Review

Effect Newcastle Disease on poultry due to high morbidity and mortality rates

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Newcastle disease (ND) is an important infectious disease of the poultry that is caused by virulent strains of Avian Paramyxovirus - 1, which is a single strand non segmented negative sense RNA virus. The virus belongs to family Paramyxoviridae and it has 10 serotypes designated as APMV-1 to APMV-10. The Newcastle disease virus (NDV) is endemic in many countries of the world. The first outbreak of Newcastle disease was observed at Newcastle during 1926. Later, it was found in various parts of the world. NDV spreads mostly by the direct contact between healthy and diseased birds or also by the excretions of infected birds. This disease can vary in nature from mild to severe depending upon the type of the virus. NDV can infect both domestic and wild birds. This disease can have a devastating effect on poultry due to high morbidity and mortality rates. In unvaccinated chickens, the morbidity and mortality rates may reach up to 100% each, depending upon the virulence of the NDV. Live virus vaccines and killed oil based vaccines are used in many countries to prevent the disease in chickens. Despite the extensive use of vaccines, outbreaks are continuously occurring in various parts of the world resulting in huge losses since few years. Moreover, extensive use of vaccines has made the situation favorable for genetic modification of the pathogenic virus. Keeping these issues in mind, future challenges are highlighted in detail.

Key words: Newcastle disease, vaccines, outbreaks, genetic modification, avian paramyxovirus-1.

INTRODUCTION

Newcastle disease (ND) is one of the most important viral diseases (Orsi et al., 2010). It is an acute infectious viral disease of domestic poultry and other species of birds regardless of variation in sex and age (Alexander, 2003; Haque, 2010; Iram et al., 2013). ND causes huge economic losses to the commercial poultry farmers round the world (Aldous et al., 2003; Qin et al., 2008; Diel et al., 2012). Etiological agents of ND are virulent strains of avian paramyxovirus - 1 (Qin et al., 2008; Yu et al., 2001; Choi et al., 2010). The disease is characterized by respiratory, nervous system impairment, gastrointestinal and reproductive problems (Nanthakumar et al., 2000; Tiwari et al., 2004). Newcastle disease is commonly known as Ranikhait disease in India (Narayanan et al., 2010; Ravindra et al., 2009) and also in Pakistan.

Newcastle disease virus (NDV) has a wide host range, including approximately 241 species of 27 orders, out of known 50 orders of birds (Madadger et al., 2013). More commonly affected species include chickens, turkeys, ducks, pigeons, (Zhang et al., 2011) guinea fowl, Japanese quail and many wild birds of all ages (Nanthakumar et al., 2000). The most susceptible avian species to this disease are chickens (Rezaeianzadeh et al., 2011) and also some mammals like humans, cats and dogs. During the last 40 years, paramyxoviruses were isolated from different animals (Miller et al., 2009).

In several developing countries, ND is endemic and has greatest impact on villages where people’s livelihood depends upon poultry farming (Mohamed et al., 2011; Rezaeianzadeh et al., 2011). APMV-1 viruses circulating
in poultry flocks are being characterized (Munir et al., 2012). ND is fatal and still top ranked poultry disease. Annual losses caused by this disease worldwide are in millions of dollars (Waheed et al., 2013; Susta et al., 2010).

ND is an economically important disease and also a major threat to poultry industry (Narayan et al., 2010). According to variation in strains of NDV, the rate of mortality and morbidity in a flock (Haque et al., 2010) varies from 90-100% (Nanthakumar et al., 2000) along with decrease in egg production (Choi et al., 2010).

Due to the severe nature of Newcastle Disease and the related consequences, NDV is included in “LISTED” agents (reportable disease) by Office International des Epizooties (OIE) (Aldous and Alexander, 2001; Boynukara et al., 2013). Notification is required by OIE of any outbreak of ND (Cao et al., 2013), when it meets certain criteria of virulence (Cattoli et al., 2011; Munir et al., 2012).

**EPIDEMIOLOGY**

The epizootics of Newcastle Disease in poultry continue to occur in Asia, Africa, Central and South America while in Europe, sporadic epizootics occur (Naveen et al., 2013). ND is reported consistently from all continents of the globe (Munir et al., 2012).

Major panzootics of ND have been recorded from different parts of the world. The very first panzootic started in 1926 in Southeast Asia from Java, Indonesia and in Europe from Newcastle-upon-Tyne, England (Seal et al., 1995; Arfin et al., 2011), and it remained till late 1950s (Qiu et al., 2011). The second panzootic began in Middle East in late 1960s and spread to other countries till 1973.

