Canine Vaccination Guidelines in Israel

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ABSTRACT

This article was written in order to provide Israeli veterinarians with general guidelines for the vaccination of puppies and adult dogs. It is based on the recent recommendations of expert opinions and the current knowledge on infectious diseases and their prevalence in Israel.

Vaccinations are strongly recommended as they have been proven to benefit both the health of the individual dog as well as the canine community by inducing or providing protection and "herd immunity" against life-threatening infectious diseases. There are different types of vaccines including those that induce active immunization such as modified live virus (MLV) vaccines, killed/inactivated and recombinant viral-vectored vaccines, and other immunological products that provide passive immunization (e.g. immunoglobulins). The latter products are not in common use in small animal veterinary medicine. The type of the vaccine should be considered when planning the vaccination protocol. The use of MLV (rather than killed viruses) for the vaccination against viral diseases results in enhanced humoral and cellular immune responses and therefore in a longer duration of immunity (DOI). This insight resulted in a shift from yearly adult-dog vaccinations to three-annual vaccinations (i.e. vaccinations every 3-years). Challenge and serological studies indicated that most canine MLV vaccines have probable DOI of 9 years or longer, when given after 16 weeks of age. These guidelines should be considered as a recommendation and not as a standard of care. They allow some flexibility to the veterinarian according to the signalment and health condition of the dog, the designation of the dog (whether a pet, a working or a kennel dog) and its lifestyle, the dog's habitat, geographic location and weather conditions, the occurrence or absence of disease outbreaks in the vicinity of its living area, and the economic condition of the owners. Accordingly, vaccinations are divided to core and non-core. **Core vaccines** are targeted against several severe life-threatening viral diseases and are recommended for all dogs regardless of their geographic location or other considerations. These include canine distemper virus (CDV), canine adenovirus type 2 (CAV-2) and canine parvovirus type 2 (CPV-2 variants). As Israel is endemic for rabies, rabies vaccine is also considered a core vaccine in our region. **Non-core vaccines** are those that should be given only when necessary, to dogs that are exposed or at risk of developing specific infectious diseases at certain periods and under certain circumstances according to their geographic location, habitat and life-style. These include vaccines against leptospirosis, canine infectious respiratory disease (Kennel cough) and canine influenza virus, among others. The list of permitted vaccines for 2020 in Israel can be found in the Israeli Veterinary Services website: https://www.moag.gov.il/vet/Yechidot/TachshirimTrufot/Pirsumim/2020/Pages/tachshirim_chimim_2020.aspx. This list is updated by the Israeli Veterinary Services annually, and is also included in these guidelines (Table 1). Only approved vaccines should be used in Israel, other vaccines are legally not allowed for importation and use. Only healthy dogs should be vaccinated, following a complete physical examination. Some vaccines are safe for pregnant bitches but others not, it is therefore advised to carefully read the manufacturer's "summary of product characteristics" sheet before their use. The 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.

Vaccination failure may occur due to several reasons including the presence of maternal derived antibodies, an inadequately immunogenic vaccine, individual poor response to the vaccine-antigen, or poor handling and/

or keeping conditions of the vaccine. Maternal derived antibodies may neutralize the vaccine and interfere with proper and sufficient immunization, therefore it is recommended to vaccinate pups with a series of 2-4 (preferably 3-4) consecutive core vaccines until the age of 16 weeks (e.g. every 2-4 weeks starting at the age of 6-8 weeks). The final vaccination as a pup should be given at the age of 16 weeks or later (Table 2), when the maternally-derived antibody concentration is expected to decrease to low levels that are presumed not to interfere, and allow adequate immunization. When only one core vaccination can be afforded by the pet owners, the World Small Animal Veterinary Association Vaccination Guidelines Group (WSAVA-VGG) recommends vaccination at the age of 16 weeks or later. Thereafter, a booster vaccine should initially be given between the age of 6-12 months, and then not more frequently than every 3 years. This is because the DOI for most core vaccines is longer than 3 years and may even remain for the entire lifetime of the dog.

Vaccination associated adverse effects may occur following vaccinations and therefore vaccination protocols should be wisely considered and administered. Adverse effects may range from anaphylaxis to autoimmunity as a result of hypersensitivity reactions to the vaccine components. Therefore, the dog should be inspected for at least 30 minutes following vaccination and its owners should be instructed to report the veterinarian of any changes in behavior or clinical signs in the days following vaccination.

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

INTRODUCTION

This article was written in order to provide Israeli veterinarians general guidelines for the vaccination of puppies and adult dogs. It is based on the recent recommendations of expert opinion of the World Small Animal Veterinary Association (WSAVA) and the American Animal Hospital Association (AAHA) guidelines (1, 2), and current knowledge on infectious disease outbreaks and their prevalence in Israel. Vaccinations are strongly recommended as they have proven to benefit the health of the individual dog and the canine community by providing protection against life-threatening infectious diseases and creating "herd immunity" against outbreaks (1).

