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Dynamics of Marek's disease in poultry industry

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Abstract
Marek's Disease (MD) is a highly contagious disease of poultry birds and readily spread from one bird to another. The MD Virus (MDV) has the tendency to survive in the litter for long periods of time and yet retaining its pathogenicity, thus creating outbreak at any point of time and causing huge losses to the poultry farmers. This property of MDV makes it utmost important to understand the disease dynamics of MD in the form of its epidemiology information allied to prevalence, outbreaks, morbidity, mortality and surveillance. Commercial poultry farming is totally based on the economic considerations and hence the mortality leads to huge economic losses, thus studying economic impact is also concerned with the dynamics of disease. The dynamism in serotypes of the virus makes the vaccines ineffective and leads to the frequent outbreak of disease. Therefore, the biological and molecular identification of the changing serotypes may lead to the effective control of the disease which will lead to economic stability among poultry farmers.

Keywords: Economic impact, epidemiology, Marek's disease, mortality, poultry

Introduction
Nowadays one of the fastest growing agribusiness in India is poultry production, an efficient and relatively low carbon-footprint means of producing the additional animal protein required for escalating human population [1]. India is the world's third largest egg producer [2], but infectious diseases impede its sustainability. Marek's disease (MD), a lymphomatous and neuropathic viral disease of fowl, accounts for about $1-2 billion annual economic loss to this industry [3]. Marek's disease virus (MDV), belongs to genus Mardivirus, alphaherpesvirinae subfamily of family Herpesviridae, is enveloped, icosahedral and single linear double standard DNA virus. Gallid herpesvirus-2 [serotype 1; all pathogenic (*i.e.* cell associated and oncogenic) strains and its attenuated variants], Gallid herpesvirus-3 [serotype 2; avirulent and non-oncogenic strains] and Meleagrid herpesvirus-1 [serotype 3; avirulent herpesvirus of turkeys] are well-established three serotypes of MDV [4]. It may occur in acute MD form, classical MD (neural form), ocular form (Grey or pearl eye), Cutaneous **(**red leg syndrome**),** transient paralytic and muscular form [5].
Major complications associated with acute MD are marked enlargement of spleen, liver, kidney, proventriculus, lung and gonad with diffuse lympomatous involvement while enlargement of peripheral nerve such as brachial and sciatic nerve observed in classical MD which in turn consequence to spastic paralysis of wings and legs (Split leg stance or Athletic foot syndrome). Ocular form (blindness) observed in poultry due to mononuclear cell infiltration in iris [6]. Oncogenic transformation of T cells, involvement of lymphoid tissues, peripheral nerves and visceral organs and complex pathogenesis usually leads to death of the affected birds [7].
The transmission of MDV occurs by direct or indirect contact, apparently by the airborne route. The epithelial cells in the keratinising layer of the feather follicle replicate fully infectious virus, and serve as a source of contamination of the environment. It may survive for months in poultry house litter or dust. Dust or dander from infected chickens is particularly effective in transmission. Once the virus is introduced into a chicken flock, regardless of vaccination status, infection spreads quickly from bird to bird [8].

MDV infectious life cycle in resistant birds
Infection in naïve birds occur *via* inhalation of dust and skin dander contaminated with virus. Primary infection occurs when virus breaches the mucosa barrier of respiratory tract and enters into the epithelial cells.

Due to virus replication at local site brings inflammatory response due to early gene transcription leading to viral interleukins (v-IL) formation. Inflammatory response activates innate immune response in which virus particles are taken up by macrophages. Due to infiltration of B cells, these cells also get infected and leads to lytic cycle of virus. Virus infected B cell secrete v-IL that acts as chemotactic factor for T cells and virus gains access to T cells. Virus replication causes B cell and T cell apoptosis ultimately causing immunosuppression. MDV integrates specifically into the genome of CD4+ T cells enabling escape from immune detection and initiates latent viral infection. Early latently infected and activated CD4+ T cells migrate to cutaneous sites of replication namely feather follicle. Infection of feather follicle epithelium enables fully productive viral replication. Infection of feather epithelium leads to secretion of mature virion in skin danders and dust that act as the major source of infectious materials. Horizontal transmission is the only recognized form for environmental persistence and infection in field conditions [9].

