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GENERAL ASPECTS OF DISEASE: LITERATURE REVIEW

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Luanda Ferreira Cipriano[1], Nicole Amoêdo Luvison[2], Ketlin Milena Zardin[3], Rafael Sartori Flores[4], Oladapo Olawale Afolabi[5], Camille Moreira Bergamo Barros[6], Isis Alexandra Pincella Tinoco[7], Gabriela Victoria Araújo Saraiva[8],

[1] Doctorate Student in Veterinary Medicine
Unesp -SP
E-mail: luanda.cipriano@unesp.br
ORCID: https://orcid.org/0000-0002-8246-3257
LATTES: http://lattes.cnpq.br/6176296921118786
[2] Undergraduate Student in Veterinary Medicine
University of Caxias do Sul- UCS
E-mail: naluvison@ucs.br
ORCID: https://orcid.org/0009-0005-5783-8810
LATTES: http://lattes.cnpq.br/7395426062661654
[3] University of Caxias do Sul- UCS
E-mail: ketlinkolling@gmail.com
ORCID: https://orcid.org/0009-0004-1683-2271
LATTES: http://lattes.cnpq.br/0685734131130293
[4] Undergraduate in Veterinary Medicine
University of Caxias do Sul -UCS
E-mail: rsflores2@ucs.br
ORCID: https://orcid.org/0009-0007-7770-3483
LATTES: https://lattes.cnpq.br/7435419528509352
[5] Doctor in Veterinary Medicine
Unesp- SP
E-mail: o.afolabi@unesp.br
ORCID: https://orcid.org/0000-0001-7176-9261
LATTES: http://lattes.cnpq.br/1325271042113321
[6] Undergraduate in Veterinary Medicine
União Pioneira de Integração Social- UPIS
E-mail: bergamovetz@gmail.com
ORCID: https://orcid.org/0009-0000-6688-3000
LATTES: https://lattes.cnpq.br/9445983420853659
[7] Doctorate student in Veterinary Medicine
Unesp- SP
E-mail: isis.pincella@unesp.br
LATTES: http://lattes.cnpq.br/6023432605431904
ORCID: https://orcid.org/0000-0001-9102-2659
[8] Undergraduate in Veterinary Medicine
Catholic University of Brasília - UCB
E-mail: gvictoriasaraiva@gmail.com
ORCID: https://orcid.org/0009-0002-0616-0956
LATTES: https://lattes.cnpq.br/9933238062460353

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Dreyd Rodrigues Medeiros[9], Barbara Fernandes Werneck Teixeira[10], Édios Meurer Lana da Silva[11], Carolina Aires Martins[12] and Antônio Carlos Paes[13].

ABSTRACT

Morbillivirus has single-stranded, negative-sense RNA and lacks the reverse transcriptase enzyme, and is therefore not a retrovirus. Systemic infection by Morbillivirus can be found in wild canines, procyonids such as raccoons, kinkajous, bears, mustelids, hyenas, large felines, domestic felines, cetaceans, non-human primates, and humans. The great ability of Morbillivirus to cross species barriers is due to mutations in the H protein of the lipoprotein envelope, making it a pantropic virus. Outbreaks of diseases caused by Morbillivirus have been recorded in different species in the same period because, in addition to high virulence, infected animals are reservoirs of the disease and agents of intraspecies and interspecies transmission. This characteristic of Morbillivirus makes it difficult to eradicate VCC (canine distemper virus) infections, although vaccines are available for some affected species. The study of the interactions of Morbillivirus with different species leads us to discuss the concepts of 'One World One Health', 'One Medicine', and 'One Health' when correlated with the risks to human and animal health that Morbillivirus represents. The epidemiological surveillance work of VCC is significantly important because it is an emerging infectious disease that represents a threat to the health of humans and animals. Some studies indicate that the measles virus is derived from the distemper virus or the rinderpest virus. This study is a compilation of articles published in the literature, which provide information about the pathological mechanisms used by Morbillivirus to infect the host and brain structures with the description of the lesions. In addition, this literature review addresses the epidemiology, etiopathogenesis, histological changes, and clinical and laboratory diagnosis of distemper.

Keywords: Morbillivirus. Distemper. Epidemiology of Distemper.

