Feline Vaccination Guidelines in Israel

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ABSTRACT

Cats are a very popular pet animal worldwide and in Israel. In addition, there is a large number of non-owned cats living next to human populations in Israel. Vaccination is an important measure for preventing infectious diseases among cats and when possible, preventing the spread of zoonotic diseases to humans, as in the case of rabies. Although feline vaccination has been a standard of care for cats for many years, there are changes in the vaccines available, current concepts of when and how to vaccinate cats, and what is considered as core vaccination for a cat versus what can be considered as non-core vaccination which should only be recommended in certain circumstances. Vaccination guidelines for cats must be tailored to the animal's environment, geographical location, and be updated regularly as knowledge progresses and new products are available. The purpose of this review was to evaluate and describe the vaccines available and used in Israel to prevent feline infectious diseases, and to update on these diseases, and their epidemiology in Israel. This review focuses on feline panleukopenia, calici and herpes viruses, rabies, *Chlamydia felis*, feline leukemia virus (EeLV) and feline immunodeficiency virus (FIV). It highlights their pathogenicity, modes of transmission, susceptibility to disinfectants and the type of vaccines produced for their prevention. These guidelines are intended to assist the small animal veterinary practitioners in Israel to vaccinate cats as efficiently and successfully as possible.

Keywords: Feline vaccination; Core-vaccines; Non-core-vaccines; Recommendations; Israel.

INTRODUCTION

Vaccination is the exposure of an animal or human to antigen of a pathogen and the induction of an immune response that will protect the host when it encounters the virulent pathogen. Vaccination of cats is intended to prevent them from becoming infected with some of the most common feline infectious diseases by inducing their immune system to produce immunity against the causative agents of these diseases, mainly viruses and bacteria. Cats are often protected against some infectious diseases by maternally derived antibodies (MDA) in their blood, but the levels of these antibodies decrease gradually after birth and eventually kittens must mount their own immune responses in order to avoid being infected and becoming ill. Cats have an endotheliochorial placenta with minimal access of antibodies from the queen's blood to the fetus and the majority of maternal antibodies in neonatal kittens are transferred via the colostrum during the first 16 hours post-partum (1, 2). Cats that have absorbed colostrum in the first 16 hours of their lives will usually be protected by MDA against pathogens that the queen has encountered or been vaccinated against (1). The duration of protection by MDA is different in individual cats and also for different pathogens and is usually two to five months (3).

Vaccination of cats is extremely important for prevention of infections with severe and life-threatening infectious diseases and in some cases also for protecting the cat's environment and owners, as in the case of rabies vaccination. Although feline vaccination has been a standard of care for cats for many years, there are changes in the vaccines avail-

able, current concepts of when and how to vaccinate cats, and what is considered as compulsory vaccination for a cat versus what can be considered as non-core vaccination which should only be recommended in certain circumstances. The realization that feline vaccination may induce injection site sarcoma, although relatively rarely (4), and that cats living in different conditions, such as cats in private households, versus those living in catteries and animal shelters, require different vaccination protocols (5, 6). The concept that vaccination guidelines for cats must be tailored to the animals environment, geographical location, and be updated regularly as knowledge progresses and new products are available is the basis for the current guidelines.

Different types of vaccines are currently available for cats and include modified live virus (MLV) attenuated vaccines, killed/inactivated vaccines, recombinant and DNA vaccines. Some vaccines are made to be injected into the muscle or subcutaneous tissue whereas others are applied directly to mucosal sites intranasally or orally. Feline and canine vaccines have been divided by the World Small Animal Veterinary Association (WSAVA) vaccination guidelines group (VGG) as core or non-core, with the core vaccines defined as vaccines that all cats or dogs throughout the world must receive (5). On the other hand non-core vaccines are optional and may be of great importance in some geographical areas or under particular circumstances.

Table 1: List of registered and approved feline vaccines for 2020 published by the Veterinary Services in Israel (the list is updated annually; published under approval from the Veterinary Services, Ministry of Agriculture, Israel).