There are different types of vaccines including those that induce active immunization such as modified live virus (MLV) vaccines, killed/inactivated and recombinant viral-vectored vaccines, and other immunological products that provide passive immunization (e.g. immunoglobulins). The latter products are not in common use in small animal veterinary medicine. The type of the vaccine should be considered when planning the vaccination protocol. This is because immunization with live vaccines is more likely to elicit both cellular and humoral responses with longer duration of immunity (DOI) in the absence of neutralizing maternal antibodies, while killed vaccines have shorter DOI and therefore require repeated vaccinations at shorter time-intervals (i.e. annually). During the years, many different vaccination protocols have been suggested and implemented, however in recent years more standardized protocols have been published (1, 2, 3, 4, 5). The use of MLV rather than killed viruses for the vaccination against viral diseases results in enhanced humoral and cellular immune responses and therefore in a longer DOI. This insight resulted in a shift from yearly adult-dog vaccinations to three-annual vaccinations (i.e. vaccinations every 3-years). Challenge and serological studies indicate that most canine MLV (CDV, CAV-2 or CPV-2) vaccines have probable DOI of 9 years or longer (some have shown DOI of up to 14 years). When the vaccine is administered after 16 weeks of age (5). The current availability of in-clinic serological kits allows the detection of antiviral antibodies which facilitates better determination of the immune status of dogs against viral diseases and therefore tailoring the vaccination protocol to the specific dog (6).

These guidelines should be considered as a recommendation and not as a standard of care. They allow some flexibility to the veterinarian according to the signalment, health condition of the dog, designation of the dog (whether a pet, a working or a kennel dog) and its lifestyle, the dog's habitat, geographic location and weather conditions, the occurrence/absence of disease outbreaks in the vicinity of its living area, and the economic condition of the owners. Accordingly, vaccinations were divided to core and non-core. **Core vac-**

cines are targeted against several severe life-threatening viral diseases and are recommended for all dogs regardless of geography or other considerations. These include canine distemper virus (CDV), canine adenovirus type 2 (CAV-2) and canine parvovirus type 2 (CPV-2 variants). As Israel is endemic for rabies, the rabies vaccine is also considered a core vaccine in our region. **Non-core vaccines** are those that should be given only when necessary to dogs that are exposed or at risk of developing specific infectious diseases at certain periods and under certain circumstances according to their geographic location, habitat and life-style (1). These include vaccines against leptospirosis, canine infectious respiratory disease (Kennel cough) and canine influenza virus, among others. The list of registered and approved vaccines in Israel is updated and published annually by the Israeli Veterinary Services at their website: https://www.moag.gov.il/vet/Yechidot/TachshirimTrufot/Pirsumim/2020/Pages/tachshirim_chimim_2020.aspx

Only approved vaccines should be used in Israel (Table 1). Other non-approved vaccines are legally not allowed. Moreover, newly developed vaccines such as leishmaniosis are being marketed in several countries abroad, however more information on their efficacy and safety is required before their use can be recommended. Only healthy dogs should be vaccinated, following a complete physical examination. Some vaccines are safe for pregnant bitches but others not, it is therefore advised to carefully read the manufacturer's "summary of product characteristics" sheet before their use.

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

Vaccine Name	Active ingredients	Authorization holder	Manufacturer	Importer	Distributer	Vaccine number
Bronchicine CAe*	*B. bronchiseptica* Strain 78-9159 antigen	Zoetis	Zoetis	Zoetis	VM	6-022-16-12
Canigen DHPPi/L	Canine distemper virus (CDV) Lederle strain, Canine adenovirus type 2 (CAV-2) Manhattan strain, Canine parvovirus (CPV) CPC780916 strain, Canine parainfluenza (CPIV) Manhattan strain, *L. canicola*, *L. icterohaemorrhagiae*	AVS	Virbac	AVS	AVS	6-027-15-01
Eurican DHPPI2L	Distemper virus, Adenovirus (CAV2), Parvovirus, Parainfluenza virus type 2, *L. canicola*, *L. icterohaemorrhagiae*	BE	Merial	BE	BE	6-052-10-04
Eurican herpes	Canine Herpesvirus (F205 strain) antigens	BE	Merial	BE	BE	6-053-10-04
Nobivac DHP	Canine Distemper virus strain Onderstepoort, Canine Adenovirus 2 strain Manhattan LPV3, Canine Parvovirus strain 154	Intervet Israel	Intervet	Intervet	VM	6-099-07-12
Nobivac DHPPi	Canine Adeno type 2, Canine Distemper, Canine Parainfluenza, Canine Parvo	Intervet Israel	Intervet	Intervet	VM	6-100-07-12
Nobivac KC	*B. bronchiseptica*, Canine parainfluenza (CPIV)	Intervet Israel	Intervet	Intervet	VM	6-101-07-12
Nobivac Lepto	*L. canicola*, *L. icterohaemorrhagiae*	Intervet Israel	Intervet	Intervet	VM	6-102-07-12
Nobivac Puppy DP	Canine Distemper, Canine Parvo	Intervet Israel	Intervet	Intervet	VM	6-103-07-12
Primodog	Canine Parvovirus	BE	Merial	BE	BE	6-117-10-04
Quantum dog DA2PPvL	Canine Adeno type 2, Canine Distemper, Canine Parainfluenza, Canine Parvo, *L. canicola*, *L. icterohaemorrhagiae*	Intervet Israel	Schering Plough AH	Intervet	VM	6-125-13-12