[9] **Undergraduate in Veterinary Medicine**
E-mail: drmedeiro@me.com
ORCID: https://orcid.org/0009-0002-5714-9642
LATTES: https://lattes.cnpq.br/9504913789155844
[10] Undergraduate in Veterinary Medicine
Catholic University of Brasilia- UCB
E-mail: barbarafwt@gmail.com
ORCID: https://orcid.org/0009-0008-7426-4769
LATTES: https://lattes.cnpq.br/1011296974890263
[11] Undergraduate in Veterinary Medicine
União Pioneira de Integração Social- UPIS
E-mail: edmeurerls@gmail.com
ORCID: https://orcid.org/0009-0002-0311-5834
LATTES: https://lattes.cnpq.br/6899580204036046
[12] Undergraduate student in Veterinary Medicine
Catholic University of Brasília -UCB
E-mail: carol.aires@gmail.com
ORCID: https://orcid.org/0009-0008-4152-0594
LATTES: https://lattes.cnpq.br/8985736732153179
[13] Full Professor in Veterinary Medicine at the Department of Veterinary Hygiene and Public Health
Unesp-SP
E-mail: ac.paes@unesp.br
ORCID: https://orcid.org/0000-0001-7774-927X
LATTES: http://lattes.cnpq.br/3221552979448328

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INTRODUCTION

Canine distemper is caused by a multi-host pathogen, canine Morbillivirus of the Paramyxoviridae family, which causes severe immunosuppression and neurological disease associated with demyelination (ANDERSON et al., 2012; LIU et al., 2016). Approximately 30% of dogs infected with Morbillivirus develop neurological syndromes one to six weeks after the onset of clinical signs. Puppies aged 3 to 6 months may develop polyencephalopathies with forebrain dysfunction (GREEN et al., 2020).

CCV (canine distemper virus) is a single-stranded, non-segmented, enveloped RNA virus of the Paramyxoviridae family, genus Morbillivirus, the same genus as human measles (VANDEVELDE & ZURBRIGGEN, 2005). Morbilliviruses have already caused epidemics in several species since these diseases have similar characteristics with signs whose severity varies from subclinical manifestations to chronic brain degeneration, which can lead to the death of the animal (UHL et al., 2019).

Morbilliviruses can cause acute and progressive neurological diseases that affect gray matter and white matter. These signs include partial or generalized seizures, myoclonus, paresis, paralysis, proprioceptive deficits, circular movements, behavioral changes, and vestibular dysfunction, leading to the death of the patient or generating chronic neurological sequelae (VON RÜDEN et al., 2021). Dogs with distemper have a pattern of neurological changes that resemble human diseases such as Alzheimer's, multiple sclerosis, leukodystrophies, lysosomal enzyme deficiency, epilepsy, cortical malformations (lissencephaly, polymicrogyria), dementia, and focal lesions, among others (DATTA et al., 2012).

The anatomopathological model of distemper supports studies on multiple sclerosis because it resembles the mechanism of demyelination. Demyelination is related to the action of the virus on different types of cells. Brain homeostasis is maintained by astrocyte-astrocyte and astrocyte-oligodendrocyte junctions. Changes in these gap junctions can trigger seizures in periodic cases (VON RÜDEN et al., 2017).

Considering that changes in microglial cells alter the mechanisms of nutrition, support, and brain defense, the study of the neuropathogenesis of distemper can help unravel the main consequences of neuroinflammation and how microglial lesions are associated with the worsening of brain injuries.

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MATERIAL AND METHODS

SYSTEMATIC REVIEW

A systematic review of the literature was conducted in the Google Scholar, Medline and Pubmed databases in order to obtain an in-depth view of the relevant studies available in the literature.

To conduct this systematic review, the following keywords were used: etiology of distemper, distemper general aspects, neuropathogenesis, Morbillivirus, and anatomopathogenesis. The articles considered in this review were published in the last 40 years, with priority given to the most recent works from the last 10 years.

The oldest studies were also used to provide the first definitions of the characteristics of the disease under study.

The research databases indicated 254 articles, of which 88 publications were selected, in English, Spanish and Portuguese, which provided detailed information about the neuropathogenesis of distemper.

After reading the studies, other bibliographies were included, such as veterinary anatomy books.

INCLUSION CRITERIA

The studies published on the general aspects of distemper that met the following criteria were systematic reviews, meta-analyses, and scientific articles, as they are works that provide scientific evidence and show the differences between studies.

EXCLUSION CRITERIA

Published articles that did not describe or did not address in detail relevant information about the general aspects of distemper were not included in this study.

LITERATURE REVIEW

EPIDEMIOLOGY

Distemper is a highly contagious viral disease that affects carnivores of the Canidae, Mustelidae, Felidae, and Procyonidae families in different countries around the world, such as the United States, Finland, Germany, Poland, and countries on the African continent. Wild animals such as foxes, ferrets, and non-human primates can also be affected by Morbillivirus (ATHANASIOU et al., 2017).

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The seroprevalence of distemper in the fox population ranges from 4 to 17%, but this value may be underestimated due to the high mortality rates in this species that acts as a recipient of the disease (BILLINIS et al., 2013). The fatality rate of distemper is 5 to 30% in primates, with the main cause of death being pneumonia followed by neurological changes (VRIES et al., 2014). In a study conducted over seven years, the prevalence of distemper in wild dogs in Africa was 16%, compared to 48% prevalence in domestic dogs (WOODROFFE et al., 2012).