Animal type	Name	Active ingredients	Authorization holder	Manufacturer	Importer	Distributer	Vaccine number
Cats	Feligen CRP	Feline calicivirus F9 strain, Feline viral Rhinotracheitis F2 strain, Feline viral Panleukopenia virus LR 72 strain	A. vetsupply	Virbac	A. vetsupply	A. vetsupply	7-054-15-01
Cats	Felocell 4	Feline Calici, Feline Panleukopenia, Feline Rhinotracheitis, *Chlamydia psittaci*	Zoetis	Zoetis	Zoetis	Vetmarket	7-055-16-12
Cats	Nobivac Tricat trio	Feline Calici, Feline Panleukopenia, Feline Rhinotracheitis	Intervet Israel	Intervet	Intervet Israel	Vetmarket	7-105-07-12
Cats	Purevax Rabies	Rabies recombinant canarypox virus (vCP65)	Beit erez	Merial	Beit erez	Beit erez	7-119-10-04
Cats	Purevax RCP	Feline rhinotracheitis herpesvirus (FHV) F2 strain, Feline Calici virus antigens FCV431 & FCV G1 strains, Feline panleukopenia virus PLI IV strain	Beit erez	Merial	Beit erez	Beit erez	7-120-10-04
Cats	Purevax RCPCH	Feline rhinotracheitis herpesvirus (FHV) F2 strain, Feline Calici virus antigens FCV431 & FCV G1 strains, Feline panleucopenia virus PLI IV strain, *Chlamydla felis* 905 strain	Beit erez	Merial	Beit erez	Beit erez	7-121-10-04
Cats	Nobivac Ducat	Live Feline Rhinotracheitis virus, Live Feline Calici virus	Intervet Israel	Intervet	Intervet Israel		7-289-07-15

Table 2: Recommended vaccination schedule for kittens in Israel starting at 6 weeks of age. Adapted from the WSAVA recommendations (5).

Week of life	Vaccine (Core)	Rabies	*Chlamydia felis* (non-core; administered in indicated situations)
6	FPV, FCV, FHV-1		
9-10	FPV, FCV, FHV-1		*C. felis*
12-14	FPV, FCV, FHV-1	Rabies	*C. felis*
16-18	FPV, FCV, FHV-1		
26 to 52	FPV, FCV, FHV-1	Rabies at 52 weeks	*C. felis* at 52 weeks
Revaccination	Every 3 years for low risk cat; Annually for high risk cats.	Rabies as instructed by producer label or local authority	Annually

FPV – feline panleukopenia virus; FCV – feline calici virus; FHV-1 feline herpes virus; *C. felis* – *Chlamydia felis*

The present article was written to provide Israeli veterinarians with general guidelines for the vaccination of cats in Israel. Global guidelines and recommendations for vaccination of cats and dogs have been published by the WSAVA and updated periodically by the VGG (5, 7, 8). In addition, more focused or local guidelines have also been published aimed at cat populations in different parts of the world or targeted at specific types of populations such as shelter animals (6, 9, 10, 11, 12, 13). The Israeli guidelines relate to the current situation in Israel, local conditions and legislation, and the vaccines permitted by the Israeli Veterinary Services as detailed in the service's website and updated annually. The latest list of permitted vaccines can be found at: https://www.moag.gov.il/vet/Yechidot/TachshirimTrufot/Pirsumim/2020/Pages/tachshirim_chimim_2020.aspx

Only vaccines approved by the Israeli Veterinary Services are allowed for importation and use in Israel (Table 1). It is advised to carefully read the manufacturer's "summary of product characteristics" sheet before their use. These guidelines below include information on each of the core vaccines, and some of the non-core vaccines, the diseases they can prevent and their usage recommendations. A recommended vaccination schedule is provided in Table 2.

A. Core vaccines

Feline Panleukopenia virus

Background

Feline panleukopenia virus (FPV), the causative agent of feline panluekopenia, belongs to the Parvoviridae family and is a small single-stranded DNA virus that does not have a protein envelope. FPV infects the domestic cat, wild felids, and some species of wild canids including raccoons and foxes. Unlike its canine counterpart, canine parvo virus 2 (CPV-2) which emerged as a canine pathogen in the 1970's, FPV has been recognized to cause disease in cats since 1928 and has possibly been a cause of feline disease also in the 19th century. FPV like CPV-2 is resistant to conventional disinfectants such as quaternary ammonium compounds and alcohol-based sanitizers, but is sensitive to sodium hypochlorite (chlorine bleach) (14, 15).