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Table 1: (Continued)

Vaccine Name	Active ingredients	Authorization holder	Manufacturer	Importer	Distributer	Vaccine number
Vanguard plus 5 + Lepto	Canine Adeno type 2, Canine Distemper, Canine Parvo, Canine Parainfluenza virus, *L. canicola*, *L. icterohaemorrhagiae*	Zoetis	Zoetis	Zoetis	VM	6-171-16-12
Versican Plus DHPPi/L4	Canine distemper virus, Canine adenovirus Type 2 strain CAV-2 Bio 13, Canine parvovirus Type 2b strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, *L. icterohaemorrhagiae*, *L. canicola*, *L. grippotyphosa*, *L. bratislava*	Zoetis	Bioveta	Zoetis	VM	6-285-22-16
Vanguard plus 5 L4CV	Canine distemper virus, Canine adenovirus type 2, Canine parainfluenza virus, Canine coronavirus, Canine parvovirus, *L. canicola*, *L. grippotyphosa*, *L. icterohaemorrhagiae*, *L. pomona*	Zoetis	Zoetis	Zoetis	VM	6-286-16-16
Nobivac Lepto 4	*L. canicola*, *L. icterohaemorrhagiae*, *L. grippotyphosa*, *L. pomona*	Intervet Israel	Intervet	Intervet	VM	6-288-07-15

VM Vetmarket; **AVS** A. vetsupply; **BE** Beit Erez; *L Leptospira*; *B Bordetella*; *Registered and approved but is not marketed in Israel.

Vaccination failure may occur due to several reasons including a poorly immunogenic vaccine; the presence of maternally-derived antibodies that adhere to the vaccine-antigens preventing the immunization of the host; poor individual response of the dog to the vaccine antigens due to poor immune system; medications such as certain immunosuppressive and anti-inflammatory drugs, or poor handling and keeping of the vaccine (1, 7). Maternally-derived antibodies neutralize the vaccine and therefore interfere with proper and sufficient immunization. Therefore, it is recommended to vaccinate pups with a series of 2-4 (preferably 3-4) consecutive multivalent core vaccines until the age of 16 weeks (e.g. every 2-4 weeks, starting at the age of 6-8 weeks). The final vaccination as a pup should be given at the age of 16 weeks or later (Table 2), when the maternal derived antibody concentration decreases to low levels that are presumed not to interfere, and allow immunization. When only one core vaccine can be afforded by the pet owners, the WSAVA Vaccination Guidelines Group (VGG) suggests vaccination at the age of 16 weeks or later (1, 2). Thereafter, a booster vaccine should initially be given at between the age of 6-12 months, and then not more frequently than every 3 years. This is because the DOI for most core viral vaccines is longer than 3 years and may even remain for the entire lifetime of the dog (5). To determine seroconversion to the vaccine components or to test the need for additional vaccines following the first-year booster vaccine (age 6 or 12 months), it is recommended to test for the presence of specific antibody levels using point of care kits (e.g. dot-ELISA) against the vaccine components (1, 6, 8). A positive result indicates the presence of antibodies and suggests that the dog is immunized and does not require additional vaccination, while a negative result indicates that the dog does not have antibodies against the specific antigen suggesting that it may be potentially susceptible to infection (1, 6, 8) It should be noted that absence of the specific antibodies does not indicate that the dog is not immunized as the cellular component of the immune system may still have memory and be effective when challenged, however the most "realistic clinical" way to test for the DOI of a vaccine component is

Table 2: Recommended core vaccines, their form and vaccination recommendations.