Other related viruses are and, such as the human measles virus and the rinderpest virus. Morbilliviruses also affect species such as cetaceans, felines, bats and rodents (UHL et al., 2019; PFEFFERMANN et al., 2018). Several studies have reported that the canine distemper virus has a common ancestor and that it has adapted to a variety of hosts over time (VRIES et al., 2014).

Outbreaks caused by VCC have already occurred in several species, such as the domestic dog (Canis familiaris), African wild dog (Lycaon pictus), black-footed ferret (Mustela nigripes), Baikal seal (Pusa sibirica), African lion (Panthera leo) and the spotted hyena (Crocuta crocuta) (NIKOLIN et al., 2012). In 1991 and 1992, captive leopards (Panthera pardus), tigers (Panthera tigris), lions (Panthera leo), and a jaguar (Panthera onca) were infected with CCV in North America. There were 17 deaths among these animals, and raccoons were considered the source of infection. In addition to these felines, two black leopards died at the Nairobi Zoo, Coal Valley, Illinois, and 2 tigers died at the Shambala Reserve, Acton, California (APPEL et al., 1994). In 1994, approximately one-third of the lion population in the Serengeti, northern Tanzania, died from infections attributed to CCV. There were also outbreaks in wild felines such as bobcats, the Canadian lynx, the Eurasian lynx, the critically endangered Iberian lynx, and the Amur tiger (NIKOLIN et al., 2012). The clinical signs found in these species were anorexia, gastrointestinal and respiratory disease, and seizures. VCC was isolated through monoclonal antibody tests that identified VCC from 3 leopards, 3 tigers, and 3 lions that died. Macroscopic and histopathological examinations revealed lesions similar to those found in canids, but there were fewer lesions in the brain and cellular proliferation in the lung with inclusion bodies. VCC antigens were also identified in immunohistology. Neutralizing antibodies to VCC were found in high titers in the serum of most animals, but were absent or low in some large felines that died after VCC infection (APPEL et al., 1994).

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Morbillivirus was identified in domestic cats in China in 2012, and the new species called feline morbillivirus (FEMV) caused tubulointerstitial nephritis (MARCACCI et al., 2016). Morbillivirus was detected by PCR of urine and blood samples in 12% of stray cats in Italy, and cytopathic effects, lysis, and syncytia formation in renal cells were observed. Histological examination of tissues obtained at necropsy revealed inflammatory infiltrate, degeneration, and tubular necrosis (WOO et al., 2012). In Japan, a study of domestic cats identified the presence of MVFE in 40% of the renal tissues of 10 cats with nephritis. Although MVFE exhibits genetic diversity, isolates from Japan and China showed an identical nucleotide sequence, suggesting that there are natural reservoirs. Gene analysis showed that recombination occurred within the F and H genes (SAKAGUCHI et al., 2015). In Italy, in a cat with chronic kidney disease (CKD), MVFE was found by RT-PCR examination of urine. In 2013, cats with MVFE were reported in Germany, and recently in Turkey and the United States (USA). Chronic infection caused by Morbillivirus may be responsible for viral recombination and heterogeneity. Furthermore, viral diversity is related to the existence of different viral ancestors involved in the origin of MVFE. In Europe, MVFE was detected in cats with CKD. Studies show that cats appear to host a heterogenic population of novel paramyxoviruses that are related to CKD in these animals (MARCACCI et al., 2016).

In VCC, the H protein is the most variable in the Morbillivirus genus, which explains a broad host spectrum. Infection can lead to the formation of multinucleated cells, the syncytia. Syncytia formation is determined by the VCC H protein. The cellular receptor for the H protein in host lymphatic cells is the SLAM molecule (signaling lymphocyte activation molecule) that binds to Morbillivirus. SLAM is expressed in humans by memory T cells, and B cells and induced by a range of immune cells upon activation. The specificity of the VCC H protein and the SLAM protein-receptor interaction represents a potential disseminator of the Morbillivirus host range (NIKOLIN et al., 2012).