Feline panleukopenia is prevalent mostly in cats under one year of age, but it may also cause disease in older unvaccinated or inadequately vaccinated cats of all ages. Feline panleukopenia occurs often in catteries, shelters and multiple cat households. Transmission of the virus is by the fecal-oral route or through contaminated inhaled fomites (15). FPV invades cells by binding to transferrin receptors on the cell's membrane. The virus initially replicates in the lymphoid tissues of the cat's oropharynx and then disseminates hematogenously to other tissues. The virus replicates in the small intestine's epithelial crypt cells and causes severe villous damage with increased intestinal permeability, bleeding into the intestine and malabsorption. In the bone marrow, it induces decreased production of leukocytes with ensuing neutropenia while it causes necrosis and severe damage to lymphoid organs and tissues. The incubation period from infection to clinical disease lasts 2-10 days, although subclinical infection with FPV with no clinical manifestations is possible. Shedding of the virus in feces can occur before the appearance of clinical signs or in subclinical infections, with shedding for up to six weeks, although most cats in an experimental infection stopped shedding in the feces three weeks post-infection (16, 17).

FPV may infect the fetus transplacentally during the queen's pregnancy. Infection in early pregnancy may result in fetal death and abortion while infection in late pregnancy, or infection of the neonate up to approximately one week of age, may damage the Purkinje cells of the cerebellum and lead to cerebellar hypoplasia that manifest as ataxia when the kitten begins to walk. Other neurological damage with hydrocephalus and seizures may also occur but are less frequent than ataxia due to cerebellar hypoplasia (14).

FPV does not bind to the canine transferrin receptor on canine cells, which is important for infection and transmission to dogs, and therefore it is probably not infectious to dogs. However, the variants of CPV 2, CPV-2a, CPV-2b, and CPV-2c can infect cats and cause sub-clinical and clinical infections with clinical signs that are indistinguishable from FPV infection (15).

Major Clinical signs

The typical clinical signs of feline panleukopenia include inappetence and lethargy accompanied in some cases by fever, which progress to vomiting, diarrhea which may be watery to hemorrhagic, dehydration, and weight loss. Terminally ill cats may be hypothermic. Death may ensue due to dehydration, bacteremia with septicemia, hypoglycemia or electrolyte imbalances. Nervous system abnormalities such as ataxia with intention tremor, behavior changes, or

more rarely seizures, may be seen in kittens infected *in utero* or neonatally.

Typically cats with feline panleukopenia have a phase of leukopenia composed of neutropenia and lymphopenia which may be extreme, however, the disease cannot be ruled out in cats with leukocyte counts that are within reference ranges, as studies have shown that a large percentage of cats with the disease were not leukopenic when tested (14). Serum biochemistry of cats with panleukopenia may show hypoalbuminemia, hypoglycemia, hyponatremia, hypokalemia or other electrolyte and acid-base abnormalities.

Type of vaccine

Cats were vaccinated successfully against FPV with tissues from sick cats inactivated in formalin as early as 1934. In 1964, FPV was isolated in tissue culture and this enabled the development of inactivated and modified live vaccines (15). MDA against FPV have been shown to wane below the concentrations that will cause vaccine neutralization in most kittens by the ages of 8-12 weeks (5). Despite this, interfering MDA may persist in some kittens until 16-20 weeks. MLV and inactivated vaccines are available for vaccination against feline panleukopenia. The FPV vaccine is considered a core vaccine by the WSAVA (5) and several MLV FPV vaccine brands are available in Israel (Table 1).

Vaccination recommendations

The FPV vaccine is usually used in combination with the other feline core vaccines including the feline calicivirus and the feline herpes virus 1 vaccines. The WSAVA vaccination guidelines (5) recommends to begin vaccinating kittens against FPV with MLV vaccines at 6-8 weeks of age and then every 2-4 weeks until 16 weeks of age or older. Reactivation vaccination (booster) is recommended initially at between 6-12 months of age, and then not more often than every three years. Initial adult vaccination is usually done according to the manufacturer's instructions with two doses 2-4 weeks apart, although one dose of vaccine is considered protective. Vaccination of queens should be avoided during pregnancy. If vaccination during pregnancy is essential, it should be done with an inactivated vaccine to prevent the possibility of neurologic damage to fetuses (18). The WSAVA guidelines have recommended that MLV vaccines should also not be used in feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infected cats (5).

Feline Calici virus

Background

Feline calici virus (FCV) causes oral and upper respiratory tract disease and also affects other body systems. It is a single stranded RNA virus which has many strains. The capsid protein of FCV may undergo variation and allow evasion of the virus from the immune system. Cats may shed the virus after infection for weeks and months as carriers and in some cases shedding persists lifelong. FCV is transmitted through direct contact and respiratory secretions and aerosols. It can survive in the environment for 28 days and is resistant to conventional disinfectants such as quaternary ammonium compounds. Generalized forms of calicivirus infections with high mortality rates of 50% referred to as virulent systemic disease (VSD) have been reported in the past 20 years and include multi-organ involvement, subcutaneous edema, oral and cutaneous ulcers (19). FCV is one of the major agents involved in the feline upper respiratory tract disease (URTD) together with feline herpes virus, *Chlamydia felis*, *Bordetella bronchispetica* and other pathogens (20).