Vaccine	Form	Route*	Vaccination of puppies	First revaccination of adults	Revaccination of adults
CDV	MLV or vector vaccine	SQ	2-4 times (preferably 3-4) until the age of 16 weeks, starting at the age of 6-8 weeks. The final vaccination as a pup should be given at the age of 16 weeks or later	At the age of 6-12 months	Every 3 years
CPV-2	MLV	SQ			
CAV-2	MLV	SQ			
Rabies	Inactivated	SQ/IM	Single dose at the age of 3 months	At the age of 1 year	Annually thereafter**

CDV canine distemper virus; **CPV**-2 canine parvovirus type 2; **CAV**-2 canine adenovirus type 2; **MLV** modified live virus; **SQ** subcutaneous; **IM** intramuscular; * as specified by the manufacturer; ** as dictated by the Israeli legal regulations of the Ministry of Agriculture.

by testing for antibody levels using commercial kits. The relatively high price of these kits, which in many cases is higher than the vaccines, drives some veterinarians and dog owners to vaccinate dogs instead of performing serological testing.

Vaccination associated adverse effects can occur following vaccinations and therefore vaccination protocols should be wisely considered and administered. Adverse effects may range from anaphylaxis to autoimmunity as a result of hypersensitivity reactions to vaccine components (9). Therefore, the dog should be inspected for at least 30 minutes following vaccination and its owners should be instructed to report of any changes in behavior or clinical signs in the days following vaccination. The increased reports of vaccination associated adverse effects and the fact that the DOI to core vaccines in dogs lasts for years suggest that there is no rational in vaccinating dogs with MLVs annually (5). The previous practice of yearly vaccination should be replaced with an annual physical check-up rather than additional unnecessary vaccinations that may increase the potential for vaccination-associated adverse effects.

C. Core vaccines

C1. Canine distemper virus (CDV)

Background

Canine distemper virus (CDV; *Paramyxoviridae*) is a single stranded RNA, highly contagious virus with a worldwide distribution. Infected dogs start shedding the virus 7 days post-inoculation via all body secretions, mainly the respiratory aerosols and exudates (10). The virus is susceptible to ultraviolet light and does not survive long periods in the environment. The seroprevalence of CDV in dogs in Israel is unknown while a prevalence of 52.2% (24/46) was reported in golden jackals (*Canis aureus*) from Israel (11). As interaction between domestic dogs and wild canids can occur, a potential cross-infection may occur. The disease is more prevalent in pups at the age of 3-6 months, when the maternal antibody levels decrease and eventually diminish (6, 8), however unvaccinated populations are susceptible and disease may occur at any age. Although widespread CDV vaccination of dogs is carried out, Israeli veterinarians frequently encounter clinical cases of the disease and infection outbreaks.

Major Clinical Findings

Clinical signs of CDV infection may vary from lack of signs due to subclinical infection to severe clinical signs, which may result in death. Dogs that develop clinical disease may present systemic, gastrointestinal, pulmonary, central nervous system and dermatologic signs. Typical systemic signs include fever, anorexia, oculonasal discharge and signs of conjunctivitis, upper respiratory signs such as dyspnea and cough which may exacerbate to lower respiratory signs and pneumonia. Gastrointestinal signs including vomiting and diarrhea are common. Digital hyperkeratosis, vesicular and pustular dermatitis may also occur. Neurologic signs may occur simultaneously with the above-mentioned systemic signs or after recovery. Usually, neurologic signs may appear one to three weeks following recovery from the systemic signs. In some dogs, neurologic abnormalities may appear months and even years later in the form of old dog encephalitis. Typical neurologic signs include hyperesthesia, seizures, "chewing-gum" fits, myoclonus, muscle twitching and ascending paresis starting from the hind legs. Damage of the enamel, dentin or teeth-roots may be seen in dogs infected before the eruption of their permanent teeth. Several studies associated CDV with rheumatoid arthritis, bone lesions such as hypertrophic osteodystrophy, and ophthalmic manifestations such as optic neuritis and blindness (10, 12, 13).

Type of vaccine

Inactivated (killed) vaccines were shown to be insufficient in protecting dogs during CDV challenge. MLV vaccines

against CDV are efficient in protecting dogs against CDV challenge. Canine adenovirus type 2 (CAV-2) or Canarypox vectored (recombinant) CDV vaccines were also shown effective in protecting dogs from CDV by production of neutralizing antibodies (1, 5). Such vaccines are recommended when MLV vaccines cannot be used, such in cases of immunocompromised dogs or Weimaraner dogs suffering vaccine-associated HOD (14). Several MLV distemper virus vaccines, in combination with other viral vaccines, are approved by the Israeli Veterinary Services and available in the Israeli market (Table 1).

