EMERGING TRENDS IN VETERINARY VIROLOGY

Editors:
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Emerging Trends in Veterinary Virology

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PREFACE

Emerging Trends in Veterinary Virology presents some emerging aspects and general principles in the field of veterinary virology. Recently, new advances in molecular biology, virology, biochemistry and structural biology have enabled the field of veterinary virology to make many exciting discoveries that have, in some cases, conceptually revolutionized our understanding of the topic. The book will provide useful information to virologists, microbiologists, students, and researchers.

Emerging infectious diseases are causing outbreaks with loss of human and animal lives and may have huge economic and societal impacts. There may be both natural and anthropogenic drivers behind the emergence of viral diseases. Zoonotic diseases are more commonly emerging, and the inborn tendency of RNA viruses to mutate makes these over-represented among the emerging diseases. A thorough understanding of the molecular biology, immunology, and pathogenesis of viruses that cause diseases is necessary for the rationale design of vaccines and diagnostics to control diseases.

In this book, eleven chapters are showcased to illustrate some of the most important findings made in the field of veterinary virology. Our first chapter starts with discussing viral evolution and moves towards discussing global changes and the impact on diseases, with a particular focus on vector-borne viruses. The second chapter is Infectious laryngotracheitis (ILT), an economically important respiratory disease of chickens that is prevalent throughout the world.

The third chapter covers avian leukosis viruses, which are the ancient RNA viruses that are notorious for causing oncogenesis in birds, especially in poultry. The purpose of this chapter is to understand the various aspects of ALV biology as well as to provide a comprehensive account of emerging trends in research for its diagnosis as well as control.

Our next chapter covers a neglected area; rabies lyssavirus (RABV) is the chief lyssavirus involved in rabies, a 100% lethal zoonotic acute encephalitis. Cats, like other mammals, are susceptible to the disease, and this is an emerging concern regarding feline health and Public Health as rabid cats might transmit the disease to humans. The next chapter covers an emerging virus, Bovine Leukemia, which is becoming a zoonotic threat.

Another chapter covers Hendra, which is a newly emerged disease of horses and humans. *Paramyxoviridae* family of viruses infect numerous species but with host specificity. Hendra virus, earlier called Horse morbillivirus, cause disease in horses but also have zoonotic importance.

The next chapter covers the West Nile virus (WNV), in which infected horses suffer from lethargy and nervous disorder. WNV causes West Nile virus disease in humans, which is characterized by skin rash, fever, vomiting, and sometimes neurological disorder.

Chapter 10 covers SARC-CoV and MERS-CoV, which belong to the group of betacoronavirus of the family *Coronaviridae*, the largest of RNA viruses. First emerged from China in 2003, it spread to other parts of the world in the following year. MERS-CoV is closely related to SARS and was reported in 2013 with 30-90% fatality.

The book ends with an updated chapter on advances in rabies research from its epidemiology, transmission, immunopathology, clinical disease, patient management and prophylaxis

measures. This chapter will also discuss the technical framework for rabies control through advanced strategies of vaccination, surveillance, laboratory diagnosis, animal movement monitoring and research. The last chapter is linked to emerging potential zoonotic issues related to virology and contains key information in detail.

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CHAPTER 1

Natural and Anthropogenic Drivers of Viral Emergence

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Abstract: Emerging infectious diseases are causing outbreaks with loss of human and animal lives and may have large economic and societal impacts. There may be both natural and anthropogenic drivers behind the emergence of viral diseases. Zoonotic diseases are more commonly emerging, and because RNA viruses have an inherent tendency to change, they are overrepresented among emerging diseases. Apart from the naturally occurring changes in the pathogens, humans also contribute to disease emergence by contributing to changes in land use and climate, which in turn affects ecosystems and biodiversity. This chapter reviews the different mechanisms behind viral disease emergence, as well as presents a framework evaluating the spill-over of zoonotic diseases at the human-wildlife-livestock interfaces. The chapter starts with discussing viral evolution and moves towards global changes and the impact on diseases, with a particular focus on vector-borne viruses.

Keywords: Arbovirus, Climate change, Disease spillover event, Disease transmission, Disease drivers, Emerging infectious diseases, Ecosystem services, Globalization, Human-animal interface, Land-use change, Urbanization, Vector-borne disease, Virology, Vector ecology, Zoonosis.

INTRODUCTION

Emerging infectious diseases in both animals and humans cause major economic and health burdens in every part of the world. On average, a new human disease appears every four months, and around 75% of emerging diseases are zoonotic [1].

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Most originate from wildlife, and the study of disease emergence has a strong focus on wildlife. However, economically important emerging diseases often involve domestic animals. For example, between 1997 and 2009, six major emerging diseases have together cost at least $80 billion; the Nipah virus outbreak in Malaysia, West Nile fever in the US, severe acute respiratory syndrome (SARS) (starting in Asia), highly pathogenic avian influenza (HPAI, starting in Asia), bovine spongiform encephalopathy (BSE) and RVF in East Africa [2]. In five of these six high-impact diseases, livestock or animals for human consumption were a reservoir or a bridge to carry disease to people. Later outbreaks of emerging infectious diseases, such as the Middle East Respiratory Syndrome (MERS) and the Ebola outbreak in West Africa, were also caused by viruses with an animal reservoir; while bats seem the most important reservoir, in the case of MERS, livestock (camels) are an amplifying host, and in the case of Ebola, a livestock interface has been suspected [3 - 5]. The 2020 pandemic of coronavirus disease-19 (Covid-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-cov2), likely originated from food markets, where both animal products and live domestic and wild animals are sold for consumption [6, 7]. The origin of this virus is believed to be bats, likely through an intermediate host, like in the case of the closely related coronavirus that caused the SARS outbreak [8 - 11].

The burden of infectious diseases is not evenly distributed, and in low-income countries, zoonotic diseases and diseases that have recently evolved from animals account for a higher proportion of diseases than in high-income countries [12]. In Africa, diseases affect poor people disproportionally and further contribute to their poverty in a vicious circle. Zoonotic diseases have the potential to harm both the livelihoods and health of those depending on livestock [13]. Africa is also the continent where more than half of all outbreaks verified by WHO between 1996 and 2009 occurred, and where the time lags between outbreak and detection and public alerts are the longest [14].

Moreover, while populations globally are stabilizing, demographic growth is predicted to remain high in Africa, with the continent's population predicted to reach 4 billion in 2100, from 1 billion in 2014 [15]. This rapid population growth is likely to drive equally rapid changes in ecosystems, including expansion of crop agriculture into marginal areas, irrigation, deforestation, urban sprawl, road building, mining, and bushmeat harvesting [16]. Depending on how these changes affect the number of susceptible animals and humans, the risks of exposure, and the infectiousness of infected individuals, they may either increase or decrease disease incidence [17]. Disease is frequently caused by land-use change; it has been estimated to be responsible for more than 20% of the disease emergence on the island continent of Australia [18]. In addition, the risks of land use-associated

diseases are often exacerbated by climate change and variability, and the poor adaptive capabilities of communities.

The fact that the emergence of viral diseases depends on factors from molecular levels to global politics (Fig. **1**) not only means that it is difficult to predict or study, it will also require scientists from different fields to understand it, and the engagement of policymakers and stakeholders from different areas to manage it.

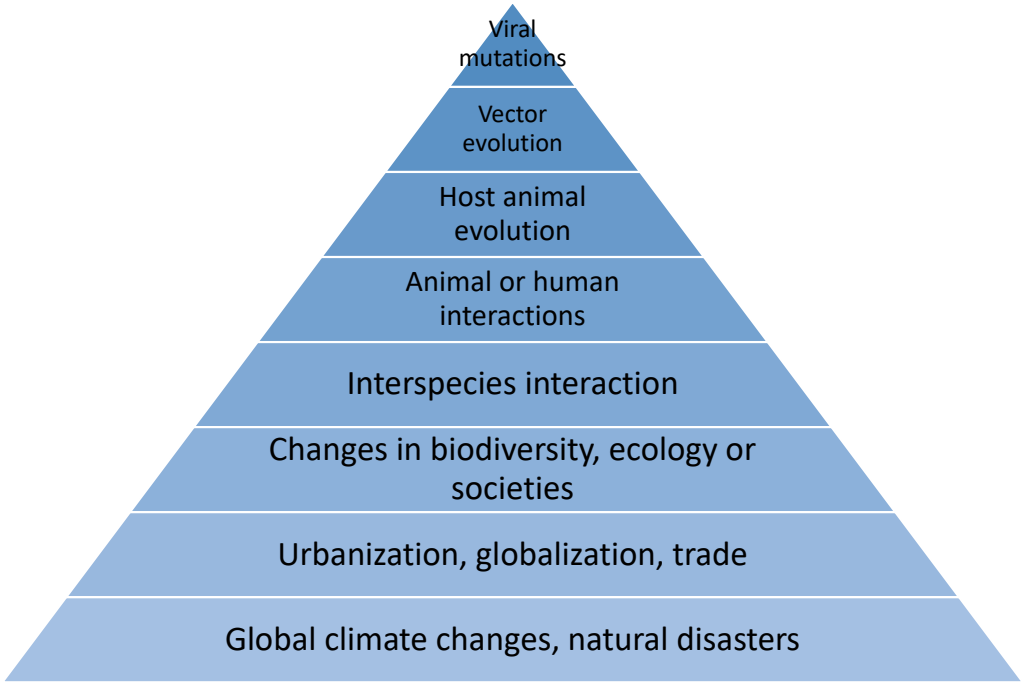

Fig. (1). Examples of various factors affecting viral emergence at a different scale.