Major Clinical signs

Erosive and ulcerative oral lesions are frequently described in FCV infection, and may last for 2-3 weeks. These lesions may appear on the tongue, nasal planum and lips. Chronic FCV infection is often associated with proliferative and ulcerative lymphoplasmacytic stomatitis. Transient lameness associated with joint synovitis has also been reported following acute FCV and also following vaccination with some FCV vaccines. The VSD form of calicivirus infection apparently attacks the liver, lungs, endothelial cells and the pancreas. It disrupts tight junctions between cells and induces vasculitis. This induces facial and limb edema with crusting, pulmonary edema, hepatitis, pancreatitis and pleural effusions, with possible coagulopathy and diathesis (21).

Co-infections with feline herpes virus and other pathogens of the feline respiratory tract are common in FCV infection. In addition to that, infection with the retroviruses FIV and FeLV should also be considered, especially in cases of feline oral and respiratory diseases involving FCV which become chronic. FCV infected cats do not have typical hematology and serum biochemistry abnormalities. Cats affected by calicivirus VSD may have mild to severe anemia, lymphopenia, neutrophilia, thrombocytopenia, hypoalbu-

minemia, hyperbilirubinemia, and increased liver enzyme activities.

Type of vaccine

Most of the commercially available live FCV vaccines are based on the FCV-F9 strain isolated in 1958 which has a broad cross-reactivity with other strains (22, 23). MLV parenteral and intranasal vaccines, as well as inactivated vaccines are available for vaccination against FCV. Inactivated vaccines that include adjuvants have been recommended to be reserved for immunosuppressed or pregnant cats, if vaccination is necessary (21). The FCV vaccine is considered a core vaccine by the WSAVA (5) and several combined feline vaccine brands which include FCV as either MLV or inactivated virus are available in Israel (Table 1). Some brands include two inactivated non-adjuvanted FCV strains (G1 and 431) combined with MLV FPV and feline herpes virus strains.

Vaccination recommendation

Kittens may be susceptible to FCV at 6 weeks of age although MDA may persist until 14 weeks (21). The WSAVA vaccination guidelines (5) recommends to begin vaccinating kittens against FCV with MLV, or combined MLV and non-adjuvanted FCV vaccines, at 6-8 weeks of age and then every 2-4 weeks until 16 weeks of age or older. Reactivation vaccination (booster) is recommended initially at between 6-12 months of age, and then annually in high risk cats and not more often than every three years for low risk cats. Initial adult vaccination is usually done according to the manufacturer's instructions with two doses 2-4 weeks apart. Although FCV vaccines provide cross-protective immunity against multiple strains of FCV, disease may still occur in fully vaccinated cats due to virulent strains that are not covered by the vaccine (5).

Feline Rhinotracheitis virus (Feline herpes virus)

Background

Feline herpesvirus (FHV) is an alphaherpesvirus that causes feline rhinotracheitis and is one of the major participants in the causation of URTD in cats together with FCV and other pathogens (24). FHV-1 is an enveloped DNA virus that is closely related to canine herpesvirus-1 and to phocid herpes virus 1 and 2, but no cross-species transfer is known. Only one FHV-1 seroptype is known, but despite the fact that virus isolates are genetically similar, there is some variation in virulence between viral strains (21). Transmission of FHV-1 occurs by direct contact with infected secretions from the oropharynx, conjunctiva and nasal cavity, and with fomites, as a result of close contact between cats in crowded environments. FHV-1 is inactivated by desiccation and most disinfectants and antispetics (25). The virus remains infective for at least 5 months at 4°C, one month at 25°C, 3 hours at 37°C and 5 minutes at 56°C (21).

After initial infection, FHV-1 replicates in the upper respiratory tract epithelium, lymphoid tissues, and the cornea and conjunctiva. Viremia occurs in some cats after initial infection, especially neonates and weakened kittens. Clinical sigs may appear 2-6 days post-infection. Eventually, infected cats develop latent infections and the virus remains in the trigeminal nerve ganglia and potentially in other sites such as the nasal cavity and cornea with the cat becoming a lifelong carrier. Reactivation of viral shedding in the presence or absence of URTD is frequent 4-12 days after stress such as lactation, exposure to new cats, concurrent disease, cat shows, transportation to a veterinary clinic or boarding in a cattery or animal shelter. Shedding of the virus during reactivation lasts 1-13 days with an average of 7 days. Shedding during lactation is responsible for transmission of the infection to the suckling kittens (21).