Vaccination recommendation

As for all core vaccines, it is recommended to vaccinate pups subcutaneously with a combination/multivalent vaccine (CDV + CAV-2 + CPV-2), sequentially, *2-4 times (preferably 3-4) until the age of 16 weeks*, depending on the age of initial admission to the veterinary clinic (e.g. every 2-4 weeks starting at the age of 6-8 weeks). *The final vaccination as a pup should be administered at the age of 16 weeks or later* (Table 2). When only a single core vaccination is allowed by the pet owner due to financial or other restraints, the WSAVA-VGG recommends vaccination at the age of 16 weeks or later (1). Thereafter, a booster vaccine should be given initially at between the age of 6-12 months, and then not more frequently than every 3 years.

C2. Canine adenovirus (CAV)

Background

Canine adenovirus type 1 (CAV-1; *Adenoviridae*) is the etiologic agent of infectious hepatitis (ICH) in dogs and other canids (15). CAV-1 is distinct from CAV-2 which causes a respiratory disease in dogs (10). The virus can be present in all body tissues and secretions during the acute phase of the disease. Thereafter, it is secreted in the urine (only) for 6-9 months. The virus is extremely resistant in the environment and resists disinfection with many currently available disinfectants. Only one report describing two cases of CAV-1 infection in Israel is available (16).

Major Clinical Findings

Infectious canine hepatitis is a disease of puppies, usually younger than 1 year of age. Unvaccinated dogs can be affected at any age. The disease can be severe and death may occur in the severe form of ICH within hours following the onset of clinical signs. Major clinical signs include fever, abdominal pain, vomiting and diarrhea which may be bloody. Tonsillar enlargement, signs of pharyngitis and laryngitis, enlarged cervical lymph-nodes, coughing and increased lower respiratory sounds during auscultation are frequently reported. Hepatomegaly, hemorrhagic diathesis, abdominal distention and edema are common findings. Dogs may develop central nervous system signs such as seizures and coma as a consequence of liver failure. Corneal edema (blue eye) and uveitis can occur and may sometimes be the only detectable clinical signs. Icterus may occur in some cases (10, 15).

Type of vaccine

CAV-2 MLV vaccines are available in combination with other anti-viral vaccines as multivalent vaccines. Currently, they are the only recommended vaccines for ICH caused by CAV-1 and for the reduction of CAV-2 associated respiratory signs (1). Several MLV CAV-2 vaccines are approved for use in Israel, and are available in the Israeli market (Table 1). Inactivated CAV-2 vaccines are no longer available as they were inferior to MLV CAV-2 vaccines (10).

Vaccination recommendation

As for all core vaccines, it is recommended to vaccinate pups subcutaneously with a combination vaccine (CDV + CAV-2 + CPV-2), sequentially, *2-4 times (preferably 3-4) until the age of 16 weeks*, depending on the age of initial admission to the veterinary clinic (e.g. every 2-4 weeks starting at the age of 6-8 weeks). *The final vaccination of a pup should be given at the age of 16 weeks or later* (Table 2). When only one core vaccine is afforded due to financial or other restrictions, the WSAVA-VGG recommends vaccination at the age of 16 weeks or later (1). Thereafter, a booster vaccine should be given initially at between the age of 6-12 months, and then not more frequently than every 3 years.

C3. Canine parvovirus type 2 (CPV-2 variants).

Background

Canine parvovirus-2 (CPV-2; three types: CPV-2a, CPV-2b and CPV-2c; *Parvoviridae*) is a single-stranded, environmentally stable DNA virus. It is the etiologic agent of a highly contagious, severe, life-threatening enteric disease in dogs, mainly puppies under the age of 6 months (17, 18). Unvaccinated or immunocompromised dogs may become infected at any age (19). Many other members of the

Canidae family are susceptible to the virus (10). Infection occurs through the fecal-oral route (20). Typically, parvoviral enteritis is characterized by damage to the enterocytes of the crypts and villi of the small intestine (10, 20). Infected dogs may also develop myocarditis in pups of less than 6 weeks of age, hypercoagulability and thrombosis, and dermatologic signs. Neurological signs may occur in rare cases. The virus is highly stable in the environment for periods of five months and longer and resistant to most detergents and disinfectants (10, 18).

All three CPV-2 types (2a, 2b and 2c) were molecularly detected in dogs suffering gastroenteritis in Israel. In a recent study, CPV-2a or CPV-2b were detected in 60 dogs with parvovirus infection (21). Moreover, CPV-2c was detected in a fatal outbreak reported in Israel in 2011 (22).

Major Clinical Findings

The disease presentation varies and may range from asymptomatic or mild infection to severe gastroenteritis presented by fever, lethargy, anorexia, bloody diarrhea, vomiting, abdominal pain and dehydration, which may lead to hypovolemic shock. Electrolytes imbalance, hypoglycemia, metabolic acidosis and sepsis are common complications. Other clinical manifestations associated with CPV-2 include myocarditis in pups, hypercoagulability and urinary tract infections. Leucopenia, lymphopenia and neutropenia are common hematological findings (23). Thrombocytopenia may also occur. Death may occur due to dehydration, sepsis or disseminated intravascular coagulopathy (DIC).