The third drastic panzootic caused by neurotropic form of NDV, termed pigeon paramyxovirus type 1 virus, appeared in Middle East about in the late 1970s. In 1981, ND reached Europe then spread rapidly throughout the globe (Mase et al., 2002). The latest and fourth pandemic emerged by late 1980s in Far East, South Africa, and Europe (Qiu et al., 2011). A sporadic form of Newcastle Disease exists in Pakistan throughout the year; only a limited number of outbreaks are reported annually (Munir et al., 2012a). In Southeast Asia, it is endemic and a cause of huge economic losses to commercial poultry (Munir et al., 2012b).

During 2012, severe outbreak of ND occurred in Jallo Wildlife Park in Lahore, Pakistan, caused by APMV 1 serotype. Within a week, it took the lives of approximately 190 peacocks with a 100% mortality rate and 50% loss of the susceptible birds. Isolation of virus and serological diagnostics, such as HI Test, ELISA and molecular diagnostic tests like real time PCR confirmed the presence of velogenic Newcastle Disease Virus (Munir et al., 2012c).

**ECONOMIC IMPACT**

Proteins are a significant part of balanced human diet. There are mainly two proteins sources which are Animals and Plants. In developing countries, human diet is deficient in the animal proteins; approximately 66% population has protein deficient diet (Maqbool, 2002). A single person per day requires 102.7 g protein, while only 69.61 g protein is used by a person per day. The main animal protein sources are mutton, beef, poultry meat, eggs, and milk (Maqbool and Bakhsh, 2007). White meat’s essential nutrients are same as red meat, but white meat has the advantage of containing less cholesterol and saturated fat. In most developing countries, meat is a very important protein sources in diet of people because it is affordability and has high quality protein (Thomazelli et al., 2012). In developing countries, the broiler meat is the cheapest source of animal protein. Availability of egg is increasing at rate of round about 4% annually (Numan et al., 2005).

Poultry production was started as a cottage industry in many developing countries of the world. The production and management for disease control measures were not sufficient because of the lack of scientific knowledge. In Pakistan, approximately 1105.91 million poultry birds are present, from which rural poultry is about 152.44 millions. In village economy, it plays vital role with the contribution of about 3611 million eggs and 100.42 metric tons of the total poultry meat (Khan et al., 2010).

Recent studies by Pakistan Economic Survey (2011-2012) reported that poultry sector generates income and direct and indirect employment for about 1.5 million people till 2012. Its contribution in agriculture is 6.40% and in livestock 11.50%. In total, meat production of country and poultry meat contributes 25.8%. Poultry sector has rapid growth of about 8-10% every year, which shows its inherent potential. According to currently conducted survey, the present investment in the Pakistan poultry industry is about Rs. 200.00 billion.

ND and avian influenza (AI) are major concerns of animal husbandry due to hazardous infections (Ge et al., 2012). All over the world, poultry industry is facing severe economic losses with every passing year (Haque et al., 2010; Khan et al., 2011).

**ETIOLOGY**

According to taxonomy of virus, NDV belongs to order Mononegavirales, family Paramyxoviridae and subfamily Paramyxovirinae (Cattoli et al., 2011). The subfamily is divided into five genera: Mor-billivirus, Respirovirus, Henipavirus, Rubulavirus, and Avulavirus (Miller et al., 2009); all the avian paramyxoviruses APMVs are part of genus Avulavirus. The virus exists in 10 serotypes; APMV-1 to APMV-10 (Waheed et al., 2013), but all NDV isolates belong to serotype 1 (APMV-1). APMV-1 is
synonymous with NDV (Cattoli et al., 2011; Miller et al., 2009). Virions are roughly spherical; 150 nm or more in diameter and filamentous (Catroxo et al., 2011). The genome is about 15.2 kb in length (Cao et al., 2013; Zhang et al., 2012) that codes for six structural and two non-structural proteins (Choi et al., 2010). ‘Rule of six’ should be followed by genome because it should be of polyhexameric length to replicate rapidly. It encodes for six proteins in 3’ to 5’ direction; these are Nucleoprotein (NP), Large RNA polymerase (L), Fusion (F), Hemagglutinin Neuaminidase (HN), Matrix (M) and phosphor-protein (P) (Linde et al., 2011; Al-habeeb et al., 2013). The proteins W and V are additionally created within the P gene during transcription of mRNA at editing site by insertion of guanines (Linde et al., 2011; Qiu et al., 2011).

In virus particles, NP is the most abundant protein which provides the NDVs core helical nucleocapsid structure. NP is the main regulator in replication of viral genome (Kho et al., 2004). The genomic RNA is associated with NP, P and L proteins to form RNP complex, which serve as template for RNA synthesis (Kho et al., 2003). NP is found to be highly immunogenic, as it induces antibody responses in chickens (Ahmad-Raus et al., 2009).