Major Clinical signs

FHV-1 causes cytolysis and injury to the upper respiratory epithelium which may lead to rhinitis, sinusitis and damage to the nasal turbinates, especially in neonate young kittens. Chronic sinusitis and rhinitis associated with FHV-1 infection are found in older cats. It is also an important cause of ocular corneal disease with acute or chronic keratitis which could be ulcerative, and it may also cause ulcerative and facial dermatitis.

The clinical manifestations of FHV-1 infection may vary from a mild disease with sneezing and conjunctivitis to severe and fatal bronchopneumonia. Ulcerative keratitis with occasional adhesion of the conjunctiva to the cornea and blindness, and facial ulceration with dermatitis are also found in FHV-1 infections (26). Typical clinical signs of FHV-1 infection include fever, lethargy, anorexia, ocular and nasal discharge, conjunctival hyperemia, sneezing, salivation and coughing. When there is a secondary infection, secretions may be purulent. Oral and skin ulcers are rarer than the latter clinical findings (27). FHV-1 infection occurs frequently with

other co-infections such as FCV, *C. felis*, *B. bronchiseptica* and other pathogens.

Type of vaccine

MLV parenteral and intranasal vaccines, as well as inactivated vaccines are available for vaccination against FHV-1. The FHV-1 intranasal vaccines are often not tolerated well by cats and can occasionally be followed by mild to moderate signs of URTD (21). It is no longer available in Europe (27). The FHV-1 vaccine is considered a core vaccine by the WSAVA (5) and several combined feline vaccine brands which include FHV-1 as MLV are available in Israel (Table 1). Vaccination against FHV-1 protects against disease but not necessarily against infection. It can significantly reduce the clinical signs of infection, with an approximately 90% reduction in clinical scores to experimental infection, and it reduces virus excretion upon infection (25).

Vaccination recommendation

MDA for FHV-1 are undetectable in most kittens by the age of 9 weeks, however they may persist up to 14 weeks of age or even longer in some cats. The FHV-1 vaccine is usually administered in combination with the other core feline vaccines including the FCV and the FPV vaccines. The WSAVA vaccination guidelines (5) recommends to begin vaccinating kittens against FHV-1 with MLV vaccines at 6-8 weeks of age and then every 2-4 weeks until 16 weeks of age or older. Reactivation vaccination (booster) is recommended initially at between 6-12 months of age, and then annually in high risk cats and not more often than every three years for low risk cats. Initial adult vaccination is usually done according to the manufacturer's instructions with two doses 2-4 weeks apart. The WSAVA guidelines have recommended that MLV vaccines should also not be used in feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infected cats (5).

B. Non-core vaccines (according to the WSAVA)

Rabies

Background

The rabies virus is a member of the Rhabdoviridae family and is the cause of one of the deadliest and widespread zoonotic diseases, which infects mammals in most countries of the world. Some islands and parts of Europe are currently free of rabies as a result of wildlife vaccination programs (28). The rabies virus is thermolabile and sensitive to the ultraviolet radiation of the sunlight. Rabid animals are the source of the virus which is usually shed in the saliva from about three days before the onset of clinical disease signs, with transmission by bites or penetration of infected saliva through a scratch, damaged skin, or the mucous membranes. The average incubation period of rabies in cats is two months but it can vary from two weeks to several months or longer (http://www.abcdcatsvets.org/rabies/). The virus replicates in striated muscle and connective tissue at the site of inoculation and then enters the peripheral nerves through the neuromuscular junction to the central nervous system through axons of nerve cells. It then reaches the salivary glands by the retrograde axonal route. The cat becomes infectious when the virus reaches the saliva a few days before the first clinical signs appear. The virus does not destroy cells during replication or maturation, and specific immune responses cannot be detected during the early stages of virus movement from the bite site to the central nervous system.

Major Clinical signs

Two forms of rabies may be identified in cats: the furious and the dumb forms. The furious form includes: prodromal, furious and paralytic phases, which are not always distinct. The dumb form has prodromal and paralytic phases. A range of non-specific clinical findings such as fever, anorexia, vomiting, neurological signs, and diarrhea, may occur during the relatively short prodromal phase of both forms which may last 12 to 48 hours. Behavioral changes may be noticed initially including a bizarrely friendly or otherwise shy or irritated behavior, and increased vocalization. The furious form is found in most rabid cats. These cats may exhibit aggressiveness, restlessness and unprovoked biting, with lameness and stumbling. They may show hypersalivation and increased water uptake (28).