Changes Within a Virus

The changes occurring within a virus can have different effects. By mutations or re-assortment events, the virus can develop new epitopes, which may change the antigenic properties. This can cause the reemergence of a virus in a population that was partly immune, either by vaccination or by natural previous infections. An example is influenza outbreaks, where a large outbreak may occur, such as H1N1, when significant changes in antigenic properties result in most people lacking sufficient immunity. Changing epitopes can also make a virus able to infect new host species and thus cause an emergence event.

Genetic changes within the virus may also mean that the virus becomes more pathogenic for the same host by changing cell predilection or increasing the viral

CHAPTER 2

Infectious Laryngotracheitis Virus: Molecular Biology, Pathobiology, and Control Strategies

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Abstract: Infectious laryngotracheitis (ILT) is an economically important respiratory disease of chickens that is prevalent throughout the world. It is caused by an infectious laryngotracheitis virus (ILTV), also named *Gallid alphaherpesvirus* 1 (GaHV-1). It is a member of the genus *Iltovirus*, subfamily *Alphaherpesvirinae*, family *Herpesviridae* and order *Herpesvirales*. The ILTV genome is a linear double-stranded DNA molecule with an average genome length of 151,607 nt. Twelve herpes simplex virus -1 homologue genes have been identified in the ILTV genome, with seven of them, glycoproteins B, C, H, K, L, M and N, present in the UL region, while glycoproteins D, E, G, I and J are present in the US region of the ILTV genome. Although chicken is the natural host of ILTV, infections have also been reported in pheasants, pheasant-chicken crosses, peafowls, turkeys, and ducks. An incubation period of 3–12 days is followed by an acute phase of the infection which lasts 1–2 weeks. During this phase, the virus replication occurs in the conjunctiva, trachea, and larynx, resulting in conjunctivitis, gasping, coughing, and expectoration of blood-mixed mucus. ILTV infection results in decreased weight gain and egg production. It causes 0 to 80% mortality depending on the virulence of the strain involved. Like other herpesviruses, ILTV establishes latent infection in trigeminal ganglia and virus reactivation and shedding occur following various stress factors.

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ILTV infections are generally diagnosed by the typical clinical signs and detection of intranuclear inclusion bodies in the affected tissues. Furthermore, the detection of virus-specific antigen by fluorescent antibody, immunohistochemical staining of smears and tissues, detection of DNA by a polymerase chain reaction, and virus isolation by inoculating embryonated chicken eggs or cell cultures can also be performed. Virus neutralization assays and different types of ELISAs have also been established. To control ILTV infections, a combined effort is required encompassing prompt disease diagnosis, the use of geographic information system technology, biosecurity, vaccination, differentiation of infected from vaccinated (DIVA), and eradication of reservoir hosts.

Keywords: Alphaherpesvirinae, Coughing, Expectoration of blood, GaHV-1, Gallid alphaherpesvirus 1, Gasping, Herpesviridae, Herpesvirales, Infectious laryngotracheitis (ILT), Infectious laryngotracheitis virus (ILTV), Iltovirus, Respiratory disease.

INTRODUCTION

Infectious laryngotracheitis (ILT) is an economically important disease that affects the respiratory tissues of chickens. It is caused by *Gallid alphaherpesvirus*-1 (GaHV-1) that is generally known as the infectious laryngotracheitis virus (ILTV) [1]. The virus inflicts heavy production losses because of mortality and reduced production of the chickens. An average mortality range is approximately 10-20%; however, in severe cases of the disease, the mortality and morbidity can reach up to 100% and 70%, respectively [2]. The morbidity and mortality can be as low as 0.5 and 0.1%, respectively, in the milder type of disease [2]. In developed poultry industries, the milder enzootic forms of the disease are frequently encountered and are seen as mucoid tracheitis, sinusitis, with low mortality [3]. Flocks with persistent infection can exist alongside flocks that are free from ILTV and serious disease outbreaks can occur periodically whenever ILTV spreads from persistently infected flocks into the flocks of unvaccinated chickens [2]. A recently published report suggests that ILTV is evolving fast with greater transmissibility and capacity to spread into ILTV-free areas [4].

Transmission of the ILTV virus usually occurs by the horizontal route, and it mainly infects the upper respiratory system of the chickens; however, it can invade the trigeminal ganglia during the initial period of replication. After an experimental inoculation, the virus or viral DNA is detectable after 2 days of infection, and the highest titers of the virus are observed between 4 to 6 days [5, 6]. The virus is detectable at sites other than the respiratory tract including the liver and caecal tonsils. It is assumed that the infection of the macrophages is involved in this spread [6, 7].

Clinical signs associated with the severe form of the disease are dyspnoea, expectoration of blood-mixed mucus from the trachea, and a variable degree of conjunctivitis. Clinical signs associated with the milder form of the disease include wet eyes, conjunctivitis, swelling of the infraorbital sinuses, constant nasal discharge, mucoid tracheitis, respiratory rales, unthriftiness, and decline in egg production [3, 8]. As observed in other herpesviruses, the establishment of latent infections and reactivation of infections, followed by virus shedding, has been observed in the tracheal-organ- cultures taken from latently infected birds with ILTV [7]. Certain stresses, for example, housing with unknown birds, are linked with the reactivation of the infection [9 - 11]. Mortality and decrease in egg production caused by ILTV inflict multimillion-dollar losses to the U.S. poultry industry every year, and similar effects are likely to be seen in other intensive poultry industries of the world. Infectious laryngotracheitis is the first avian-viral disease for which an effective vaccine has been developed. The disease is considered to be of no public health concern [3].

MOLECULAR BIOLOGY OF *GALLID ALPHAHERPESVIRUS*-1

Virion Structure, Replication, and Morphogenesis

Electron microscopy of chicken embryo cells infected with ILTV has demonstrated the presence of nucleocapsids with icosahedral symmetry (Fig. **1**). The spherical virion consists of a core, capsid, tegument, and an envelope. Packed into a capsid protein, the genome of the virus is comprised of a linear, single, double-stranded DNA (ds DNA) molecule [12]. The nucleocapsid of ILTV is comprised of 162 capsomeres, including 150 hexons and 12 pentons. The triangulation number (T) is 16. There are 960 copies of the capsid. The diameter of the ILT virion is approximately 195-250 nm. A lipid-bilayer envelope surrounding the nucleocapsid is connected with the outer surface of the tegument. As observed in other avian herpesviruses, ILTV infects a narrow range of hosts, both *in-vivo* and *in-vitro*. Besides chickens, natural infection of ILTV has been observed in pheasants only [13]. The virus can be grown on the chorioallantoic membranes of the embryonated chicken eggs [14] and the primary chicken embryo cells of the kidney and liver [15]. The virus also grows on leghorn male hepatoma (LMH) stable cell lines; however, these cell lines are not much sensitive to ILTV [16]. The replication cycle of ILTV is not well-understood; however, it seems similar to that of other alphaherpesviruses, for example, herpes simplex virus type 1 (HSV-1) [17]. One-step growth curve analysis in primary embryo kidney cells reveals that the first progeny viruses are produced after 8-12 hours post-infection and reach a maximum after 24 to 30 hours [18].

CHAPTER 3

Avian Leukosis Viruses

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Abstract: Solving the complications of oncogenesis caused by retroviruses is a challenging task for veterinary and biomedical scientists. Avian Leukosis viruses (ALVs) are a group of avian oncogenic retroviruses that can cause neoplastic diseases in chickens. The viral invasion starts due to the interaction between glycoproteins in the viral envelop and receptor sites of host cells. The pathogenesis of ALVs could be explained by three theories which include promoter insertion, enhancer activation, and the presence of oncogenes in their genome. Additionally, these viruses show great diversity due to the high mutational rate that enables them to escape from the action of the host immune system and antiviral drugs. Therefore, due to the high mortality rate of chickens, ALVs are responsible for huge economic losses in the poultry industry. Due to horizontal & vertical transmission and genetic variations, there is no effective vaccine to prevent infections of ALVs.

The aim of this chapter is to summarize various research aspects related to the pathogenesis and transmission of ALVs. It is essential to understand these processes to get further insight into the biology of ALV's. Likewise, to design the control strategies for ALV infections, it is invaluable to explore the interactions between ALVs and host immunity.

Keywords: Avian Leukosis viruses, ALVs, Leukosis, Oncogenesis, Retroviruses, RNA tumor viruses.

INTRODUCTION

Neoplastic infections in chickens are a major economic problem in poultry industry. The oncogenic viruses that infect chickens include Avian Leukosis viruses (ALVs), Marek's disease virus (MDV), and reticuloendotheliosis virus (REV) [1]. Avian Leukosis viruses (ALVs) are contagious and immunosuppressive viruses that are the prevalent cause of tumorigenesis in avians, especially in chickens. Thy belongs to the genus alpharetroviruses of the retroviridae family [2]. These oncogenic viruses are divided into 11 different

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subgroups (ALV-A to ALV-K) based on their envelope structure, specific host type, and mode of transmission [3, 4].

These genotypes may be exogenous and endogenous [5]. Among different types of ALVs, seven subgroups A-E, and J-K, cause avian leukemogenesis in poultry [6]. Avian Leukosis (AL) is the most commonly occurring type of fowl neoplasm that originates due to the formation of cancerous lymphocytes in the infected that originates due to the development of cancerous lymphocytes in the infected chikens [7, 8]. Although researchers are working on different aspects of ALV infections, since last 100 years, however there is still lack of commercial vaccines that can prevent ALV infection and its transmission [5, 9].

