILTV infection. An appropriate regulatory agency should be contacted to determine the approved vaccines and the vaccines application procedures.

Biosecurity

The eradication of ILTV from intensive poultry production areas appears to be an effective process due to several factors including host-specificity, fragility, and antigenic stability of the virus. The high levels of strict biosecurity measures including quarantine, restriction of workers, equipment, feed, vehicles, and bird movement, litter decontamination, thorough cleaning and disinfestation, and extension of downtime between subsequent batches should be properly adopted. Moreover, the entrance of free-living backyard and fancy birds, pet animals, and rodents to the flocks should be prohibited (Mallinson et al., 1981; Volkova et al., 2012). Further, dead carcasses should be hygienically disposed.

Herbal treatment

Some herbal treatments have shown efficacies against ILTV infections. For instance, a product containing Almond, Gypsum fibrosum, Herba ephedrae, Radix astragali, and Radix glycytthizae has shown an antioxidant activity and enhanced the mucosal immunity against ILTV infection through IgA production (Cheng et al., 2011). Besides, a concentration of Chinese herbal mixture has been reported to decrease the concentration of ILTV in the infected chickens' tissues with a development of mucosal immunity following 72 hours post-infection (Zhang et al., 2018).

Vaccines

ILT was the first viral disease of poultry in which the virulent virus vaccine was administrated via cloaca (Gibbs, 1934; Coppo et al., 2013). The ILTV strains are antigenically homogeneous, so a single vaccine can induce a cross-protective immune response to all ILTV strains.

Live attenuated vaccines

Since 1960s, live attenuated ILTV vaccines have been developed either from chicken embryo or tissue culture origins and they have been extensively used for controlling ILTV outbreaks all over the world (Samberg et al., 1971; García, 2017; Garcia and Zavala, 2019). These types of vaccines are used to prevent infections and also, during the outbreaks, to control the spread of the virus and shorten its duration (Lee et al., 2011; Vagnozzi et al., 2012). Moreover, they elicit the protective immune response by producing a mild tracheal infection without induction of a disease condition (Fulton et al., 2000). The tissue culture-derived vaccines are more attenuated and less immunogenic than the vaccines of chicken embryos origin or recombinant types (Andreasen et al., 1990; ElSaied et al., 2022). The tissue culture-derived vaccines are commonly used in layer and breeder chicken flocks. In the USA, the ILTV vaccines derived from chicken embryo have successfully prevented several outbreaks in broiler flocks (Vagnozzi et al., 2012).

However, ILTV in the live attenuated vaccine has the ability to spread from vaccinated to non-vaccinated chickens (Hilbink et al., 1987). The in-vivo passages of ILTV may result in a reversion to its virulence causing outbreaks of ILT (Guy et al., 1991; Dufour-Zavala, 2008; Blacker et al., 2011; Chacon et al., 2015) or a disease condition in non-vaccinated chickens due to insufficient attenuation of the virus (Perez-Contreras et al., 2021). Moreover, vaccination could induce infected chronic carriers which may be persisted as a source of ILTV infection to non-vaccinated neighbouring flocks (Bagust, 1986). Besides, the latent virus in the live vaccine may undergo reactivation, shedding, and spread to susceptible birds so that the occurrence of new outbreaks of ILT in several parts of the world may be due to the massive use of live attenuated vaccines. The direct contact between vaccinated or infected chickens and non-vaccinated chickens helps in the transmission of the virus infection (Ou and Giambrone, 2012). A prolonged ILTV infection has been reported following the extensive vaccination with a live attenuated vaccine of the chicken embryo origin (Garcia, 2016). Therefore, it is recommended to use these types of vaccines in geographic endemic areas only.

The ILTV vaccines are usually given to chickens at 6 to 8 weeks of age, followed by a booster dose in 12 to 15 week-old layers and breeders. It is recommended to use a live attenuated ILTV vaccine of chicken embryo origin at 35 weeks of age than using a tissue culture or a recombinant type to obtain better protection (Palomino-Tapia et al., 2019). The ILTV vaccination is not recommended for broilers due to economic concerns (Giambrone et al., 2008). The maximum protective level of immunity is obtained at 15 to 20 weeks post-vaccination and it may last over a year (Neff et al., 2008). There is no interference between the ILTV vaccine and the other vaccine when the interval between both is more than 2 weeks (Aston et al., 2019). The live attenuated vaccines can induce a good immune response when they have been given through the intranasal (Shibley et al., 1962) or eye drop (Sinkovic and Hunt, 1968) instillation and orally through drinking water (Samberg et al., 1971).

It is advisable to apply ILTV vaccines using the eye drop technique which is safer and gives more protection than the drinking water method (Raggi and Lee, 1965). However, the administration of ILTV vaccines through the drinking water method may result in non-homogeneity and failure of some chickens to develop protective immunity (Robertson and Egerton, 1981). In addition, the spray route of vaccination may show adverse reactions due to insufficient attenuation of the virus and the deep penetration of the small droplets size particles into the lower respiratory tract (Purcell and Surman, 1974), or using of excessive dose (Clarke et al., 1980).