Type of vaccine

Passive immunity with MDA against rabies in kittens born to vaccinated queens does not persist usually for much longer than 12 weeks. It is generally recommended to perform the primary vaccination in kittens over 12 weeks of age. There are live canary pox vectored recombinant vaccines against rabies which are non-adjuvanted for parenteral injection, and also inactivated adjuvanted vaccines. These vaccines are ad-

ministered every year or every three years. There is currently only one brand of rabies vaccine among the permitted feline vaccines in Israel and it is a canary pox vectored recombinant vaccine (Table 1).

Vaccination recommendation

Although the WSAVA guidelines recommend the rabies vaccine as a core vaccine in areas where the disease is endemic (5), it is not compulsory by law to vaccinate cats against rabies in Israel. This may be due to the low number of rabid cats detected in Israel. During ten years, from 2010 to 2019, there were only 7 cats diagnosed with rabies in Israel, three in 2010, one in 2011, one in 2015, and two in 2017, out of a total of 361 rabid animals diagnosed (1.9%) (https://www.moag.gov.il/vet/Yechidot/Machon/maabada_kalevet/airueim%20kalevet/Pages/default.aspx). Vaccination of cats against rabies in Israel should be recommended for cats at high risk of exposure to the disease, such as cats living in rural areas where rabies is prevalent in wildlife or other domestic animals, and in areas of risk for urban rabies outbreaks. According to the WSAVA vaccination guidelines, the canary pox virus recombinant vaccine should be administered as a single dose as early as 12 weeks of age with revaccination one year later. Revaccination thereafter should be performed as required by the local regulations.

Chlamydia felis

Background

Chlamydia felis is an obligate intracellular gram-negative bacterium. It belongs to the genus *Chlamydia* together with more than 10 other species of Chlamydiaceae including *Chlamydia psitacci*, *Chlamydia pneumonia* and *Chlamydia trachomatis*, which infect people and have an important public health significance. *Chlamydia felis* was renamed *Chlamydophila felis* (29) and then changed back to its pervious name *C. felis* (30). *Chlamydia felis* does not seem to present a significant public health risk, although there is a small number of reports of conjunctivitis with this pathogen in immunodeficient and immunocompetent humans infected by this bacterium (31, 32). *Chlamydia* spp. are found in two forms, the larger reticular body which replicates inside cells to produce elementary bodies, which are smaller and infect new cells. The elementary bodies are able to survive for a few days in room temperature and are inactivated and killed by most disinfectant and antiseptics.

Transmission of *C. felis* occurs by direct contact and through aerosols. Infection is most common in multiple cat households and catteries. The main target of *C. felis* is the cat's conjunctiva and it may cause unilateral conjunctivitis which usually becomes bilateral within two days. The incubation period from infection to the appearance of conjunctivitis is about 2-5 days. Conjunctival shedding of *C. felis* continues for about 70 days after infection, and some cats may be persistently infected, especially if they are immune-suppressed by co-infection with a retrovirus (33). Shedding may also occur from rectal and vaginal secretions, and kittens may be infected at birth.

Major Clinical signs

Infection with *C. felis* is most common in young cats, 2-12 months of age, while cats older than 5 years are unlikely to be infected (34). Infection causes conjunctivitis with or without signs of rhinitis such as nasal discharge and sneezing. Cats infected just with *C. felis* tend to remain well and maintain a good appetite. Infection may become chronic with mild conjunctivitis. Corneal disease with keratitis and ulceration is likely a result of co-infection with FHV-1 or other infections. Co-infections with FCV, FHV-1, bacterial or fungal organisms, as well as with retroviruses may exacerbate the disease and prolong shedding and healing. Ocular abnormalities in *C. felis* infection include conjunctivitis with serous to purulent discharge, blepharospasm, chemosis, hyperemia of the nictitating membrane, serous to mucopurulent nasal discharge and sneezing (29, 34).

Type of vaccine

Immunity against *C. felis* infection involves both the cell-mediated and humoral responses and protection appears to be of short duration allowing re-infection, however an age-related resistance may protect older cats who rarely show clinical disease due to the bacterium (34). MDA may protect kittens from infection until 7-9 weeks of age. Both modified live and inactivated vaccines are commercially available against *C. felis*. They do not entirely prevent infection but minimize its clinical severity. The vaccines currently permitted and marketed in Israel contain attenuated live *Chlamydia* in combination with FPV, FHV-1, and FCV vaccines (Table 1). *Chlamydia felis* vaccines are considered non-core vaccines by the WSAVA vaccination guidelines and are recommended for animals in a multicat environ-

ment where clinical *C. felis* infections have been confirmed (5).