Type of vaccine

Inactivated CPV-2 vaccines have been developed and shown to be protective for a limited time. They require booster vaccination, which prolongs the protection time. These vaccines were replaced by MLV vaccines that have a longer DOI against CPV-2. Several modified live parvovirus vaccines, alone, in combination with distemper virus vaccine, or with several other viral or bacterial vaccines (multivalent vaccines) are approved for use in Israel, and are marketed in the country (Table 1).

Vaccination recommendation

As for all core vaccines, it is recommended to vaccinate pups subcutaneously with a combination vaccine (CDV + CAV-2 + CPV-2), sequentially, *2-4 times (preferably 3-4) until the age of 16 weeks*, depending on the age of initial admission to the veterinary clinic (e.g. every 2-4 weeks starting at the age of 6-8 weeks). *The final vaccination as a pup should be administered at the age of 16 weeks or later* (Table 2). When only one core vaccine is afforded due to financial or other restrictions, the WSAVA-VGG recommends vaccination at the age of 16 weeks or later (1). Thereafter, a booster vaccine should be administered initially at between the age of 6-12 months, and then not more frequently than every 3 years.

C4. Rabies

Background

Rabies is a fatal zoonotic disease affecting the central nervous system, killing about 59,000 people each year, mainly in developing countries (OIE website (https://www.oie.int/animal-health-in-the-world/rabies-portal/). Most human cases occur due to dog bites (24). The disease is caused by an RNA virus belonging to the genus *Lyssavirus* of the family *Rhabdoviridae* (10). It affects all warm-blooded animals however, in nature, mammals are the only known reservoirs and vectors (10, 24). Canines are very susceptible to rabies. Infections occur mainly via the bite of a susceptible animal by an infected animal that contains the virus in its saliva (10). Israel is endemic for rabies and each year dogs, domestic animals and other wild canids, mainly jackals, are diagnosed by the Israeli Veterinary Services as infected (Table 3).

Major clinical Findings

The typical history of rabies in dogs includes a bite or scratch by an infected animal. The presentation in dogs may vary although two types have been classically reported: the furious form (also called encephalitic) and the paralytic form (also called dumb rabies). The incubation period may vary considerably, ranging from several weeks to six months after exposure (https://www.oie.int/doc/ged/D13127.PDF). A short prodromal phase, usually lasts 2-3 days, when dogs may present behavioral changes such as apprehension, nervousness, anxiety and fever. Dogs may lick and chew the wound site and pruritus may develop (10). *The furious form* usually lasts 1-7 days and is associated with aggression, agitation, restlessness, high excitability, hyperesthesia, hypersalivation, hydrophobia, photophobia, seeking quite places, attacking the owners and others, barking on imaginary objects, incoordination, disorientation and grand mal seizures. Dogs may bite

Table 3: Number of diagnosed rabies cases in domestic and wild animals in Israel, 2016-2019, as reported by the Israeli Veterinary Services.

Year/Animal	Dog	Cat	Jackal	Fox	Cattle	Horse	Sheep	Badger	Total
2016	12	0	5	7	5	1	0	0	30
2017	10	2	47	0	14	0	1	0	74
2018	6	0	44	0	7	1	1	1	60
2019	10	0	7	0	0	0	0	0	17

and eat foreign objects, which may become gastrointestinal foreign bodies. *The paralytic form* usually develops 2-4 days (range of 1-10 days) after the appearance of first clinical signs. It is characterized by muscle weakness and paralysis. Cranial nerve paralysis may occur, change in sound of barking, laryngeal paralysis, excessive salivation, frothing, difficulties in swallowing and dropped jaw are common. As the disease commences the animal will develop coma and eventually die due to respiratory failure (10). It is important to note that the clinical presentation of rabies may vary considerably. This may complicate the diagnosis of the disease and may risk humans and other animals.

Type of vaccine

The Israeli Veterinary Services issue a tender for a national supplier of rabies vaccine every two years. Currently, Rabisin® by Boehringer Ingelheim Animal Health UK is the vaccine approved and marketed in Israel for the active immunization of dogs against rabies. It is an inactivated and adjuvanted vaccine.