Each ALV (retrovirus) is an infectious particle with the membranous envelope of lipoprotein, the outer core of capsids, the inner core comprising of double-stranded RNA, and the reverse transcriptase enzymes. The genome of ALVs consists of three genes; the gag gene, which translates to form core proteins, a pol gene encoding for transcriptase enzyme, and env gene that encodes for envelope proteins (Fig. **1**).

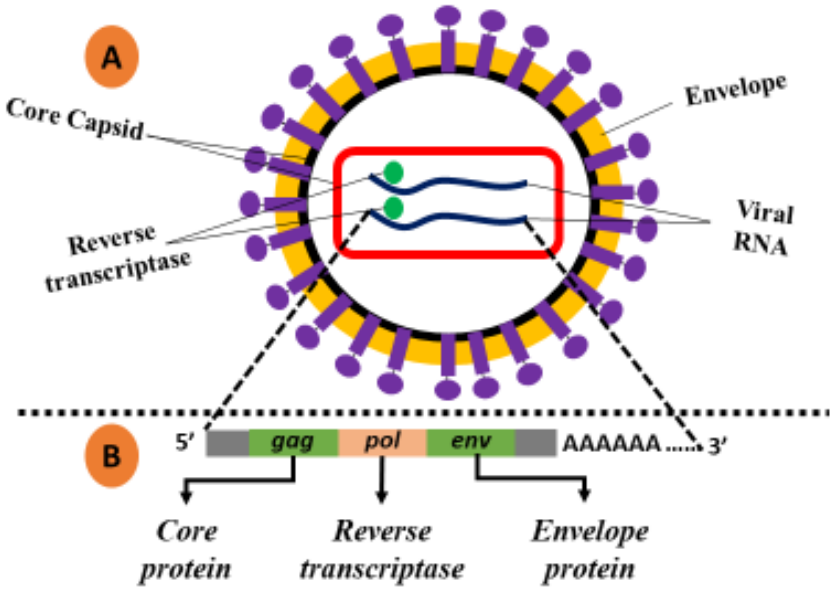

Fig. (1). Structure of ALVs. **(A)** Morphological features; **(B)** Genomic structure of ALVs.

EPIDEMIOLOGY OF ALVS

Epidemiological Triad in the spreading of diseases depends on the environment, virulent agent, and host. As an environmental factor, seasons provides the number

of chances in which pathogens can set a new prevalence rate in the host populations at different places in different times [10]. The worldwide occurrence of diseases due to ALVs cause severe/lethal suppression of immunity, growth reduction, motility due to tumor casing activity and results in severe economic losses [11]. The highest incidence rate of ALVs infections has been reported from China in 2018 [12]. Variation in the prevalence of ALVs is dependent on viral transmission, interaction with the host immune system, and genetic resistance of the host against different ALVs [13]. The incidence rates of different genotypes are shown in Table **1**, the years 1997 and 1998 are known as the years of leukosis by ALVs-J types worldwide. Whereas little is known about its effective control [14 - 17]. Other epidemiological features like origin, prevalence, and molecular features of different genotypes are given in Table **1**.

Table 1. Origin, prevalence and molecular features of various genotypes of ALVs.

Genotypes	*Origin*	*Prevalence*	*Oncogenisity*	*Host Cell Receptor*	*Causing Disease/s*	*Use of Molecule During Entry into Host*	*Cytotoxicity*	*References*
A	Exogeneous	Common	+	Tva	Lymphoid leukosis	LDLR	Non-cytopathic	[4, 8, 14, 18 - 20]
B	Exogeneous	Common	+	Tvb	Lymphoid leukosis	TNFR	Cytopathic	
C	Exogeneous	Rare	+	Tvc	Lymphoid leukosis	Butyrophilin	Cytopathic	
D	Exogeneous	Rare	+	Tvb	Lymphoid leukosis	TNFR	Cytopathic	
E	Endogeneous	Common	-	Tvb/Tve	Several neoplastic/not pathogenic to chicken	TNFR	Non-cytopathic	
J	Exogeneous	Common	+	Tve	Myeloid leukosis	Na/H exchanger type I protein	Cytopathic	
K	Exogeneous	Rare	-	Tva	Avian Leukosis	?	?	

Abbreviations: LDLR: low-density lipoprotein receptors, TNFR: tumor necrosis factor receptor, +: present, -: absent, ?: not confirmed

CLINICAL SYMPTOMS

Physical and clinical observations show that various organs and tissues are found abnormal in chicken affected with Avian Leukosis; its different clinical symptoms of Avian Leukosis in chicken include enlargement and nodular growth in various body organs or tissues as shown in Fig. (**2**).

CHAPTER 4

Feline Rabies

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Abstract: Rabies lyssavirus (RABV) is the main lyssavirus involved in rabies, a 100% lethal zoonotic acute encephalitis. Cats, like other mammals, are susceptible to the disease, and this is an emerging concern regarding feline health and Public Health as rabid cats might transmit the disease to humans. Transmission to cats occurs from other cats or canids, but bats are of growing concern as reservoirs to feline rabies. Upon infection, RABV spreads *via* axons to the central nervous system (CNS) and leads to either the paralytic or the furious form of the disease, depending on the immune response and the virus strain. A definitive diagnosis is based on immunofluorescence and virus isolation in cell cultures or mice using post-mortem samples of CNS; PCR is of value in cases of poorly conserved samples and DNA sequencing is of uttermost importance for the molecular epidemiology of rabies. Vaccination using an inactivated virus is the core preventive measure regarding cats.

Keywords: Cats, Diagnosis, Epidemiology, Prevention, Rabies.

A GENERAL OVERVIEW OF RABIES

Rabies is an acute zoonotic infectious encephalitis of lethal outcome caused by species in the *Lyssavirus* genus, to which mammals are naturally susceptible. Though eradicated or absent in some parts of the world, including Western Europe, Oceania and Japan, classic rabies is a major burden to canine and feline health elsewhere due to either its endemic occurrence of sporadic cases because of the introduction of these animals from endemic to free countries.

Bats of all feeding habits are natural reservoirs to species of *Lyssavirus* and can transmit these viruses to dogs and cats. Rabid bats lose their ability to fly and become more susceptible to predatory behavior or cats and dogs, which, in turn, might acquire rabies *via* defensive bites of bats.

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In herbivores of economic interest such as cattle and horses, rabies is a cause of significant losses in Latin America, where rabies is transmitted by the vampire bat *Desmodus rotundus*.

Once the symptoms manifest, after a period of incubation ranging from one to several months, depending on the host species, death is currently an inevitable outcome after an acute clinical course of circa one week; only a few well-documented human patients have survived after a massive anti-viral treatment, and no treatment is available for other animals.

The disease is effectively preventable with the use of inactivated virus vaccines in a pre-exposure protocol; the use of vaccines and anti-rabies virus hyperimmune sera in a post-exposure protocol, approved only for human patients exposed to the risk of infection, is a secure way to avoid the disease.

Due to its higher prevalence in dogs and the focus on this species when it comes to control and eradication, rabies in cats has been overlooked.

LYSSAVIRUS TAXONOMY

Rabies lyssavirus (RABV, *Rhabdoviridae* family of the *Mononegavirales*) is involved in all cases of rabies in cats and other mammals, including the 40,000-70,000 annual human cases, worldwide [1, 2].

Further species of *Lyssavirus* have a more regional occurrence, such as *Mokola lyssavirus* in Africa and *European bat lyssavirus 1* and *2* in Western Europe, but *European bat lyssavirus 1*, *West Caucasian Bat Lyssavirus* and *Mokola Lyssavirus* [3 - 5], are the only non-RABV lyssaviruses reported in cats hitherto.

RABV shows a diversity of variants and lineages not seen in the other members of the *Lyssavirus*. Bats are hosts to the widest number of lineages of RABV worldwide, while dogs harbor the clades Arctic, Arctic-like, Africa 2 and 3, Cosmopolitan and SE Asia 1, 2 and 3 [5, 6]. RABV vaccines protect against all variants, but not against other lyssaviruses.

The Antigenic variant 1 (AgV1) of Cosmopolitan is the clade most frequently associated with rabies in cats and dogs and is now eradicated from Canada, the USA, and Western Europe, but this and the Antigenic variant 2 (AgV2) of this clade is still a risk for cats in Latin America.

Further lineages might be associated with rabid cats elsewhere, and the biology of lyssaviruses poses no barriers to the infection of cats by any lineage.

Due to the similarities of RABV with other lyssaviruses and the dominance of data from this virus species when compared to the other ones, this chapter will focus on RABV.

RABV MOLECULAR BIOLOGY AND REPLICATION

RABV genome is a negative-sense single-stranded linear RNA of circa 12kb coding for only five proteins in the order 3'-nucleoprotein (N)-phosphoprotein (P)-matrix protein (M)-glycoprotein (G)-large protein (L)-5' [8].

The envelope is anchored by the M protein and populated with trimers of G; internal to the envelope, there is a nucleocapsid formed by proteins N, P, L, and the genome. Virions are of a spiked appearance and show a rod-like morphology with 75 nm × 180 nm in size [9].

The G protein participates in receptor binding and is the target for neutralizing antibodies; in muscle cells, G binds the acetylcholine receptor and can also bind to NCAM (neuronal cell adhesion molecule) and p75NTR (75 neurotrophin receptor) of neurons, including those at the neuromuscular junctions [10, 11].