Vaccination recommendation

According to the WSAVA vaccination guidelines, the *C. felis* parenteral vaccine should be administered with an initial dose at 9 weeks of age and a second dose 2-4 weeks later. Initial adult vaccination should be done by injection of two doses, 2-4 weeks apart. An annual booster is indicated for cats with sustained risk (5).

Feline Leukemia Virus (FeLV) and feline immunodeficiency virus (FIV)

Background

Vaccination against FeLV and FIV is not considered core-vaccination by the WSAVA vaccination guidelines (5). FeLV and FIV are enveloped RNA viruses that belong to the family Retroviridae. Despite this relatedness, their infections have very different epidemiological characteristics. FeLV is mainly a disease of young cats that induces fatal clinical phenomena relatively rapidly at an early age, while FIV may infect cats at a young age or later, however, its consequences are typically seen many years after infection manifesting as progressive chronic disease. Both FeLV and FIV remain viable for just a few minutes outside the body and are susceptible to most disinfectants and antiseptics.

1. FeLV - FeLV was first described in 1964 and it has a global distribution. Transmission of FeLV is due to contact with salivary secretion of an infected cat through licking, grooming and food dishes. It can also be transmitted by bites and blood transfusions, and less frequently thorough the milk and transplacentally. Cats up to four months of age are much more sensitive to infection with FeLV than older cats, and the likelihood that they will develop infection if exposed to the virus is considerably higher. There are three FeLV subtypes, A, B, and C. Subtype A is the infecting subtype which is involved in all infections, whereas subtype B develops in FeLV A-infected cats from recombination of FeLV A with endogenous FeLV sequences present in the cat's genome. Subtype C is the result of mutations in the envelope gene that arise in subtype A. Subtypes B and C have been found to be associated with different clinical manifestations of FeLV with subtype B associated to the development of lymphoma and neurological disease, whereas subtype C is associated with non-regenerative anemia (35).

Following infection of the oropharynx, FeLV might reach the bone marrow by a first viremia, and its nucleic acids will be integrated as proviral DNA into the cat's host cells. A stress response to some stimulus and immunosuppression may induce the reactivation of the infection, the production of virions, and a second viremia which leads the virus to the salivary glands, epithelial tissues and other target tissues. At this stage, infection with FeLV can be detected by serology to detect antigenemia with circulating p27 capsid antigen. FeLV induces neoplasia, pure red blood cell aplasia, myelodysplasia or myelofibrosis, immune-mediated cytopenias, neurologic disease, opportunistic infections and more (35).

2. FIV - FIV was first described in 1968 and like FeLV has a worldwide distribution. FIV is transmitted mainly through bites and less frequently transplacentally and via the milk. It can also be transmitted by blood transfusions. Like FeLV, it is transmitted by viremia after the initial infection to the bone marrow, and when it is reactivated in the bone marrow, it is spread to other tissues. However, clinical diseases associated with FIV usually ensue years after the virus's reactivation and spread, when the T lymphocyte count decreases dramatically and the cat is no longer able to defend itself from opportunistic infections and neoplasia.

Five genetically distinct subtypes of FIV designated A to E have been defined based on nucleotide sequence diversity of the viral envelope gene. It is not clear if the clinical manifestations of FIV are related to these subtypes, however vaccines produced for FIV are more protective against some subtypes and less against others.

Contrarily from FeLV, FIV is detected mainly by serology for antibodies against its p24 capsid protein or against a transmembrane glycoprotein (gp40). FIV has an acute phase that is often not recognized by the owners, a long sub-clinical phase, and then a chronic phase, which may not be reached in all infected cats. Cats in the chronic phase may suffer from a multitude of clinical phenomena including signs induced by opportunistic infections of the skin, eyes, periodontal space, gastrointestinal system, and internal organs. In addition to that cytopenias, anemia, neoplasia of several types, neurological disease and more are associated with this infection.

Major Clinical signs

The major clinical findings associated with both FeLV and FIV are very variable and include a multitude of possible abnormalities which depend on the organs and tissues

involved and the nature of the pathology induced. These include clinical findings related to lymphoma or leukemia, anemia, bone marrow suppression, opportunistic infections of the skin, oral cavity, respiratory and urinary systems and other systems, neurological disease, and other disorders (36).