Vaccination and legal regulations

Rabies vaccination is considered a core vaccination in Israel. According to the manufacturer, the vaccine should be administered at the age of 3 months or later and "immunity is achieved one month after initial vaccination, and persists until the first booster (1 year after primary vaccination) and up to 3 years following booster vaccination" (http://www.noahcompendium.co.uk/?id=-453997). According to the Israeli legal regulations, *every dog must be vaccinated with the above-mentioned vaccine, parenterally (intramuscularly or subcutaneously), at the age of 3 months and yearly thereafter.* Most vaccination protocols recommend the first revaccination at the age of 1 year (1). The number of dogs vaccinated for rabies in Israel in 2019 was about 350,000 (data provided by the Israeli Veterinary Services). There are certainly more dogs in Israel that are not vaccinated.

D. Non-core vaccines

D1. Leptospirosis

Background

Canine leptospirosis is a zoonotic disease caused primarily by one of several *Leptospira* serovars of the *Leptospira interrogans* sensu lato and *Leptospira kirschneri* species (25). Leptospirosis is considered a professional disease of health workers including physicians, veterinarians, technicians, laboratory and abattoir workers, and animal farmers. Leptospires are worldwide distributed, flexible, spiral-shaped bacteria (spirochetes), classified historically in one of many serovars according to their antigenic elicitation of the humoral immune response. Serovars that cross react belong to the same serogroup. In the last 5 decades, most vaccinated dogs were vaccinated against serovars Canicola and Icterohaemorrhagiae (10) however globally, most reported cases in the last 2-3 decades were associated with other serovars. This might be the outcome of vaccinations with serovars Canicola and Icterohaemorrhagiae over the last decades or due to overlooking of the other serovars (10). Among wild animals, rodents are commonly infected. Tropical geographic regions with high precipitation are highly endemic. In Europe, serovars Grippotyphosa, Pomona, Bratislava, Autumnalis and Australis are common in addition to Canicola and Icterohaemorrhagiae (26). In Israel, serovars Pomona and Hardjo are common in cattle, and Pomona, Icterohaemorrhagiae, Bratislava, Canicola and Grippotyphosa are commonly detected in dogs. Serovars Pomona, Icterohaemorrhagiae and Bratislava (in decreasing order) were the predominant serovars infecting dogs in Israel during the years 2018-2019. In 2017, most *Leptospira* confirmed canine-cases (all serovars) occurred in central Israel, while in 2019 most cases occurred in Northern Israel (Galilee and Golan regions). Moreover, serovar Pomona became the predominant, mainly detected in the Galilee and Golan regions (2018-2019), however, the Gilboa, Hasharon, Hashfela and the Negev regions were also affected by this serovar (data provided by the Israeli Veterinary Services).

Table 4: Non-Core Vaccines – their form and recommendations for vaccination

Vaccine	Form	Route*	Vaccination of puppies	First revaccination of adults	Revaccination of adults
Leptospirosis	Inactivated	SQ/IM	At 8 weeks or older, booster 2-4 weeks later	12 months later	Annually
CIRD (*B. bronchiseptica* + CPIV)	MLV	Intranasal	At 3 weeks or older	12 months later	Annually
B. bronchiseptica**	Inactivated	SQ	At 6-8 weeks or older, booster 2-4 weeks later	12 months later	Annually

MLV modified live virus; **CIRD** canine infectious respiratory disease; **CPIV** canine parainfluenza virus;
* as specified by the manufacturer; ** Approved but is not marketed in Israel.

Leptospires are transmitted by excretions such as urine, milk and semen of the infected animals. Outbreaks are commonly reported following rainy seasons and flooding. The bacteria can survive for months in water reservoirs and infect humans or other animals when drinking or getting in contact with them.

Major Clinical Findings

Clinical findings may vary according to the age and immune status of the dog, the virulence of the infecting serovar and the affected body systems (e.g. pulmonary, renal, hepatic, ocular, cardiovascular). Disease may be acute, subacute or subclinical. Common clinical findings include fever, dehydration, pale mucous membranes and increased capillary refill time, muscle tenderness, recumbency, epistaxis, petechiae, ecchymoses, hematemesis, hematochezia, melena, icterus, coughing, dyspnea, gastrointestinal signs (e.g. vomiting, diarrhea), renal failure signs (polyuria, polydipsia, oliguria, anuria), cardiac arrhythmias, conjunctivitis, rhinitis and tonsillitis (10). Supportive treatment should be directed towards correcting abnormalities in the affected body systems. In addition, antibacterial treatment with penicillins or tetracyclines is indicated. Cephalosporines or macrolides are also in use. Doxycycline is considered the drug of choice for eliminating the bacteria from the tissues (27).

Type of vaccine

Until 2019, approved multivalent vaccines in Israel contained inactivated bacterial antigens belonging to Canicola and Icterohaemorrhagiae serovars. These vaccines are still approved in Israel, however, in 2020, due to the increase in detection of canine infections with serovar Pomona, bacterins containing inactivated Pomona and Grippotyphosa serovars in combination with Canicola and Icterohaemorrhagiae serovars were approved and are available in Israel (Table1).