After binding of G to the cell receptor, the virions reach the cytoplasm *via* endocytosis, fuse with the endosome membrane, and a pH-dependent (<6.4) uncoating then follows [12]. The genomic RNA then serves as a template to mRNA synthesis by the RNA-dependent RNA-polymerase L protein with the P protein, a co-factor.

Transcription starts at the 3' leader (Le) sequence and results in a positive-sense copy of Le (+Le, 58 nt) and the 5 subgenomic mRNAs in a start-stop mechanism in which transcription start sequences at the beginning, and transcription termination sequences at the end of each gene guide the polymerase activity, resulting in capped and polyadenylated mRNAs. Due to the loss of the transcription efficiency from the 3' to the 5' ends, a decreasing mRNA gradient is formed and thus, a higher amount of N is synthesized. Alternatively, transcription might start at N gene and not at the leader [13].

N protein accumulation leads to its association with +Le, starting RNA encapsulation and resulting in the inaccessibility of the transcription termination sequences to the polymerase and the shift from transcription to genome replication and the genomic RNA is then encapsidated by N, L and P proteins and the resulting ribonucleocapsid of helical symmetry buds through the membrane incorporating G and M proteins [13].

CHAPTER 5

Canine Distemper: Current and Emerging Perspectives

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Abstract: Canine distemper virus can cause infections in domestic canines and in many wild animals belonging to families *Canidae, Felidae, Hyaenidae, Procyonidae, Ailuridae, Ursidae, Mustelidae, Viverridae* and some non-human primates. Among six proteins encoded by the genome of the virus, genetic drift has been associated with the hemagglutinin protein. Based on phylogenetic analysis of different strains, the virus is categorized into six groups. RT-PCR, ELISA, indirect fluorescent antibody test, serum neutralization test and immunohistochemistry can be used for diagnosing canine distemper. Recombinant canarypox vectored vaccine is currently used for the prevention of the disease in domesticated canines, but now researchers are focusing on the development of new vaccines with new strains of the virus from different genetic groups.

Keywords: Canine distemper, Morbillivirus, Rockborn like strains, Vaccine.

INTRODUCTION

Canine distemper (CD) is a highly contagious disease of canines caused by the canine distemper virus (CDV). CDV has emerged as a multi-host pathogen, infecting a wide range of wildlife and carnivore species [1]. CDV is an enveloped, non-segmented, negative-sense, single-stranded RNA virus and belongs to the family *Paramyxoviridae* and genus *Morbillivirus*. The mortality rate of CD reaches up to 80 percent in puppies [2].

The transmission of CD between the susceptible hosts occurs through direct contact or *via* the aerosol route. It is recently reported that fleas can also act as a vector for the transmission of CDV [3]. The canine distemper virus is sensitive to

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lipid solvents, such as ether, and most disinfectants, including phenols and quaternary ammonium compounds. It is highly sensitive to UV radiation, heat, desiccation and detergents [2].

Clinical signs produced by CDV depend on the virus strain, as well as the age and immune system of the particular host [4]. Clinical signs in the dogs include disorders of respiratory and gastrointestinal systems, such as nasal discharge, sneezing, coughing, pneumonia and loss of appetite, vomiting, diarrhea, respectively. Nervous signs include abnormal behavior, convulsions, seizures, chewing gum movements, blindness, cerebellar and vestibular signs, paresis or paralysis, incoordination, and circling. The clinical signs of CD reported in wildlife are mostly similar to that of domestic dogs [2, 5]. Currently, no antiviral drug is available that works specifically against CDV; therefore, the control of the disease is the best option. For control and prevention, vaccination of susceptible animals along with the maintenance of general sanitation practices is necessary.

VIRUS AND ITS CHARACTERISTICS

Canine distemper virus is a negative sense, single-stranded RNA virus, and the size of the virions ranges from 100-250 nm. The viral RNA genome encodes 6 proteins; a single envelope-associated protein, *i.e*., the Matrix protein (**M**), two glycoproteins, the hemagglutinin protein **(H)** and the fusion protein **(F)** are inserted through the viral membrane, two transcriptase-associated proteins, phosphoprotein **(P)**, and the large protein **(L)** along with nucleocapsid protein **(N)** [6].

It is reported that the H protein undergoes genetic drift according to environmental conditions. So, the canine distemper virus can be prevented by providing immunity against H protein. H protein is the main protein involved in antigenic changes in the virus. A poly-dynamic analysis of the CDV hemagglutinin gene revealed co-circulation and extensive diversification of canine distemper virus due to the H gene [7].

The majority of CDV strains are categorized into six major genetic lineages designated as America-1, America-2, Asia-1, Asia-2, Europe and Arctic. Other genotypes include South America 2 and 3, Rockborn, Africa-1 and Africa-2 [8]. Modified live vaccines are produced mainly by using America-1 and Rockborn like strains [9]. Vaccination failure in some animals is due to the infection of other strains. In a recent study, sequencing of emerging canine distemper virus strain revealed a new distinct genetic lineage in the United States associated with disease in wildlife and domestic canine populations [10, 11].

EPIDEMIOLOGY

Canine distemper occurs worldwide in domestic, captive and free-ranging carnivores. Severe population decline has resulted from the spread of canine distemper in domestic dogs, felines and other wild species all over the world [12]. It was thought that canine distemper is a disease of domestic dogs only, but later, it was found that CDV infection may affect multiple species with the pathogenesis and clinical signs resembling that of domestic dogs. CDV can infect multiple species, including wild canids, felids, hyaenids, procyonids, ailurids, ursids, mustelids and viverrids [13]. The outbreak of canine distemper has also been reported recently in marine animals as well as in non-human primates like rhesus monkeys and cynomolgus macaques [14]. The canine distemper outbreak of 1994 in the lion population of Tanzania is the best-known epidemic as it was the cause of huge causalities in lions at that time. Due to this broad and expanding host range of CDV, eradication of the disease is difficult. CD is not yet reported in humans [12, 14].

CDV AS A CROSS-SPECIES PATHOGEN

Initially, CDV was considered as a threat to domestic dogs only, but later, it was proved that unlike measles viruses, which are maintained by single host species, CDV could affect a variety of carnivores and non-carnivore species. A CDV infection resembling the disease in domestic dogs has also been reported in wild canids (wolves, foxes), procyonids (raccoons), ailurids (red pandas), ursids (black bears, giant pandas), mustelids (ferrets, minks), viverrids (civets, genets), hyaenids (spotted hyenas) and large felids (lions, tigers). Furthermore, lethal infections of CDV have also been reported in non-carnivore species, such as peccaries and non-human primates.

In African wildlife, the epidemic of CDV has spread throughout the Serengeti National park, Tanzania, in 1994, killing one-third of the lion population with additional deaths in other species, such as bat-eared fox, African wild dogs, silver-backed jackals and spotted hyenas [16]. Other wildlife species in which reports of the outbreaks of CD are confirmed are the Ethiopian wolf, Amur tiger, and some captive populations of the giant panda [17]. The first case of CD in brown hyenas was reported during an outbreak in Waterberg, South Africa, in December 2015 [11]. Phylogenetic and molecular analysis of CDV reveals that mutations in the H protein required for virus attachment to host cell receptors are associated with the occurrence of disease emergence in novel host species [18].

CHAPTER 6

Emerging Trends in Epidemiology, Diagnosis and Control of Bovine Leukemia Virus

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Abstract: The bovine leukemia virus *(BLV*) is responsible for the enzootic bovine leukosis, an infectious lympho-proliferative disease of the cattle. This can result in economic fatalities for the cattle industry as it is responsible for the low productivity and low milk production, higher early culling in turn increasing the death rates with high charges on the prevention measures of the outbreaks. This chapter summarizes the occurrence, diagnosis, preventative, and therapeutic approaches in managing bovine leukemia.

INTRODUCTION

Bovine leukemia virus (BLV) is an exogenous B-lymphotropic Deltaretrovirus, as shown in (Fig. **1**), oncogenic member of the *Retroviridae* family and is responsible for enzootic bovine leukosis in cattle [1]. It can result in economic fatalities for the cattle industry by reducing the productiveness, low milk production, high early culling, and increasing the death rates with high charges on the prevention measures of the outbreaks and is distributed worldwide [2]. The existence of faintly yellow nodules of bovine leukosis in the enlarged spleen of cattle was initially reported in 1871 [3]. BLV infection is spread mostly by horizontal means but can also be transmitted vertically by the intake of colostrum or in utero infection [4]. BLV is encoded by crucial genes for making of infectious virions, which are Group Specific Antigen (gag), protease (pro), polymerase (pol) and envelope (env), with a pair of same long terminal repeats (LTRs) [5].