Type of vaccine

1. FeLV - The first commercial vaccine used in veterinary practice against FeLV was introduced in the USA in 1984. A number of FeLV vaccines are currently available including adjuvanted inactivated and recombinant DNA vaccines. Some vaccines use recombinant DNA technology with the viral envelope glycoprotein and part of the transmembrane protein expressed in *E. coli*. Another recombinant vaccine uses a canarypox virus vector with inserted genes for the envelope glycoprotein and the capsid protein. After vaccination of the cat with this vaccine, there is a single cycle of replication by the vector poxvirus with expression of the inserted FeLV genes. Unlike other cat vaccines, neutralizing antibodies do not develop following vaccination with this vaccine and a protective effect is likely achieved by stimulating cell-mediated immunity. However, neutralizing antibodies develop if vaccinated cats are exposed to the field virus (37). Although no FeLV vaccine prevents infection and provides complete protection, most vaccinated cats are protected from progressive infection and the development of FeLV-associated disease.

2. FIV - An inactivated vaccine against FIV (Fel O Vax, Fort Dodge Animal Health) was made available commercially to veterinarians in 2002 in the USA, and in Australia and New Zealand in 2004. This vaccine was not licensed in Europe and it is no longer available in the USA. The vaccine is based on FIV subtypes A and D and was not shown to have reliable protection against other sub-types. It induces the production of antibodies which may not be discriminated from those produced by natural infection.

The prevalence of FeLV and FIV infections among a cohort of cats from municipal shelters, feral cats and client-owed cats in Israel were 4% and 12%, respectively, in a survey from 1999 (38). Retroviral infections in Israel have also been associated with feline hemoplamosis in another study (39). A summary of all the tests performed at the American Medical Laboratories (AML) in Herzeliya, Israel, using the ImmunoRun serololgical kits (Biogal- Galed Labs., Israel) from January 2018 to June 2020, was kindly provided by Dr. Tzachi Even Zur. Of 235 cats tested for FeLV antigenemia during two and a half years, only one cat was positive for FeLV, whereas of 390 cats tested for FIV antibodies, 86 (22%) were positive. The FIV positive cats were from all areas of Israel, from the Galil region in the north to the Arava in the south, with no clear geographic predilection. More incidence studies are needed to evaluate the current prevalence of these infections in Israel.

Vaccination recommendation

FIV and FeLV vaccines are not considered as core vaccines necessary for every cat by the WSAVA vaccination guidelines (5), however, the FeLV vaccine may be recommended as a routine vaccine for certain feline populations such as cats with high risk of exposure to this infection, including those with outdoor access in areas where this infection is highly prevalent. No FeLV and FIV vaccines are currently imported and permitted in Israel (Table 1).

1. FeLV - According to the WSAVA guidelines, the inactivated and recombinant FeLV vaccines should be administered to kittens as early as eight weeks of age and then a second dose 3-4 weeks later. Adults should be vaccinated with two doses 3-4 weeks apart. Only FeLV negative cats should be vaccinated. Thereafter, a single dose should be administered one year following the last dose of the initial series, and then not more often than every 2-3 years in cats that have sustained risk of infection (5).

2. FIV - The FIV inactivated vaccine should be administered to kittens in three doses. The initial dose is administered as early as eight weeks of age, and two subsequent doses are administered at an interval of 2-3 weeks. Adults are also vaccinated with three doses 2-3 weeks apart. A single dose is required for revaccination one year after the last dose of the initial series, and then annually in cats who are at risk of exposure (5).

Vaccination against feline panleukopenia, calici, herpes and rabies in the shelter environment

The cat shelter or multicat household environments are more challenging with regard to exposure to feline pathogens, in comparison to kittens raised in regular owner's homes (6). The WSAVA vaccination guidelines recommend vaccination with FPV, FCV and FHV-1 for kittens in shelters with a single dose prior to, or at the time of admission, as early as 4-6 weeks of age, and then every two weeks until twenty

weeks of age, if the cat is still in the facility. For adult cats in shelters, the WSAVA guidelines recommend a single dose of vaccination with the above viruses at the time of admission, which should be repeated in two weeks if the animal remains in the shelter (5).

For rabies vaccination in the shelter environment in rabies-endemic areas, it is recommended that kittens and adults should be vaccinated with a single dose at the time of discharge from the facility (5).

DISCLOSURE

These vaccination guidelines for Israeli Veterinarians were invited by Intervet Israel LTD., (also known as MSD animal Health). The author declares no conflict of interests.

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