In humans, the measles virus is a type of Morbillivirus. Measles virus and VCC use two cellular receptors, CD150 expressed on subsets of immune cells and nectin-4 expressed on epithelial cells. The measles virus infects immune cells that express CD150, and these cells migrate to the draining lymph nodes (SAKAGUCHI et al., 2015). The genus includes the Rinderpest virus (RPV) already eradicated by vaccination, ruminant plague, and canine distemper virus. There is evidence that Morbillivirus in marine animals, such as cetaceans, this virus being called Phocid distemper virus-1 (PDV-1), and in

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felines, Morbillivirus was recently observed in domestic cats, bat species, and rodents (PFEFFERMANN et al., 2018). Morbilliviruses were also found in bats, in RT-PCR tests of blood serum, at an incidence rate between 3.3 and 3.1% in a total of 86 species of bats, with 4,954 individuals from Brazil, African countries, and Europe (DREXLER et al., 2012). Morbilliviruses are responsible for epidemics that have decimated many populations over the centuries. These diseases have similar characteristics among species, with signs whose severity ranges from subclinical manifestations to fever, respiratory and gastrointestinal signs, dermatitis and immunosuppression, facilitating immune-mediated bacterial infections, brain damage, spinal cord and chronic brain degeneration, which can lead to death (UHL et al., 2019).

It is estimated that dogs, as reservoirs, may represent a source of infection of the distemper virus for non-domesticated animals. This transmission may pose a threat to populations of wild species (COSTA et al., 2019).

Epidemiological studies of the distemper virus, combined with constant epidemiological surveillance and prophylaxis measures such as vaccination, are necessary to contain the spread of the disease from dogs to other species. After rabies, distemper is considered the most relevant disease due to its severity (COSTA et al., 2019).

Morbilliviruses cause diseases with very high morbidity and mortality in human and animal populations. Outbreaks of measles and rinderpest occurred at the same time in Europe, Asia, and Africa between the 17th and 19th centuries. During these centuries, measles was endemic in Europe. The first record of distemper occurred in Ecuador and Peru in 1735. It can be seen that the occurrence of diseases caused by Morbillivirus in different species such as humans, cattle, and dogs occurred concomitantly on several continents, showing that the distemper virus has a pandemic nature (UHL et al., 2019).

Table 1 shows that a serious measles epidemic occurred at a time when distemper was established in South America and Europe, as well as rinderpest, which became endemic on several continents. Historical records of outbreaks of canine distemper in a setting where measles and rinderpest were endemic indicate a broad understanding of multi-host pathogens that continually threaten human and animal populations (UHL et al., 2019). Figure 1 describes the historical moments in which outbreaks and endemics of diseases caused by Morbillivirus occurred, suggesting that this pathogen originated from a common ancestor and was transmitted to several species. Morbillivirus may have adapted

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to humans after the first outbreak in animals. The development of resistance in people reduced morbidity and mortality rates. When the occurrence of canine distemper in dogs was recorded in 1809, similarities with the transmission of measles and greater susceptibility in puppies were noted. (NAMBULLI et al., 2016).

Table 1: The widespread measles epidemic in the Americas preceded the first distemper epizootics between the 16th and 17th centuries

Disease	Location	Countries	Century XVI	Century XVII	Century XVIII	Century XIX
Distemper	**America**	Quito, Ecuador, South	NRF	NRF	1748, 1759	NRF
	Europe	England	NRF	NRF		
		France	NRF	NRF	1761-64, 1782-84, 1799	1808
		Germany	NRF	NRF	NRF	1834
		Ireland	NRF	NRF	1761-64	NRF
		Italy	NRF	NRF	1799	NRF
		Russia	NRF	NRF	1771	1820
		Spain	NRF	NRF	1761	NRF
Measles	**Americas**	Caribbean, Guatemala	1517, 1519, 1523, 1529	NRF	NRF	NRF
		Argentina	1628, 1634-35, 1645	NRF	NRF	NRF
		Ecuador	1558, 1585, 1591, 1597	1611, 1612, 1618, 1628, 1634-35, 1645	Endemic from 1785	Endemic
		Central America	1531-34, 1559-63, 1576-80	1604, 1613-17	Endemic	Endemic
		Peru	1531-33, 1557-62, 1585-91	1611, 1614, 1618, 1628, 1634-35, 1645	Endemic	Endemic
		United States	1533-1533, 1592-96	1635, 1657, 1687	1713-1715, 1727, 1729, 1739-40, 1747, 1759, 1772, 1788	1802, 1820, 1837, 1848, 1861-65, 1878, 1879, 1883, 1884
	Europe	Canada	NRF	1635, 1687	NRF	1819, 1844, 1846, 1865
		European Union	Endemic	Endemic in 1629-1700, 1665, 1675	Endemic in 1700, 1800, 1740, 1762, 1751, 1781, 1783	Endemic in 1808, 1811-1812, 1839, 1846-49, 1882
Rinderpest	**America**	Entire region				
	Africa	Entire region	NRF	NRF	1726-65	1887-97