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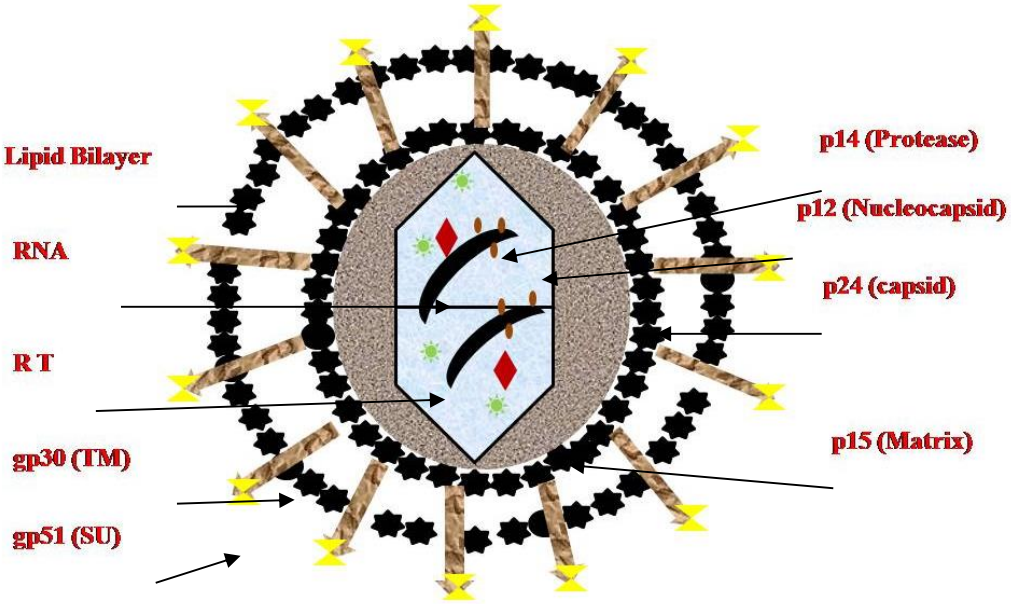

Fig. (1). Structure of BLV.

GLOBAL OCCURRENCE OF BLV

The cattle-producing territories have a high ratio of EBL all over the globe [6]. The presence of EBL has been reported right after the Second World War, and up to 2012, about 51 nations had reported bovine lympho-sarcoma to OIE [7]. The widespread of EBL is possibly due to the marketing exchange of livestock in the entire globe, but in most of the countries, the burden of EBL is not obvious, and the EBL shows different prevalence rates within the same state [1].

The highest proportion of livestock being infected by BLV is in America (89% in 1997 and 83% in 2007) [8]. In South America, 34-54% of the cattle population is infected, certain countries having higher prevalence [9, 10], while in 1997, 70% and currently, 89% infection rate has been reported in North America.

There is great uncertainty in the distribution of BLV infection in Asia as it is found in China, Mongolia, Indonesia, Taiwan and Cambodia [11] and 68 and 86% of the BLV burden has been recorded in Japan and Korea, respectively [12]. The rate of BLV in the Middle East was 20%, which is comparatively lesser than the other countries [13], and 64 and 48% infection burden had been recorded in Iran and Turkey, respectively [14].

GENOTYPIC DISTRIBUTION OF THE BLV

Previously, BLV had eight genotypes on the basis of a phylogenetic assessment of envelope (env) gene [15]; then in South America, the ninth genotype of BLV has been detected [9] and currently, it can be classified as 10 genotypes (G-1 to G-10), as revealed by the full sequence analysis of the env gene in Thailand [1, 16]. The most common genotypes detected from almost all the continents are G-1, G-4, and G-6, whereas G-1 is one of the exceedingly leading genotypes of BLV [1] and the second commonly spread genotype is G-4. In USA and Japan, G-1 and G-3 are frequent; on the other hand, in South America, G-2, G-5 and G-6 were commonly found; Russia and Eastern Europe have G-4 and G-7, while Bolivia has G-9 and Thailand has G-10 [17].

RISK RELATED TO THE HEALTH OF HUMAN BEINGS

The contradiction about the zoonotic potential of the BLV has not yet been cleared, and there is a need to explore its relationship with humans. In order to decipher this ambiguity, there are few studies establishing a relationship between breast cancer and BLV [18]. Moreover, the genome fragment of BLV has been identified from breast cancer patients, but until now, the exact etiology has not been properly declared [19]. There are some more studies showing the capability of BLV in infecting human mammary cells *in-vitro* [20], and antibodies to BLV have been detected from human blood, suggesting that the threat related to BLV attainment and propagation in humans is not a matter of negligence [21 - 23].

ECONOMIC IMPACTS OF BLV

The economic impact of BLV embarrasses all of the services of the veterinary and livestock industry, as the low level of the production of milk and the estimated loss is more than 525 million dollars due to premature culling of infected animals and reduced reproduction rate [24]. Selling BLV positive animals overseas has limitations along with the high cost, which would have a strong negative impact on global trade. Thus, bovine leukosis is listed as an important disease regarding worldwide trade [11]; additionally, in malignant lymphosarcoma, life durability of the diseased animals would become low, resulting in terrible profitable impacts [25].

DIAGNOSIS AND MOLECULAR IDENTIFICATION TECHNIQUES

The capsid protein CA and the envelope surface protein are used as the antigen for the serological based diagnosis of the BLV [26]. There are numerous methods for the diagnosis of the BLV, including serological findings like:

CHAPTER 7

West Nile Virus

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Abstract: West Nile virus (WNV) is an arthropod-borne RNA virus, first time isolated in 1937 from Uganda. Now, WNV has been reported from throughout the world virus with 9 possible phylogenetic lineages. Mosquitoes of the genus *Culex* are mainly responsible for WNV transmission to birds and humans. In horses, WNV cause the disease, and the infected horse suffers from lethargy and nervous disorder. WNV causes West Nile virus disease in humans, which is characterized by skin rash, fever, vomiting and sometimes neurological disorder. In contrast to the WNV vaccine in animals, no vaccine against WNV is commercially available for humans. For veterinary use, RecombiTEK is a commercially available recombinant vaccine against WNV. WNV can be detected in horses by serological tests like hemagglutination inhibition, ELISA, and plaque reduction neutralization or by necropsy of the brain. People who have direct contact with birds and horses are more prone to WNV exposure than others.

Keywords: ChimeriVax-WN, *Flavivirus*, Mosquitoes, West nile, Wild birds.

INTRODUCTION

West Nile virus (WNV) is a zoonotic virus that belongs to the family *Flaviviridae*, genus *Flavivirus* [1]. It is transmitted by mosquitoes to birds, humans, and horses [2]. Although WNV has been isolated from almost 60 species of mosquitoes, the genus *Culex* mosquitoes play the main role in WNV transmission [3]. Birds act as amplifier hosts and have been reported from more than 300 species of birds. WNV has been isolated from canines, felines, and bats [4]. Humans and horses act as dead-end hosts of WNV. In horses, WNV infection results in lethargy, ataxia, and nervous incoordination [5, 6].

In humans, WNV causes West Nile virus diseases (WNVD), which is a notifiable disease. Along with vector transmission of WNV to humans, human-to-human transmission is also possible [6].

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WNV is transmitted from one infected human to another *via* blood transfusion, organ transplant, breastfeeding and intrauterine route [7]. WNV infection in humans shows no signs and symptoms in 80% of cases, but in the remaining 20% of cases, patients suffer from fever, vomiting, nausea, lethargy and skin rash. In 1% of patients, WNV invades the neurons and causes neurological problems like meningitis, encephalitis and flaccid paralysis [8, 9].

WEST NILE VIRUS STRUCTURE

WNV contains a single-stranded, positive-sense RNA genome of 11,000 nucleotides in a single open reading frame [10]. This RNA genome encodes a total of ten proteins, seven nonstructural and three structural proteins. Three structural proteins include capsid protein, envelope protein and pre-membrane protein. Capsid protein, also named core protein, is made up of charged amino acids. Capsid protein contributes to the replication of the virus by its chaperoning activity [11, 12].

Envelope protein is glycosylated that helps the WNV to invade the cells of non-vertebrates and vertebrates [13]. Due to its immunogenic properties, envelop protein has attracted the interest of many researchers. Envelope glycoprotein plays a key role in the attachment of the virus to host cells and the fusion of membrane [14]. After folding, envelope glycoprotein has three domains (DI, DII and DIII). DI and DII are involved in the invasion of the cell membrane [15]. DIII helps in receptor recognition and binding [10]. DIII contains various epitopes that can be blocked by neutralizing antibodies and decreasing the virulence of WNV. Pre-membrane glycoprotein supports the function of envelop glycoprotein [16, 17].

Seven nonstructural proteins of WNV include NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. The first nonstructural protein is NS1 that is glycosylated [18]. It exhibits different forms varying from dimers, monomers and hexamers depending upon the cellular location of the virus. NS1 acts as a cofactor during virus replication inside the cell and outside the cell; it turns into an immunomodulator [10]. NS2A protein is involved in membrane functions and viral RNA replication [18]. NS2B and NS3 are involved in the unwinding of viral RNA [19, 20]. NS4A protein aids in evading host immune response and acts as a cofactor for NS3 too [21]. In contrast, NS4B blocks the WNV interferon [22]. The NS5 protein has enzymatic activities of methyltransferase and RNA-dependent RNA polymerase [10]. NS5 is a crucial target for antiviral because of its larger size and involvement in key processes [23].

WNV PHYLOGENETIC LINEAGES

WNV was first isolated from the African country of Uganda in 1937 [24]. Later in the mid-20th century, WND outbreaks in humans and horses were reported from Egypt, India, France, Israel, South Africa. During the last decade of the 20th-century, sporadic outbreaks of WND in some European and Mediterranean countries clinked the danger alarm [25]. The first case of WND was reported from the United States of America in 1999. Since then, alone in the United States of America, WNV has caused 1,783 case fatalities in humans [26].