Epidemiology

Marek's disease (MD) is a ubiquitous viral infection that predominantly occurs in domestic chickens throughout the world. The infection in other species is often rare; however this disease has also been reported in turkeys and quails. The infection is rampant and spreads rapidly within the first few weeks of life amongst the birds reared in commercial chicken hatcheries. Conversely, the delayed infection may be witnessed in some instances [10]. The prevalence of more than one MDV strain *i.e.* serotype 1 viral strains with varied pathogenicity and avirulent serotype 2 strains in the poultry houses, worsens the situation [11].

According to the annual report of Department of Animal Husbandry, Dairying and Fisheries (2015-16), there were 14 outbreaks of Marek's Disease affecting 9,32,000 birds [12]. During 2016-17, 9 outbreaks were reported in which a total number of 75,451 birds were infected [13]. Jayalakshmi and Selvaraju (2016) performed a cross sectional study to assess the epidemiological factors of the disease in 12 different layer flocks of white leghorn breed commercially reared in the state of Tamil Nadu and found that a total of 4,047 birds were affected from the MD. They further notified that the morbidity and mortality rates were ranging from 2.01 to 9.15 and 1.03 to 7.6 % respectively, in birds of the age group between 16 to 76 weeks [14].

The presence of high level (>0.02 ppm) of aflatoxin than the permissible limits (0.02 ppm or 20 ppb) in feed aggravated the MD outbreaks. Balasubramaniam *et al.* (2017) reported an outbreak of visceral (acute) form of Marek's disease (MD) in two different flocks of 12 week-old non-descriptive chickens reared for meat purpose in Tamil Nadu [15]. Genetic constitution, sex, age, immune status of chicken, environmental factors and stress level are major decisive factor for the disease progression. Birds carrying MHC alleles B 21 exhibit superior immune response and are less likely to be affected with MDV, than those possessing allele B22 [16]. The young females are more prone to MD. Acute MD is more prevalent than classical MD in India. The mortality rate is comparatively low in classical MD. Classical form most frequently noticed at the onset of sexual mortality 16 weak and at time of peak layering [4].

Economic Impact

Globally, there is a gradual upsurge in poultry production and 75% of the world's poultry market is mainly confined to the developing nations [2]. Several infectious viral diseases *viz.* avian influenza (AI), Newcastle disease (ND), infectious bursal disease (IBD) (Gumboro disease) and MD are the major constraints hampering the expansion of poultry industry. The mortality in the day to seven day old broiler chicks and adult laying birds attributes direct loss to the poultry farmers. The economic losses range from degradation of bird's value, depressed performance, mortality, mass culling of diseased bird management cost and additional costs arise from the development, production and use of vaccines for disease control.

Before the introduction of vaccination of commercial flocks in 1971, MD was a major global disease in chickens. The vaccination follow up has dramatically reduced mortality rate and economic losses; however, the periodic evolution of new MDV strains render the existing vaccines futile and consequently existing vaccine provide suboptimal protection. The testing of new circulating MDV strain, potency testing of existing vaccine and formulation of new vaccine using circulating MDV also divulge economic burden [17].

The economic impact of MDV earlier analysed by Graham Purchase and Fred Schultz reported that the benefits made out of vaccines nearly accounted for US $30 million in 1971[18]. In 1984, this sum had crossed a total of more than $2 billion and steadily increasing since then. The total loss per layer due to MD has been estimated to US $14.85 or 60.6% of the total production value [19].

The very virulent MD virus poses huge economic losses due to mortality despite preventive vaccination carried out at hatch. Chickens of native breeds are believed to be resistant for various diseases including MD. Till date, the economic losses due to the disease have been accounted for $1-2 billion annually in the commercial poultry industry [20].

Tactics to minimise MD

MD can be diagnosed on the basis of history, clinical signs, lesions distribution, affected age group, histopathology etc. The differential diagnosis from lymphoid leukosis, botulism, deficiency of thiamine, deficiency of Ca/Phosphorus/Vitamin D, especially at the start of lay should be made. Usually, the diagnosis of this disease is made from enlarged nerves and lymphoid tumors in various viscera [21]. The absence of bursal tumours helps in distinguishing this disease from lymphoid leukosis. MDV usually infects the younger chickens of 3 weeks old, whereas lymphoid leukosis typically occurs in >14 week old chicks [22].

The enlarged nerves are the most consistent gross lesions in the affected birds. Various peripheral nerves, in particular the vagus, brachial and sciatic nerves, become enlarged and lose their striations. Diffused or nodular lymphoid tumours are formed in various organs *viz.* liver, spleen, gonads, heart, lung, kidney, muscle, and pro-ventriculus. Enlarged feather follicles/ skin leucosis may be observed in broilers after de-feathering and during processing which is a cause for condemnation. The bursa is atrophic more frequently and rarely tumorous [23].