During a field study in Pakistan, 5% of the field isolates were reported as velogenic, 55% as mesogenic and 40% as lentogenic (Waheed et al., 2013). For chickens, different strains of NDV have great variation in pathogenicity. On the basis of clinical signs in infected chickens, strains of NDV are grouped in to five pathotypes: 1) Asymptomatic enteric: a form that has subclinical enteric infection without clear symptoms; 2) Lentogenic: virus present with the mild respiratory infections; 3) Mesogenic: virus presents with rare nervous and respiratory signs while mortality rate is related with the age of susceptible birds (young birds are more susceptible as compare to adults); 4) Viscerotropic velogenic: virus cause haemorrhagic intestinal lesions it is highly pathogenic; 5) Neurotropic velogenic: virus cause high mortalities followed by respiratory and nervous signs (OIE, 2012).

The NDV isolates are differentiated on the basis of in-vivo estimation of pathogenicity (Pham et al., 2005). These in-vivo tests are mean death time (MDT) in SPF embryonated eggs of chicken, Intracerebral pathogenicity index (ICPI) in 1 day old SPF chicks, and Intravenous pathogenicity index (IVPI) in six weeks old SPF chicks (Wise et al., 2004; Adi et al., 2009; Mohamed et al., 2011). The MDT classifies ND virus strains into the groups: velogenic (takes less than 60 h to kill); mesogenic (takes from 60 to 90 hto kill); and lentogenic (takes more than 90 h to kill). The ICPI classifies ND virus strains by giving indices scores from 2.0 to 0.0. The maximum score of 2.0 is given to most virulent ND virus strain while lentogenic strains are given score close to 0.0. The IVPI classifies the ND virus strains from lentogenic to velogenic. Lentogenic strains and some mesogenic strains have IVPI values of 0.0, whereas the maximum IVPI indices for a virulent strain is 3.0 (OIE, 2004).

MOLECULAR BASIS OF PATHOGENICITY

The genome of NDV encodes for six major structural proteins. Viral replication, transcription and translation occur in the cytoplasm of the host cell, while virus particles are assembled in plasma membrane by budding (Zanetti et al., 2003). Important pathogenic marker of NDV exists in F protein (Madadgar et al., 2013). Disulphide linkage is present between F1 and F2. These proteins enable the virus to attach to the host cell membrane (Wen et al., 2007). At cleavage site, F0 protein has two pair of basic amino acids that can be cleaved by the host proteases (Pham et al., 2005). Highly virulent NDV has three or more basic amino acids, which are lysine (K) or arginine (R) present at 113 - 116 residues and phenylalanine (F) at position 117 (OIE, 2012). Cleavage of F0 protein is due to the presence of these basic amino acids in virulent NDV (Boostani et al., 2013). It has been found that avirulent viruses have 112G/E-K/R-Q-G/E-R-L117 and virulent viruses have 112R/K-R-Q-K/R-R-F117 amino acid sequence at cleavage site (Pham et al., 2005). Most of the pathogenic APMV-1 viruses for chicken have sequence 112R/K-R-Q/K/R-F116 (Choi et al., 2010). Office of International Epizootics (OIE) accepts F cleavage sequence as determinant of primary virulence (Wise et al., 2004). However, if this cleavage sequence is not found, then an Intra Cerebral Pathogenicity Index (ICPI) is required for determination of the virulence.

TRANSMISSION

NDV can infect more than 240 species of birds and it spreads primarily through direct contact between healthy and infected birds. The disease transmits through droppings and secretions from the nose, mouth and eyes of infected birds. The disease spreads by contaminated water, feed and transport. Airborne transmission of the virus is also an important route of transmission for ND (Li et al., 2009).

Mechanical transfer of infected faeces occurs by rodents, insects, dogs, fleas, or scavenging animals (Ullah et al., 2004). Infection takes place by virus inhalation, ingestion or by contact with conjunctiva. The disease may vary from subclinical with no mortality to severe infection, with 100% mortality.

SIGNS AND SYMPTOMS

Clinical signs are dependent on factors such as the virus strain, host species, age of the host, co-infection with
other micro-organisms, environmental stress, and immune status (Al-Habeeb et al., 2013). In chickens, the general symptoms are loss of appetite, listlessness, abnormal thirst, weakness, drop in egg production, air sacculitis, tracheitis and conjunctivitis. Respiratory signs can include sneezing, gasping for air, nasal discharge and coughing, whereas a clear intestinal symptom is a greenish watery diarrhea. Nervous symptoms may consist of paralysis of wings and/or legs, twisting of head and neck or complete paralysis (Bhaiyat et al., 1994). Layers show drop in egg production and misshapen soft egg shells (Hadipour et al., 2011). In acute and severe cases (like neurotropic velogenic strain), death is very sudden and birds die without showing any clinical signs. Dead birds have hemorrhagic or necrotic lesions in mucosa of intestine, cecal tonsils, proventriculus and gizzard. Swollen kidneys and deposition of urates are also common lesions.