During the past 15 years, WNV has spread in the whole world mainly due to the transmission of the virus by migratory birds. WNV is a phylogenetically diverse virus with 9 possible phylogenetic lineages [27, 28]. Lineages 1 and 2 are considered the most virulent and widespread lineages of WNV. Lineages 1 and 2 are endemic in southeastern and central Europe [29, 30]. Lineage 1 has 3 distinct clades that contain a strain prevalent in specific regions. Clade 1a includes strains that are isolated from Africa, America and Europe. Clade 1b and 1c include strains prevalent in Australia and India, respectively [31].

Until 2004, lineage 2 was only reported in sub-Saharan Africa and Madagascar, but recent studies showed the spread to Hungry, Italy, Greece, Austria, South Africa [32]. Three clinical cases of encephalitis in humans caused by WNV lineage 2 were reported from Austria in 2009-2010 [28]. Lineage 3 isolates are prevalent in the Czech Republic [33, 34]. Lineage 4 and 5 are reported from Russia and India, respectively [35]. The 6th lineage of WNV is proposed based on a variation of the small gene fragment. Lineage 6 isolates are reported from the sequencing of WNV prevalent in Spain [36].

Lineage 7 isolates are different from all other WNV strains as these were first reported and isolated from ticks and rodents. Lineage 7 isolates were also named as Koutango viruses initially because they were considered as separate virus species. But now, these isolates are clustered in Lineage 7 of WNV [33]. Lineage 8 isolates of WNV were reported in Senegal in 1992 [37]. An assumed lineage 9 or a clade of lineage 4 was reported in Austria [27, 33].

DIAGNOSIS OF WNV

WNV infection can be detected by the detection of viral antigens or antibodies against the virus. The efficacy of either of these methods depends upon the extent of virus replication inside the host [38]. As in horses, viremia is for a few days, so mostly serological tests and necropsy of the brain and spinal cord are used for clinical confirmation. But, in birds, the situation is changed as both serological and viral antigens detection tests can be performed [39]. Just like horses in

CHAPTER 8

Hendra: An Emerging Viral Disease in Equine

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Abstract: Number of diseases have been emerged in the recent past and many of these have been emerged with a new fate. Hendra is a newly emerged disease of horses and humans. Members of the family *Paramyxoviridae* infect numerous species but with host specificity. Hendra virus of this family has become more important due to its zoonotic potential. Fruit bats have been considered as an asymptomatic reservoir host for this virus due to high seroprevalence against Hendra virus, earlier called "horse morbillivirus." Horses become affected after ingesting contaminated material polluted with fruit bat urine. Disease transmission from horses to humans occurs while touching the horse's fluids. Hendra is a fatal disease and causes death within a few days following the appearance of the clinical picture. Clinical signs involving the respiratory and nervous systems are evident during the disease course. Postmortem lesions are also associated with the lungs. Electron microscopy, Immunofluorescence, PCR and ELISA are laboratory diagnostic tools for Hendra. With the advancement of the world, the load of emerging diseases is increasing. Although Hendra has not been considered as a widespread disease yet but is a transboundary threat, so there is a need to control it. A Viral G glycoprotein-based vaccine has been produced in Australia against the Hendra virus. For the control of this disease, handling of infected horses and vaccination are important strategies.

Keywords: Emerging infection, Fruit bat, Hendra, Hendra virus, Horse.

INTRODUCTION

There is a need for advancement in every field of life. Like other disciplines, humans have also progressed blindly in the field of medicine and have tried their best for the control of diseases. A vast number of antibiotics have been discovered so far for the control of infectious agents. Parallel to all advances, the problems, including drug resistance, pesticide-resistant vectors, lack of specific antiviral drugs, and lack of specific treatment for parasitic and fungal infections, have also emerged [1]. All of these growing pains have made it difficult for the world to control existing infections, resulting in the creation of new diseases.

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Few diseases have been eradicated so far, but thousands of new diseases have emerged, and many of them re-emerged with a new fate. Stephen Morse of Columbia University has defined emerging diseases as rapidly increasing infections in incidence or geographic range. Hendra is a newly emerged disease of horses and humans [2]. The disease is sporadic and contagious in nature.

HISTORY

The history of Hendra is only two decades old. The first outbreak of the Hendra Virus occurred in 1994 in the state of Queensland, Australia [2 - 4]. In this outbreak, severe influenza like disease occurred with respiratory signs in horses. In only 14 days, 14 out of the 21 sick horses (property of Brisbane Queensland) died or were euthanized following an acute course of the disease, characterized by elevated temperature and severe respiratory difficulty. Brisbane property also lost 2 pregnant mares before this incidence due to a similar disease. This disease was also transmitted from dying mares to a trainer and a stable hand, who had severe influenza-like condition. The former could not survive the condition, but the stable hand survived. The postmortem report revealed severe interstitial pneumonia [2]. In the same year, a similar disease was reported from Mackay, Queensland, Australia [4]. In this outbreak, two horses died, and on the basis of postmortem examination, avocado toxicity and snakebite, respectively, were suspected as the cause of death. Until August 2017, 60 outbreaks of Hendra have been confirmed, with 102 deaths of horses.

Seventy outbreaks of Hendra have been reported in Australia until 2016 [10]. So far, the disease is not reported from any other country, but Bangladesh, China, Malaysia, India, Indonesia, Taiwan, and Thailand are declared as at-risk based on serological evidence. Although Hendra is a lethal disease, outbreak-pattern is sporadic in nature [11]. Susceptible hosts for Hendra include horses, guinea pigs and cats, golden hamsters, pigs, ferrets, non-human primates, and humans [12, 13].

VIRUS CHARACTERISTICS

Hendra virus belongs to *Paramyxoviridae* family [5] and genus *Henipavirus* (Fig. **1**) [4, 6]. The genus has emerged with two pathogenic species Hendra (HeV) and Nipah (NiV) virus [7]. Hendra virus has similarities with Morbillivirus [5], so initially, the name was given as Equine morbillivirus [5, 8]. Hendra virus particles are pleomorphic in shape and contain a single-stranded, negative-sense RNA genome [5]. Genome, surrounded with Matrix proteins, has a size of 18kb, larger than that of other members of the *Paramyxoviridae* family [9]. Attachment (G) and Fusion (F) are surface glycoproteins. In total, nine types of proteins are encoded by the virus genome.

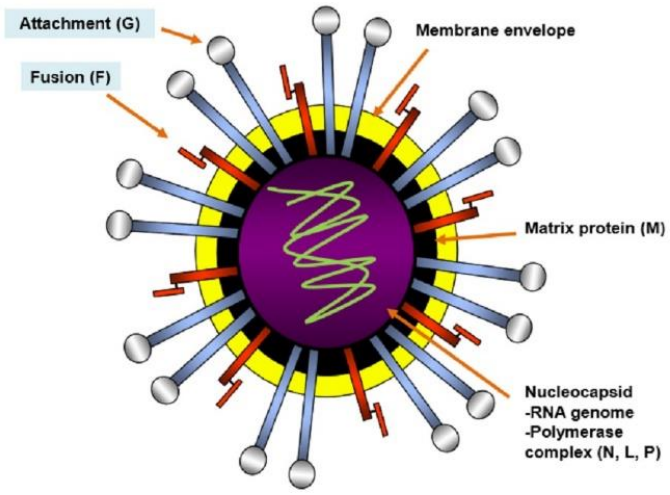

Fig. (1). Henipavirus structure, Courtesy of J Pallister.

Reservoir Host

Reservoir Host for virus, Fruit bats (*Pteropus*), also called flying foxes (Fig. **2**), belongs to the family *Megachiroptera* [4, 5]. Reservoir hosts play a key role in the transmission and epidemiological incidences of disease. With the emergence of Hendra in horses, the serological survey was started in other animals, followed by wildlife and birds. In the first attempt, no antibodies were found in any type of sera, but the second survey revealed antibodies capable of neutralizing HeV in 4 species of Pteropid bats/flying foxes in eastern Australia [6]. Due to the absence of clinical disease, flying foxes were said to be reservoir hosts. Seroprevalence of antibodies in flying foxes, tested through neutralization test, has been reported as 20% [5].

Fig. (2). Caged flying foxes (Courtesy of Dr H. A. Westbury, CSIRO).

CHAPTER 9

Advances in Rabies Research

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Abstract: Rabies is known to humans since long time. Rabies is a viral disease that induces neuro-encephalitis and produces 59,000 casualties globally on an annual basis. Once the viral pathogen produces neurological symptoms, the disease is almost 100% fatal. Despite of this risky condition, the disease is preventable through timely administration of post-exposure preventive measures (PEP) and/or pre-exposure prophylactic measures (PrEP). About 15 million heads receive PEP annually throughout the world. This chapter provides updated information on advances in rabies research from its epidemiology, transmission, immunopathology, clinical disease, patient management, and prophylaxis measures. This chapter will also discuss the technical framework for rabies control through advanced strategies of vaccination, surveillance, laboratory diagnosis, animal movement monitoring, and research. Internationally, the WHO and OIE are committed to formulating a comprehensive methodology for the control of rabies of human and animal origin by the year 2030. Conclusively, this chapter will widely focus on those aspects for rabies elimination globally.

Keywords: Diagnosis, Immunopathology, One health, Prophylaxis, Population management, Pre-exposure prophylaxis, Post-exposure prophylaxis, Rabies, Rabies free status, Rabies control, Vaccination.

INTRODUCTION

The clue for the existence of rabies during ancient times is found in archeological studies. Rabies is originated from the Sanskrit word “rabhas” which means “to do violence.” The saliva of rabid dog would acted as a poison (called “virus” in Latin) due to which rabies disease became endemic in ancient times [1].