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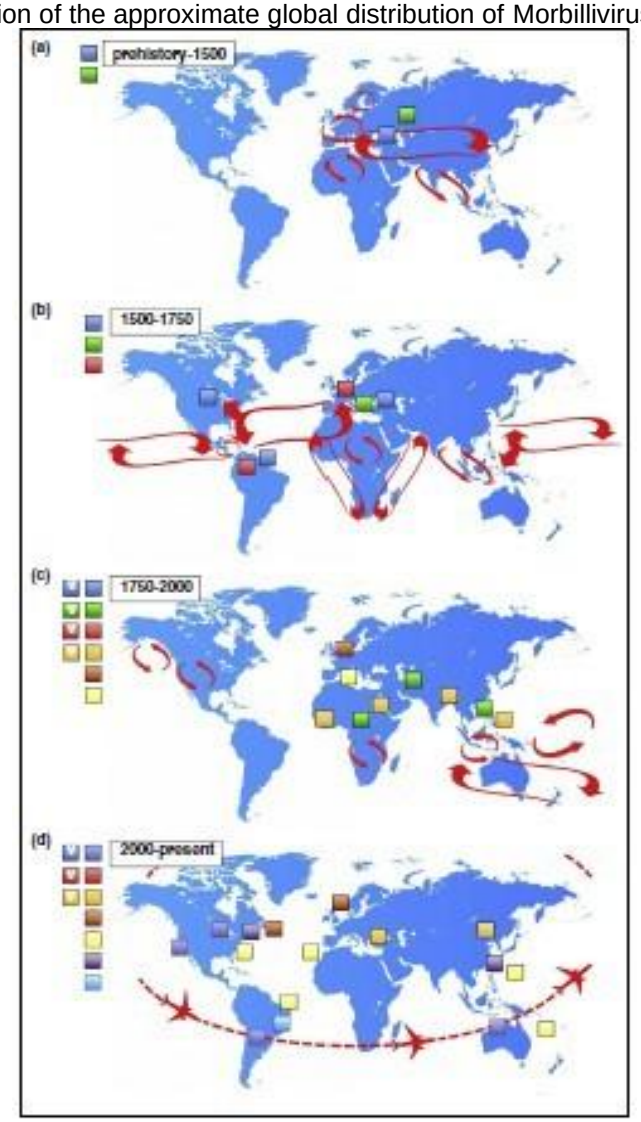
	Europe	European Union	1514, 1559, 1598	1609, 1616, 1618, 1625, 1665, 1673-74, 1682-83	1709-22, 1726-65, 1769-1800	1887-97, 1800, 1816, 1825-37, 1844, 1863-67, 1877

Source: Modified from UHL et al., 2019.

Figure 1: Representation of the approximate global distribution of Morbilliviruses throughout history.



(a) Morbillivirus (blue) and Rinderpest morbillivirus (green) are the oldest Morbilliviruses that spread along ancient trade routes (red arrows).
(b) Importation of Morbillivirus into the New World and canine distemper virus (red) into the Old World during the Age of Exploration.
(c) Spread of Rinderpest morbillivirus to Africa and Asia due to transboundary movement of livestock and establishment of the first globally distributed Morbillivirus. Discovery of ruminant plague (light orange), rinderpest (dark orange) and Morbillivirus in cetaceans such as seals, respectively. Development of attenuated vaccines against Morbillivirus in different species has brought greater control of the disease in many parts of the world.
(d) Discovery of feline Morbillivirus (purple), a proposed new member of the genus in Asia and the United States.
Sequence determination of bat Morbillivirus (light blue with dashed line) from clinical material obtained in Brazil. Morbillivirus expands its geographic range in Asia and Africa and is isolated in Turkey and China. Reemergence of Morbillivirus (blue with red line) in regions of the world where it was endemic.

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Detection of Morbillivirus in cetaceans (yellow) occurred in a broader range of widely distributed marine mammals. After the eradication of Rinderpest morbillivirus, use of the vaccine in cattle was suspended. Morbillivirus remains globally distributed(NAMBULLI et al., 2016).

ETIOPATHOGENESIS

Canine morbillivirus of the Paramyxoviridae family causes a severe and highly contagious systemic disease that affects domestic and wild carnivores (SATO et al., 2012, LOOTS et al., 2017). Infectious diseases in general are the evolutionary result of complex interactions between infectious agents and their hosts, such as adaptation of agents to host cells, specific tropism, neuroinvasiveness, immune response to the virus, specific tropism, among other factors (VANDEVELDE & ZURBRIGGEN, 2005).