Vaccination recommendation

It is recommended to vaccinate dogs with one dose subcutaneously at the age of 8 weeks or older. Booster vaccine should be given 2-4 weeks following the first vaccination, or when a shift from bivalent (two serovars) to quadrivalent (four serovars) vaccine is made. As the vaccine contains inactivated bacteria, and its DOI is relatively short compared to live vaccines, annual revaccination is recommended (table 4). The vaccines containing all four serovars (Canicola, Icterohaemorrhagiae, Pomona and Grippotyphosa) should be considered as a core-vaccine with a recommended annual vaccination for all dogs living in endemic regions in Israel (i.e. the Golan Heights and Galilee).

D2. Canine infectious respiratory disease (Kennel cough)

Background

Canine infectious respiratory disease (CIRD) also known as "kennel cough" or "infectious tracheobronchitis" is a disease of the upper respiratory tract (10, 28). The two main etiologic agents include the bacteria *Bordetella bronchiseptica* and the **canine parainfluenza virus** (CPIV). Other pathogens associated with CIRD include canine adenovirus type 2, canine distemper virus, canine herpes virus type 1, canine reo virus, canine respiratory corona virus, canine influenza virus, *Mycoplasma* spp., *Streptococcus* spp. and other bacteria (10, 28, 29).

Major Clinical Findings

Canine infectious respiratory disease (Kennel cough) is usually a self-limiting disease manifested by a typical hoarse productive coughing, sensitive trachea and sometimes sneezing. In rare cases, when CIRD is complicated and the lower respiratory tract becomes involved, fever, inappetence and

dyspnea may occur. The latter cases may require antibacterial and supportive treatment.

Type of vaccine

Approved *B. bronchiseptica* vaccines in Israel appear in two forms, the first is a live lyophilized *B. bronchiseptica* in combination with CPIV-MLV (Nobivac KC®, Intervet) administered intranasally (Table 1). This vaccine was shown to be highly effective. The second vaccine is a killed cellular antigen extract of the bacteria (Bronchicine CAe®, Zoetis) administered subcutaneously. The latter vaccine has been registered and approved in Israel but is not marketed in the country. Several different CPIV-MLV vaccines in combination with CPV, CDV and CAV in the form of multivalent vaccines are approved and marketed in Israel (Table 1). They should be administered subcutaneously.

Vaccination recommendation

Vaccination against CIRD (CPIV and *B. bronchiseptica*) is considered non-core and should be administered to dogs that interact with other dogs either during dog-walks, playing in playgrounds, before dog-shows or before entering a kennel. When justified, the intranasal vaccine (Nobivac KC®) should be administered to puppies at the age of 3 weeks or older. This vaccine should be requested by kennel owners for any dog before entering a kennel (preferably 2-3 weeks before; table 4), in addition to verification that the dog is fully vaccinated with all core-vaccines (in Israel: CDV, CAV-2, CPV-2 and rabies). Yearly vaccination against *B. bronchiseptica* and canine parainfluenza virus is recommended for dogs that are at constant risk for developing CIRD. Veterinarians should consider avoiding the use of multivalent vaccines that contain CPIV when vaccination against CIRD is not justified, by using specific multivalent vaccines that do not contain CPIV.

E. Additional vaccines

Several additional canine vaccines, all are non-core, were developed in the last two decades. Some are not marketed in Israel, some are not relevant to Israel (e.g. *Borrelia burgdorferi* vaccine) and some have restricted efficacy or there is inadequate information to justify their recommendation (e.g. leishmaniosis or canine corona virus vaccines). Most of these vaccines are not registered or approved in Israel and therefore are not discussed in this guideline. The only new vaccine to be discussed in brief is the canine influenza vaccine.

E1. Canine influenza virus (CIV)

Canine influenza is a respiratory disease caused by the equine-origin H3N8 influenza-A virus (which was first reported in the USA) (30) and the avian-origin H3N2 influenza-A virus (which was first reported in China and Korea, and later in Thailand and the United States (31,32). No reports are available on the current situation of CIV infection in dogs from Israel. CIV infection may be manifested by fever, tachypnea, nasal discharge and cough. Dogs may develop pneumonia which in severe cases may be fatal (10). Influenza viruses of animal origin were documented to infect dogs, however their spread from dogs to humans was not reported to date. Uni- or bivalent, live or inactivated H3N2 and H3N8 CIV vaccines were developed and are marketed abroad. CIV vaccine is considered as a non-core vaccine. It is recommended abroad for dogs at risk and dogs visiting endemic regions during outbreaks. However, CIV vaccines are not registered in Israel and should therefore not be used in the country.

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DISCLOSURE

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