The pathogen involved in the disease induction is linked with the *Mononegavirale*s order, *Rhabdoviridae* family, and the *lyssavirus* genus.

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The disease pattern has changed a little throughout the globe, but the canine is still considered as the main reservoir of rabies and continues spreading the disease in animals and humans [2].

Rabies is one of the deadliest diseases in the world that induces death in clinical patients. Once the rabies virus enters the neuron cell or the central nervous system, it is almost impossible to reverse the viral entry. The disease imposes a human death burden of approximately 50000-70000 per year, as estimated by World Health Organization (WHO). Most cases of causalities are reported from developing countries in the Asia and Africa regions, while 40% of victims are children [3]. More than 95% of rabies cases are reported due to dog bites. The neurotropic nature of the rabies virus and the wide range of its host species highlighted the importance of definitive control of this disease [4].

One Health Approach

Rabies has been considered a major health issue, and 95% of cases are reported from Asia and Africa, where the huge human population is at risk due to this disease. Although rabies is prevalent throughout the world in Asia, Pakistan and India have higher rates of deaths, *i.e*., 5000 and 20000 cases, respectively. The World Health Organization (WHO), along with The Office of International Epizootics (OIE) and The Food and Agricultural Organization (FAO) joined their hands to work for One Health (OH). The OH concept urges to eliminate such infections through a definitive approach for control.

Rabies Free Status

The pathogen has a wide range of host reservoirs, but canine/carnivores are notified to be most suitable host for rabies. The disease is prevalent throughout the world except on the islands. Many of the countries are endemic for rabies, except Australia and Antarctica. In the Asian region, the rabies-free countries are Bahrain, Japan, Hong Kong, Malaysia, Cyprus, Maldives, Singapore, Lakshadweep, Qatar, Andaman and Nicobar Islands of India and Timor-Leste. The other countries that also got rabies-free status are Antigua and Barbuda, Bahamas, Barbados, Belize, Jamaica, Falkland, Saint Kitts, and Nevis, Uruguay of America subcontinent and Albania, Trinidad and Tobago, E.Y.R. of Macedonia, Gibraltar, Finland Greece, Isle of Man, Malta, Iceland Portugal, Norway (except Svalbard), United Kingdom and Spain (except Melill + Ceuta). Among the African countries, Cape Verde, Libya, Mauritius, Congo, Seychelles, and Reunion are free from rabies. Oceana group of Islands like Cook Islands, Fiji, Vanuatu, French Polynesia, Guam, New Zealand, Solomon Islands, New Caledonia, and Papua New Guinea have also got rabies-free status [5].

Rabies Virus

The rabies virion is an enveloped particle that is covered by a lipid membrane, looks like a bullet in shape, and attains a size of 0.1-0.3 micron in length while 0.075 microns in width [6]. The external layer of the virion contains several protruding spikes of 10 nm long. These spikes are, in fact, trimmers of its glycoproteins. The virion particles get help from three glycosylated ectodomains of G-protein during the attachment to host cell receptors.

The rabies virus contains a non-segmented, negative-sense, single-stranded RNA genome of 12 kb size. The viral genome encodes for five structural proteins, namely a glycoprotein (G), a nucleoprotein (N), a phospho-protein (P), a matrix protein (M), and an RNA-dependent RNA polymerase (or large protein, L while the genomic RNA designed or arranged this five protein in a manner of N-P---G-L A rabies viral particle consists of two major components; the first component is an internal helical nucleocapsid that contains ribonucleoprotein, which tightly engages with N, P and L proteins. The second component is the external lipid envelope which originates from the cytoplasmic membrane of the host cell during budding. The matrix protein develops oligomers that bind outside the nucleocapsid [7].

CLINICAL ONSET OF DISEASE

Clinically, the disease has two main forms, the furious and the dumb. These two clinical positions are dependent on the viral inoculation site, a viral concentration that is deposited to the site of injury, and the viral movement to CNS [8]. The response to external stimuli differs from time to time. Clinical features of the disease have been divided into several stages started from patient history, viral incubation period, convalescence period, acute neurological period, coma, and death.

The other silent symptoms that are not usually observed are ataxic movements, radicular and neuropathic pain, objective sensory and motor deficits. Moreover, convulsion, semi-sensory loss, and uncontrolled behavior are also common. The susceptible patient of rabies showed unconsciousness, anxiety and hyperactivity during night time. The impulsive ejaculation, paraphasia and bilateral weakness are also observed in patients. The paralysis and weakness expand respiratory spasms. The heartbeat rate and its pulses change their rhythm and induce myocarditis due to rabies viral involvement in the various portions of the heart (like in the sinus and/or atrioventricular node). These conditions induce comma in the patients that further result in the deficiency of circulatory material and cause death. About 50% of the patients showed hematemesis six hours before death. Rabies antigen can be detected from cerebrospinal fluid (CSF) through RT-PCR

CHAPTER 10

Severe Acute Respiratory Syndrome (SARS)

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Abstract: SARC-CoV belongs to the group beta-coronavirus of the family *Coronaviridae*, the largest RNA viruses. First emerged from China in 2003, it spread to other parts of the world in the following year. A closely related MERS-CoV was reported in 2013 with 30-90% fatality. The virus contains four structural proteins (S, E, M, and N) along with non-structural and accessory proteins involved in viral pathogenesis and virulence. The virus mainly spreads through aerosols; bats are reservoir hosts; human-human transmission is also reported. It attacks lungs' tissue by virus-specific ACE2 receptors. Pro-inflammatory cytokines and chemokines increase during infection. Fever, pain, and dyspnea are important clinical signs, and death occurs due to acute and severe respiratory distress. Autopsy lesions resemble the HPAI H5N1 strain. RT-PCR is mainly used for accurate detection of the virus. No specific treatment or vaccine is available at this stage, but certain drugs like ribavirin have shown potential results.

Keywords: Coronavirus, MERS-CoV, SARS-CoV, Severe Acute Respiratory Syndrome.

INTRODUCTION

Family *Coronaviridae* is a large group of enveloped, positive-sense single-stranded RNA viruses, which infect a variety of avian and mammalian species [1]. Within this group, members of sub-family *Coronaviranae* are involved in respiratory and gastrointestinal problems [2]. Severe acute respiratory syndrome virus (SARS-CoV) is an important member of the genus *Betacoronavirus*, causing severe atypical pneumonia in humans, often leading to death [3]. It was first observed in 2002 in China and soon recognized as a global threat to the human population [4]. Wild animals like bats and chimpanzees serve as reservoir hosts [5].

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SARS-COV

It is an enveloped single-stranded RNA virus having a genome size of about 27 kb, which encodes for proteins that are translated from full-length and sub-genomic mRNAs [6]. Its polycistronic genome contains 8 ORFs (3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b) that encode for replicase genes (1a and 1b) along with structural genes, spike (S), membrane (M), envelope (E) and nucleocapsid (N) which are common to all coronaviruses [7]. ORFs are also involved in programmed host cell death through necroptosis and pyroptosis pathways [8]. The two replicase polyproteins (1a and 1b) are cleaved by two or three ORF1a-encoded proteases, resulting in a total of 16 nonstructural proteins (nsp1 to nsp16) [9]. These nsps form a replication and transcription complex (RTC) that directs the intricate machinery of viral RNA synthesis [10]. Fig. (**1**) shows the structure and organization of important SARS-CoV proteins.

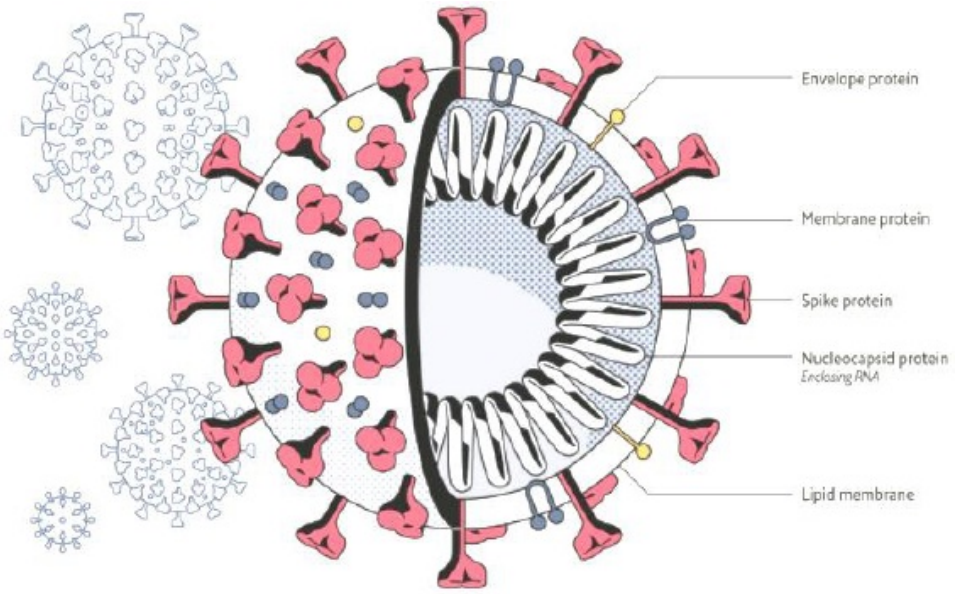

Fig. (1). SARS-CoV Structure.