The VCC genome is 15,690 nucleotides long and contains six genes. Of these, two are non-structural and six are structural proteins, which are encoded by messenger RNAs (PLATTET et al., 2007). Morbilliviruses are enveloped in a lipoprotein envelope with a non-segmented negative-sense RNA genome that encodes a single envelope-associated matrix protein. The envelope consists of the nucleoprotein N and the M protein, which is located on the inner surface of the envelope, displaying two surface glycoproteins: the attachment protein (H) and the fusion protein (F). The cellular receptor for the H protein “in vivo” has not been determined. Morbilliviruses also have two proteins associated with polymeric RNA (polymerase complex), which are the phosphoprotein P and large protein L, and a nucleocapsid protein (N) that encapsulates the viral RNA (VANDEVELDE & ZURBRIGGEN, 2005; SATO et al., 2012; LOOTS et al., 2017). The fusion protein (F) is a classical type I glycoprotein, composed of 662 amino acids essential for viral penetration and spread in the host. Translation of the F protein begins at the first start codon, AUG1, or at the second codon, AUG61, generating the pre-F0 AUG1 and pre-F0 AUG61, which are translocated to the endoplasmic reticulum and cleaved between amino acids 135 and 136 by a cellular signal peptidase, thus producing a peptide of 75 or 135 amino acids, depending on the translation codon (VANDEVELDE & ZURBRIGGEN, 2005; SATO et al., 2012; LOOTS et al., 2017).

For membrane fusion to occur, the F protein undergoes a cascade of changes: the F protein represents a potentially active fusion structure for the plasma membrane that is dependent on the receptor and hemagglutinin (H); the F protein undergoes conformational changes that finally lead to membrane fusion (PLATTET et al., 2017).).

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a)

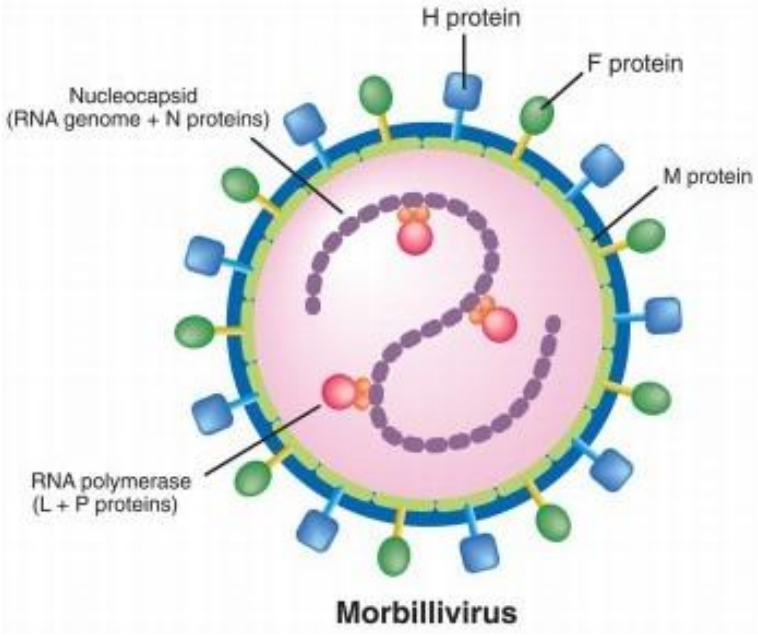
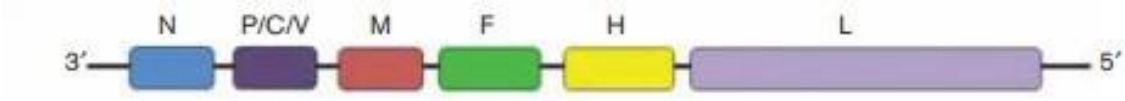


Figure 2



A) The figure shows the viral particle with the lipoprotein envelope, containing the ribonucleoprotein complex consisting of the nucleocapsid. In the envelope, there are the M proteins, the fusion protein F and the hemagglutinin (H). The viral RNA polymerase contains the L and P proteins (Adapted from SATO et al. 2012 and LOOTS et al., 2017).

B) The two glycoproteins, the hemagglutinin protein (H) (yellow) and the fusion protein (F) (green) together with the large L protein (purple) constitute the ribonucleoprotein complex (RNP) (Adapted from SATO et al. 2012 and LOOTS et al., 2017).

SLAM: THE MORBILLIVIRAL RECEPTOR AND MECHANISMS OF VIRUS ENTRY INTO THE HOST CELL

SLAM (Single-stranded lymphocyte activation molecule) acts as a cellular receptor for Morbillivirus (FUKUHARA et al., 2019). SLAM is a member of the immunoglobulin superfamily subset and has two extracellular domains (V-loop and C2-loop) along with a transmembrane region and a cytoplasmic tail. The interaction between the Morbillivirus H

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protein and the V domain of the SLAM molecule in target cells is responsible for Morbillivirus infection (YADAV et al., 2019).

Morbilliviruses mainly use three types of receptors, which play a role in host specificity and tissue tropism of viruses. The signaling lymphocyte activation molecule, SLAM, is the main cellular receptor for viruses in humans, cattle and dogs, first identified in humans as an activation receptor for T cells, B cells and B cells induced after activation (YADAV et al., 2019).