Recombinant vaccines

Recently, recombinant vector vaccines do not transmit from chicken to chicken, decrease the severity of clinical signs, are safe and very stable, and do not revert to their virulence. However, they are not as effective as live attenuated ILTV vaccines in reducing the shedding of the virus (Garcia, 2017; Maekawa et al., 2019). Despite the safety of recombinant ILTV vaccines, they have shown a limited practical application due to their failure to stop the virus shedding as well as the neutralization of the virus vaccines by antibodies against the vector. The first application of a DNA recombinant ILTV vaccine was by Keeler et al. (1995) when intramuscularly vaccinated chickens with DNA encoding glycoprotein B showed a high level of protection in comparison with vaccinated chickens with live attenuated ILTV vaccines. In addition, the results of Gamal and Soliman (2023) have revealed that the developed ILTV DNA vaccine coding for the surface gpB could elicit potent antibody titers which are positively correlated with those of the live tissue culture-propagated vaccine as well as with an increase in the production of interferon-γ gene transcript compared with the live vaccine. Similar results have been obtained by Shahsavandi et al. (2021). Therefore, the ILTV DNA vaccines may exhibit several advantages including the long-persisted immunogenicity, induction of both humoral and cell-mediated immune responses, lack of the risks of infection or the vaccine virus replication, and absence of the possibility to revert to the virulent status with a consequence of later outbreaks (Guy et al., 1990, 1991; ElSaied et al., 2022).

In the areas with high incidences of virulent ILTV infections, it is recommended to administrate a recombinant vaccine in the hatchery accompanied by live attenuated vaccines during the production period to enhance the immune response (Maekawa et al., 2019). The immune protection can be obtained within a week following the administration of live attenuated vaccines, while this period is 4 weeks for recombinant vaccines. The role of the cell-mediated immunity against ILTV is more significant than the humoral immunity (Ou and Giambrone, 2012). The local immune response in the trachea is the principal mechanism in the defence against this infection (Garcia et al., 2013). The recombinant / subunit herpesvirus of turkey (HVT) (rHVT-LT) and the live attenuated chicken embryo origin vaccines against ILTV are commercially used (Vagnozzi et al., 2012; Maekawa et al., 2019). This type of ILTV vector vaccine has the ability to completely prevent the viral shedding after a challenge with the virulent virus strain (Catalina et al., 2021). Moreover, the produced recombinant vaccines using HVT or fowl pox virus (FPV) as a carrier for ILTV glycoproteins B and D could provoke protective immunity in vaccinated chickens (Garcia, 2017). The FPV vector vaccine carries gpB and UL32 g genes of Gallid herpesvirus 1 (FPV-LT) (Davison et al., 2006), but the HVT vector vaccine carries gpD and gpI of the virus coat that provides immunity against both Gallid herpesvirus 1 and Marek's disease (HVT-LT) (Bublot et al., 2006). A vaccination with a subunit ILTV vaccine made of a 205 kDa complex containing gpB has been reported to give a 100% protection against the development of the clinical disease and the virus replication (Chen et al., 2010, 2011)

However, the HVT vector vaccines could not reduce the virus shedding as much as the live vaccines (Johnson et al., 2010; Esaki et al., 2013). Therefore, priming vaccination with rHVT-LT followed by using a live attenuated vaccine (chicken origin) may reduce the circulation of the virus during a long term application (Maekawa et al., 2019). This combined vaccination strategy provides a safer alternative than the uninterrupted use of only living attenuated vaccines of chicken embryo origin. Both types of vector vaccines could be applied via inoculation of 18-day-old chicken embryos in-ovo or subcutaneous injection of one-day-old chicks. Moreover, the FPV vaccine can be applied though the intradermal wing web method (Menendez et al., 2014).

Many outbreaks of ILT have occurred in some regions, such as Egypt and Australia, due to the exchange of the genetic material resulting in recombination between the vaccine strains with high transmission rates. The virulent recombinant strains of Gallid herpesvirus 1 have been isolated in many Australian outbreaks (Lee et al., 2012). Some outbreaks have been reported in Egypt between 2007 and 2010, and the ILTV strains were related to the used strains of the live attenuated vaccines that revert to their virulence through bird-to-bird transmission (Shehata et al., 2013). Additionally, the gD, gG, gJ, and ICP4 gene have been characterized from 5 prototypes of ILTV strains in the Egyptian outbreaks between 2018 and 2019 (Bayoumi et al., 2020). According to phylogenetic analysis of ICP4 and gJ, these 5 strains were further genotyped into recombinant ILTV strains (3 prototype strains) and live attenuated vaccine-like ILTV strains (3 prototype strains) (Bayoumi et al., 2020; El-Saied et al., 2021). Interestingly, the outbreaks caused by

recombinant vaccine strains could be more severe than those produced by live attenuated vaccine-like strains. Besides, the pre-existence of antibodies against vectors could neutralize the virus vaccines, particularly in endemic areas (Tong et al., 2001).

Conclusion

Despite the adoption of strict biosecurity measures and administration of different vaccines against ILT, the disease still causes serious economic losses especially in endemic areas. Therefore, the development of genetically modified/engineered protective vaccines against ILT is essential for the eradication programme and the avoidance of latent infected carrier chickens. The enhancement of DNA vaccine efficacy and the development of a practical cost-effective application of this technology will be required before its acceptance by the poultry industry.

Conflict of Interests

The author declares that there is no conflict of interest.

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