**DIAGNOSIS**

Rapid and accurate diagnosis of ND outbreak is important because it clinically resembles highly pathogenic avian influenza (AI) (Khan et al., 2010). Clinical diagnosis based on history, signs and lesions may establish a strong index of suspicion but the laboratory confirmation must be done. Hemagglutination and hemagglutination inhibition test, virus neutralization test, Enzyme linked immune-sorbent assay, plaque neutralization test and reverse-transcriptase polymerase chain reaction (RT-PCR) can be used for confirmation of the ND virus (Chaka et al., 2013). Now RT-PCR is the most exclusively used method to detect AIVs and NDVs (Liu et al., 2011; Haque et al., 2010; Wakamatsu et al., 2007). RT-PCR assay is more sensitive, specific and less labor intensives as compare to other conventional methods used for lab diagnoses such as virus isolation, Immuno-Fluorescence Staining, Neuraminidase Inhibition and ELIZA (Tang et al., 2012; Shahzad et al., 2011). Using modern technologies, new diagnostic techniques are being developed for identification and differentiation of NDV strains (Rezaeianzadeh et al., 2011). Other molecular diagnostic tests like real time PCR and nucleotide sequence analysis are also important in viral disease diagnosis (Shabbir et al., 2012; Shah et al., 2011).

**PREVENTION AND CONTROL**

Vaccines are being used to control and prevent ND. Currently, many inactivated and live ND vaccines are available around the world (Shim et al., 2011; Xiao et al., 2013). Chickens and turkeys are immunized against New-castle disease. Live virus vaccines are administered by variety of routes and schedules from hatching till grow-out (Cho et al., 2008). Killed virus oil emulsion vaccines are administered parentally prior to the onset of egg production. Although proper vaccination protects the birds from clinical disease but it does not prevent virus replication and shedding, which results in a source of infection (Chukwudi et al., 2012).

Therefore, the prophylactic vaccination is not used in developed countries (OIE, 2012). In developing countries, there is wide use of vaccines on commercial flocks (Munir et al., 2012b). Anti NDV antibody titers of flocks are continuously monitored and flocks are revaccinated to maintain the protective antibody titers. The breeders and layers are vaccinated against NDV and oil based vaccines are being used prior to onset of egg production for long term immunity (Nadeem et al., 2004). Anti NDV antibody titers of breeder flock is also important to maintain the anti NDV maternal antibody titers of progeny. These maternal antibodies protect chicks from the disease during the first week of life. In spite of extensive vaccination, outbreaks are continuously occurring (Shabbir et al., 2012). To overcome this problem poultry producers are using different com-binations of live and killed vaccines in a flock.

Good biosecurity measures are essential to prevent Newcastle disease in poultry flocks. Commercial flocks should not have any contact with domesticated poultry or wild birds or any pet birds. Workers should avoid contact with birds outside the farm. Biosecurity measures include bird-proof houses, feed and water supplies, minimizing travel on and off the facility, disinfecting vehicles and equipments that enter the farm. Pests such as insects and mice should also be controlled. If possible, employees should shower and change into dedicated clothing prior entry into the poultry farm.

**PUBLIC HEALTH**

Humans are among the many species that can be infected by NDV in addition to avian species. NDV may cause conjunctivitis in humans, when a person has been exposed to large quantities of the virus (Alexander, 2000). Mostly, Laboratory workers and vaccinators are affected.

The use of personnel protective equipment and biological safety cabinet has reduced the exposure of laboratory workers. Infection is rarely seen in the workers of a farm; moreover persons handling or consuming poultry products do not appear to be at risk (Nolen, 2003).

The conjunctivitis usually resolves rapidly, but the virus will be shed in the ocular discharges from 4 to 7 days. In some cases, mild, self limiting influenza like disease with fever and headache has also been reported in humans (Alexander, 2000; OIE, 2012). There is no evidence found to support human to human transmission but the potential for human to bird transmission exists (Alexander, 2000; David and Daniel, 2003).
FUTURE CHALLENGES

The Newcastle disease virus has not been studied for its evolutionary origin among various outbreaks time to time. Most of the research work was focused on immunological properties of the virus rather than the genomic properties. Further, the extensive use of vaccines makes the situation more favorable for genetic modifications in pathogenic strains. Therefore in International interest, it is essential to address these issues by conducting research on the following lines: 1) Isolation and molecular characterization of velogenic strains of NDV; 2) complete genome sequence analysis of different NDV isolates for further studies of epidemiology, vaccinology and evolutionary origin; 3) existing real time PCR assays should be validated and measures should be devised for prevention and control of epidemics in future.

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