Human SLAM is selectively expressed in lymphoid tissues, so human SLAM has tissue tropism. Dogs and cattle have a SLAM molecule homologous to human SLAM that acts as a cellular receptor for VCC and RPV, respectively (TATSUO & YANAGI, 2002).

The mechanisms of entry of Morbillivirus into host cells are important to determine its multi-host characteristic and tissue tropism. Morbilliviruses have two glycoproteins, hemagglutinin (H) and fusion protein (F) on the viral surface. During virus invasion, the H protein binds to the host entry receptor, SLAM, which is also known as CD150. SLAM is an immune cell-specific protein expressed on the surface of thymocytes, activated lymphocytes, mature dendritic cells, and macrophages (FUKUHARA et al., 2019).

The SLAM receptor is considered a determinant of immunosuppression and induces conformational changes in the F protein, resulting in fusion of the virus with the plasma membrane of the host's immune cells. During fusion, some amino acids of the H protein are important for favoring binding to nectin-4, which is expressed on the cell surface and is responsible for susceptibility to Morbillivirus infection.(MESSLING et al., 2005; FUKUHARA et al., 2019).

Figure 3: Wild-type VCC strain 5804PeH infects nectin-4-expressing cells in humans and dogs. Members of the VCC and measles virus groups share common tropism and disease. The study suggests that the abundance of nectin-4, as a VCC receptor, on the cell surface is related to its susceptibility to VCC infection. Fluorescence images were captured four days after infection and overlaid with phase contrast; nectin-4 in the corresponding cell line shaded with IgG; nectin-4 antibody, nectin-4-red (NOYCE et al., 2013).).

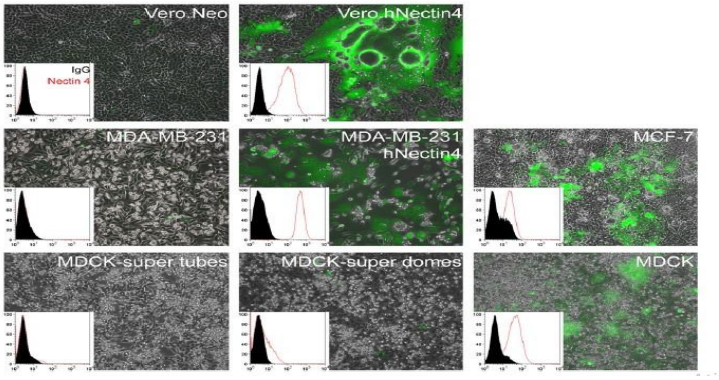

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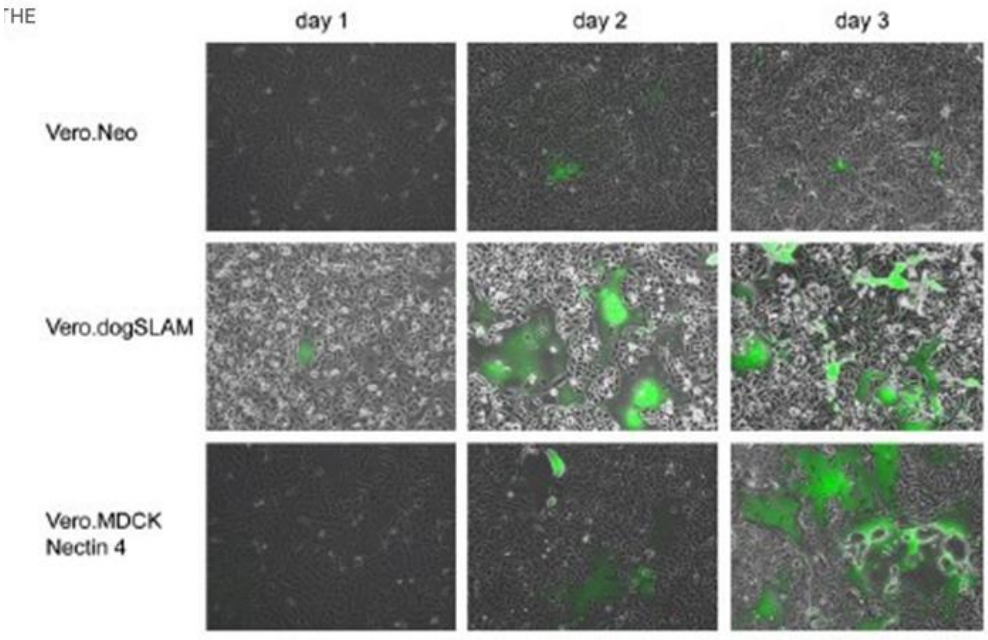
Figure 4: Wild-type CDV5804PeH efficiently infects Vero cells expressing dog nectin-4. Canine Vero cells express SLAM. MDCK (canine kidney cells) nectin-4 cells expressing dog nectin-4 and a plasmid in the control group were infected with the CDV5804PeH strain. Phase contrast and fluorescence: Images were captured and overlaid to visualize the extent of virus replication, with a significant increase in CDV5804PeH. (Adapted from NOYCE et al., 2013).