The viral infection in a flock can be detected by isolating the virus from the infected tissues, buffy coat cells from heparinised blood samples or suspensions of lymphoma and spleen cells. As MDV is highly cell-associated, the suspensions must contain viable cells. These cell suspensions are inoculated into monolayer cultures of chick kidney cells or duck embryo fibroblasts. Chicken embryo fibroblasts (CEF), although less sensitive may also be used for the primary isolation of serotype 1, 2 and 3 of MDV. The replication of MDV in the culture can be seen as plaques which appear within three to four days. Exceptionally, the feather tips from which cell-free MDV can be extracted are also used for the isolation of this virus [24].

Marek's disease (MD) tumour-associated surface antigen (MATSA) is not tumour specific but activated T cell marker. MDV antigen detection and MDV genomic DNA can be detected in the feather tips of infected birds using the radial immuno precipitation test and polymerase chain reaction (PCR) respectively. The MD specific antibodies can be identified by the agar gel immunodiffusion test, or the indirect fluorescent antibody test [25].

There is no specific treatment for the disease. Any broad spectrum antibiotic like enrofloxacin, levofloxacin, ciprofloxacin can be prescribed to prevent secondary bacterial infections.Vitamin supplements are also advised in this disease. The strict hygiene in compliance with the biosecurity measures, the production of the lines of all-in/all-out system and vaccination follow up generally with 1500 PFU of Herpesvirus of Turkey (HVT) at day old (but increasingly by in-ovo application at transfer) [26], association with other strains (SB1 Sero-type 2) [27] and Rispen's may be helpful to combat MD [28].

The MDV serotype 1 attenuated variants are best suited for longer immunological memories. Serotype 2 strains may also be used; particularly in bivalent vaccine together with HVT. The vaccine formulated from serotype 1 or 2 are only available in cell-associated form. Live HVT widely clinically in use are available in cell free (lyophilized) form or cell-associated forms. Bivalent (serotypes 1and 3) and trivalent (serotypes 1, 2 and 3) vaccine frequently used clinically [26]. Vaccination is the well-known method to prevent horizontal transfer of MD by reducing the amount of virus shed in the dander as well as to check the development of tumours in infected chickens. However, the administration of vaccine does not preclude complete transmission of the virus (*i.e.* the vaccine is not sterilizing). MD does not spread vertically. The most MD vaccines usually stored in liquid nitrogen. The freeze-dried vaccine is available for small flocks or used in countries where liquid nitrogen is not available. Cell-associated vaccines should only be stored in specialised liquid nitrogen containers (-196 degrees centigrade), reconstituted in a specifically supplied diluent, and administered following precise procedures provided by the manufacturer. *In-ovo* MD vaccination consequences better and early protection against MD. Still the vaccination can be given in day old chicks or soon after hatching in hatchery itself through subcutaneous route.

The immunity develops after 4-5 days of immunization against MD in chicks. Meanwhile, the chicks remain un-protected until the MDV vaccine strain *in-vivo* multiplies and starts circulating in the blood. So, it becomes essential to diminish the risk of early environmental exposure to MDV and/or delay the time of infection as long as possible so that the birds can remain fully protected. Those farms which rear birds of different ages and do not follow all-in all-out system of rearing and built-up litter pose a very high risk of early exposure to the field MDV [29]. The proper vaccine selection and timely administration of vaccines will result in effective and optimum control.

Conclusion

MD is a ubiquitous virus infection occurring in commercial poultry operations world-wide. The disease is difficult to eradicate as the virus is able to survive for long periods both in the host and in the environment of the poultry house. Successful vaccination therefore, remains the only strategy to control the disease. The vaccine strains are however non-pathogenic viruses that establish a permanent infection in the vaccinated birds but still these strains are capable of preventing formation of lymphomas and clinical disease. Hence, surveillance for MD should verify that the birds do not suffer from clinical disease and are properly vaccinated. To achieve this, various aforesaid tests mention can be applied. In case a country is importing birds, it should ask the exporter to provide international animal health certificates to ensure that imported chickens and day-old chicks are free from clinical disease and are vaccinated against MD and that the hatching eggs originate from a vaccinated source and have been shipped in clean unused packages. As MDV is not vertically transmitted, these measures are sufficient to prevent introduction of infection through day-old chicks or hatching eggs.

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