The spike protein of SARS-CoV responsible for its antigenicity is post-translationally cleaved into two subunits; the N-terminal S1 subunit (~700 bp) carries a receptor-binding domain (RBD) while the C-terminal S2 subunit (~600bp) contains a hydrophobic fusion peptide region [11]. Recent cryo-electron microscopy (cryo-EM) results have shown the dramatic conformational changes in spike glycoproteins of SARS-CoV from the prefusion to the post-fusion transition of the virus [12]. Like all coronaviruses, this virus exhibits a high rate

of mutations, possibly due to large genome size, which results in the emergence of new strains [2]. Recent studies have also suggested that SARS-CoV encodes an RNA proofreading activity linked with the 3' to 5' exonuclease activity of nsp14, resulting in rapid virus evolution and antiviral drug resistance [3].

Epidemiology

Originating from China in 2003, SARS-CoV has been reported in all parts of the world with more than 8000 cases [13]. Though under control ever since in 2012, a related virus was discovered in Saudi Arabia called Middle-east respiratory syndrome coronavirus (MERS-CoV) with zoonotic importance [14]. It is now circulating in the human population and is responsible for 484 deaths in Asia [15]. The fatality rate for both these viruses ranges from 30% in SARS-CoV to 90% in MERS-CoV, with the majority of these in elderly cases [16].

Transmission

SARS emerged mainly in animal food handlers of the southern Chinese province of Guangdong in 2002 [17]. The primary route of transmission is through direct contact of the virus with mucus membranes. Other ways include aerosols, feco-oral route and fomites [18]. There are many risk factors associated with the spread of SARS-CoV in the susceptible human population, with the health care persons being at increased risk of the disease [19]. Other factors include increasing age and gender as this disease predominantly affects male [20].

Various super-spreading events have also been reported in the spread of SARS-CoV during its outbreak as the pathogen can spread at a rapid speed [21]. The role of reservoir hosts in the spread of the virus also becomes very important as SARS-CoV is reported to spread from bats to humans through infected palm civet cats [22]. Human-human transmission also occurs mainly through the nosocomial route [23].

Virulence Factors

A variety of genes are involved that impart virulence to SARS-CoV by the production of structural and accessory proteins [24]. S protein helps in the entry of the virus into the host cell, Matrix protein and 3a accessory protein induce neutralizing antibodies, while Nucleocapsid protein generates a T-cell response [25]. Envelope protein contains a PDZ-binding motif (PBM) that binds to PBM in protein-protein interaction, which modulates cellular pathways, allowing the virus to replicate and disseminate in the host cell [26]. SARS-CoV p6 brings ER stress in transfected cells, p7 inhibits the translation of cellular proteins while p8 and p9 induce caspase-dependent apoptosis [6].

CHAPTER 11

Potential Reservoirs of Viral Zoonotic Disease

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Abstract: One-third of infectious diseases have a zoonotic origin. Rapid urbanization and industrialization have affected the environment and increased the chance of spillover of different viral zoonotic pathogens. Viral epidemics of zoonotic origin are now becoming a menace for humanity. The most notable example is the COVID-19 pandemic that spread all over the world within weeks. Different animals such as bats, canines, non-human primates and birds act as reservoir hosts of many viruses. Sudden amplification of these viruses by amplifier hosts can lead to drastic outcomes. Researchers from different biological fields should work in liaison for a better understanding of genetic factors of viruses that can become the source of sudden mutation and increased pathogenicity and transmission to other hosts.

Keywords: Bats, Corona, Epidemic, Pandemic, Viral reservoirs.

INTRODUCTION

During the last 30 years, more than 70 percent of new human infectious diseases had a zoonotic origin. Zoonotic infections have always remained a threat for humans starting from anthrax, tuberculosis, plague, yellow fever and influenza [1]. But nowadays, change of habitat, more interaction of humans with wild animals, and environmental changes have increased the risk of emergence of zoonotic infections from wild animals [2, 3].

Despite rabies and influenza that are well recognized viral zoonotic diseases, some new zoonotic diseases have emerged from wildlife reservoirs during the last two decades [4]. One of the most striking examples is the coronavirus disease (COVID-19) pandemic in 2020 that is caused by the novel severe acute respiratory syndrome coronavirus type 2(SARS-CoV2). COVID-19 outbreak is considered to have started from the wet animal market in Wuhan City, China, in December 2019 and later on spread worldwide [5, 6].

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Other examples of newly emerged viral zoonotic viruses include the Ebola virus, SARS-CoV1 and the Middle East respiratory syndrome (MERS) CoV [7].

Some zoonotic viruses such as the Hendra virus and Nipah virus are highly pathogenic, but human-to-human transmission is not reported [8]. With extensive urbanization, there are increased risks of spillover of viruses with a high rate of transmission. There is a big gap in the understanding of genetic mutations of viruses that can induce pathogenicity and transmission to other hosts [9].

FACTORS AFFECTING EMERGENCE OF ZOONOTIC DISEASES

The emergence of zoonotic viral disease is often linked to ecological or biological changes. This includes contact of domestic animals with wild animals or human and wildlife contact [11]. Human encroachment, wildlife trade, climate change, livestock production systems and habitat destruction of wild animals are some key factors that are linked with the emergence of zoonotic diseases [12].

Socioeconomic development and modernization have increased the demand for agricultural land, water, and wood. It is necessary to assess the effects of these changes on host-pathogen interaction and transmission to other species. Understanding these interactions can help in the establishment of strategies to limit the transmission of zoonotic diseases [13]. Wild and aquatic animals are consumed as food in some countries. It has been reported that bushmeat consumption played an important role in the Ebola virus and the Nipah virus spillover [12, 14]. In the SARS outbreak, the virus was transmitted to humans via civet cats. Similarly, the COVID-19 pandemic started from a wet market in Wuhan, China [5].

Climate change affects the distribution of vectors and can introduce new pathogens to naïve and susceptible populations. Chikungunya virus (CHIKV), Crimean Congo hemorrhagic fever virus and West Nile virus (WNV) are increasing due to the increase in vectors population [15]. Intensive livestock farming also enhances the chances of zoonotic diseases. Genetic diversity of hosts can decrease the possibility of the epidemic. For example, during 1998–1999, the Nipah virus outbreak was started from the transmission of the virus from bats to swine reared in an intensive swine farming system [16, 17].

EMERGING ZOONOTIC VIRUSES FROM BATS

Bats act as perfect reservoir hosts as they are distributed in all continents except Antarctica, with more than 1300 species [18]. Bats live in large colonies and search for food from dusk to dawn. Due to their ability to fly, they can transmit

pathogens even on islands [19]. Until now, more than 200 viruses have been isolated from bats belonging to 27 different virus families [20].

Coronaviridae

Severe Acute Respiratory Syndrome Virus (SARS-CoV1)

In 2002, Severe Acute Respiratory Syndrome Virus (SARS) outbreak was for the first time reported from China, and within a year, it spread to 25 countries, causing the death of more than 800 people. Research on causative agents revealed that the SARS coronavirus was transmitted from palm civets to humans in live animal markets [18, 21]. Further epidemiology and laboratory investigations revealed that palm civets only acted as an amplifying host, while bats were found to act as reservoir hosts of many alpha and beta coronaviruses that include SARS-CoV and many SARS-like viruses [22].

The Middle East Respiratory Syndrome Virus (MERS-CoV)

The first outbreak of the Middle East respiratory syndrome coronavirus (MERS-CoV) was reported from Saudi Arabia in 2012. MERS has a mortality rate of 30%. Camels act as a reservoir host of MERS-CoV, and more than 50 percent of human cases have direct contact with camels [23]. The genome sequencing of the virus indicated that although camels act as the main source of spread to humans, bats are an ancestral reservoir of MERS-CoV. Middle East respiratory syndrome coronavirus belongs to group C betacoronavirus and has been isolated from bats of the family *Vespertilionidae* in different countries [24].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

In December 2019, many patients with respiratory problems of unknown origin were admitted to hospitals in Wuhan, Hubei Province, China [25]. Within two months, the disease spread all around the world, and till now, it has been reported in more than 200 countries and declared as a pandemic. WHO named the causing agent as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the disease as COVID-19 [26].

The genetic makeup of SARS-CoV-2 has 50 percent of similarity with MERS-CoV and 80% with SARS-CoV. Based on genome sequencing, SARS-CoV-2 has been categorized into the genus of betacoronavirus [27]. Although there are many missing links to understand the origin of SARS-CoV-2 and its transmission to humans, some early phylogenetic studies support the argument that SARS-CoV-2

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Muhammad Abubakar

Muhammad Abubakar, a scientist from the National Veterinary Laboratory, Islamabad, Pakistan, has experience of more than 15 years in various fields of veterinary sciences. His main expertise lies in the field of Transboundary animal diseases (TADs) and Antimicrobial Resistance (AMR) at the national as well as international level. He has worked both in academic and field implementation of disease control programs. He has worked with local and international projects for the establishment of diagnostic laboratories for TADs in the country. He has also conducted various trainings for the field as well as laboratory staff. He has published numerous research papers, review articles, and book chapters on different areas of veterinary sciences, especially on TADs (Avian influenza, FMD, PPR). He is the co-editor of the book "The Role of Biotechnology in Improvement of Livestock" by Springer Publisher, Germany and edited many books with Intech Open Publisher. He is currently working as an editor in chief of two journals in veterinary sciences (Research journal for Veterinary Practitioners and Veterinary Sciences; Research and Reviews).

Photo: Göran Ekeberg/AddLight

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