For many years, it was believed that VCC replicated in the respiratory epithelium before disseminating, but it has recently been concluded that VCC infects macrophages and dendritic cells of the airways using SLAM as a cellular receptor. Infected cells cross the respiratory epithelium and transport the infection to the lymphoid organs, where viral replication occurs. Nectin-4 is an immunoglobulin known as a host egress receptor that interacts with high affinity with the viral attachment protein through its distal membrane domain, enabling viral dissemination in the airways (MÜHLEBACH et al., 2011).

Morbilliviruses infect cells that express CD46 and SLAM, but they also infect other cells through the cellular receptor, nectin-4. The cells that express nectin-4 are epithelial cells, cells of the trachea, bronchi, lungs, oral cavity, pharynx, esophagus, intestines, liver and urinary bladder. Nectin is a family of adhesion molecules, but only nectin-4 is an epithelial receptor for Morbillivirus (YADAV et al., 2019).

Nectin-4 has a transmembrane glycoprotein structure with three similar ectodomains, a transmembrane region and a cytoplasmic tail. It is expressed basolaterally in epithelial cells near infected lymphocytes and dendritic cells and acts as a viral receptor through a mechanism similar to the interaction between the SLAM V domain and the Morbillivirus H protein (YADAV et al., 2019).

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SLAM is an efficient receptor for wild-type VCC in canine tissue cultures. In immunocytochemical analyses, SLAM is expressed to a limited extent in the CNS compared to lymphoid tissues, showing that other viral receptors probably exist (VANDEVELDE & ZURBRIGGEN, 2005). Morbillivirus is transmitted through aerosols to the respiratory tract, and the first replication occurs in lymphoid tissues, causing severe long-lasting immunosuppression (VANDEVELDE & ZURBRIGGEN, 2005; COSTA et al., 2019). The SLAM receptor in the immune system correlates with the immunosuppression associated with Morbillivirus-mediated cytolytic infection in lymphoid tissue. Other receptors are responsible for the entry of VCC into nectin-4, as the epithelial cell receptor contributes to the multitropism of Morbillivirus. The SLAM receptor binds to the H protein of the canine distemper virus in specific regions, which comprise 500 to 550 amino acids (COSTA et al., 2019). After six days of infection, all lymphatic tissues are affected and viremia develops (KIM et al., 2001). The incubation period is approximately 1 to 4 weeks, depending on the immune status of the affected dogs (AWAD, 2019). Dogs without antibodies against the canine distemper virus die approximately three weeks after infection (KIM et al., 2001).

At the beginning of the infection, the canine distemper virus invades macrophages, the respiratory tract and subsequently affects other organs such as the gastrointestinal tract, lymphoid organs, urinary bladder and the central nervous system. Manifestations can be subclinical to lethal, with the main clinical signs being fever, respiratory, gastrointestinal and dermatological changes (ATHANASIOU et al., 2017).

The depletion of lymphocytes, mainly CD4 T cells, due to the apoptosis of lymphoid cells, in the initial phase, causes persistent immunosuppression, and secondary bacterial infections may occur. (BEINEKE et al 2009).

During the acute phase of infection, T cells are more affected than B cells, while CD8 + cells are less affected and recover faster compared to CD4 lymphocytes. After 10 days of infection, VCC replicates in epithelial tissues, causing multisystemic involvement in the respiratory tract, gastrointestinal tract and dermatological changes (BEINEKE et al 2009; VANDEVELDE & ZURBRIGGEN, 2005).

When it reaches the CNS, the VCC invades the brain through infected mononuclear cells, circulating through the cerebrospinal fluid (CSF) and fusing with the ependymal lining of the ventricles, causing periventricular and subpial lesions. When it affects the CNS, it determines the neurological syndrome with demyelinating lesions, which can occur within

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3 weeks of the onset of infection. Neurological signs may occur in the absence of systemic signs (VANDEVELDE & ZURBRIGGEN, 2005).

The virus can cause damage to the brain, such as demyelinating leukoencephalomyelitis, and to the spinal cord, which induce chronic immune-mediated neurological manifestations, with increasing levels of MHC class II molecules due to the permanence of the virus in the nervous tissue (BEINEKE et al. 2009; KLEMENS et al., 2019; RENDON-MARIN et al. 2019). Demyelination occurs mainly in astrocytes, with hypertrophy of these cells, isomorphic gliosis, reactive astrocytes (gemistocytes) and, occasionally, the formation of astrocytic syncytial cells (KLEMENS et al., 2018).

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