How frequently should we be vaccinating cats in South Africa?

This article follows on from one earlier this year entitled 'How frequently should we be vaccinating **dogs** in South Africa. It will detail current recommendations on cat vaccines and elaborate on vaccine side effects in cats, particularly vaccine-associated sarcoma (and their management). It will compare the South African veterinary Council (SAVC)'s guidelines with those of other bodies, discussing the differences regarding core vaccines, feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) vaccination and summarise experimental evidence on duration on immunity in cats published in peer reviewed literature.

Table 1: Current recommendations on feline vaccination by the SAVC
(see www.savc.co.za under 'policies and guidelines')

CATS
Kittens - age when start vaccinating against core antigens and interval between vaccinations determined by likely maternal antibodies, local disease risk and manufacturer's recommendations - typically start **core** vaccines at 8-9 weeks - repeat 3-4 weeks later
Adolescents: Booster at 12-15 months essential
Adults: boosters every 3 years assuming modified live vaccines (MLV) are used Annual boosters if killed vaccines are used against FPV, FHV and FCV
Use **non-core** vaccines only if specifically indicated for that individual Use MLV if possible unless any virus multiplying in the cat is a risk (eg pregnancy, immunosuppression)

Core vaccines are indicated in all animals, non-core ones only in individuals whose lifestyle, concurrent diseases or geographic situation places them at risk from rare or relatively less pathogenic agents. Core vaccines are highly effective, safe and protect against diseases that have a high mortality, are highly infectious and/or are zoonoses. Non-core vaccines protect against diseases with a low mortality, that may be treated effectively and /or diseases that only specific population segments are at risk from.

Table 2: Core vaccines in South Africa

Core vaccines for cats in SA	Non-core vaccines for cats in SA
Feline panleukopenia (FPV)	Bordetella – indicated if kennelling, during outbreak or once isolated in a colony
Feline herpes virus (FHV)	Chlamydophila – indicated in colonies with known previous infections
Feline calicivirus (FCV)	Feline Immunodeficiency virus
Rabies	Feline leukaemia virus

Why not vaccinate annually?
In the mid-1990s, reports of a dramatic increase in fibrosarcoma at injection sites in cats emerged from the USA [14,21]. Prior to 1985, 10-20% of feline sarcoma occurred at injection sites. From the mid 1990s, 80-90% of sarcoma occurred at these sites [14]. Injection site sarcoma affected younger cats and were more likely to recur following excision [15]. During the same period, FeLV vaccines were introduced and new state legislation made rabies vaccination mandatory for cats. Retrospective studies showed that the relative risk of developing an injection site sarcoma was significantly increased in cats vaccinated against FeLV or rabies [14,15,21]. It was hypothesised that the adjuvant was associated with the pathogenesis in some way. One group identified aluminium (commonly used in adjuvants) within 28% of 149 injection site sarcomas, but pointed out that it could represent a marker of vaccination that included an adjuvant rather than being the actual trigger for neoplastic transformation [14].

The increased prevalence of injection site sarcoma was one of the causes for the ensuing debate on whether side effects of annual vaccination (in the feline patient as well as the owner's bank account) outweigh the benefits. (For complete discussion see previous article 'How frequently should we be vaccinating dogs in South Africa?')

Quantifying the risks
The information on South African cats is incomplete. A retrospective study of 1.2 million vaccine doses administered in a large US hospital group recorded 20.34 adverse events /10 000 doses in cats in the 30 days following vaccination [28]. Seventy five to 80% of these adverse events were limited to lethargy with or without fever or a localised swelling.

Table 3: Vaccine reactions in cats [28]

Reaction	% of population
Lethargy +/- fever	54%
swelling at injection site	25%
Vomiting	10%
Facial / periorbital oedema	6%
Generalised pruritus	2%
Anorexia / upper respiratory tract signs* / collapse	rest

* MLV vaccines against FHV, FCV and Chlamydophila may cause clinical signs when administered by an incorrect route. This may happen when vaccine is accidentally aerosolised or if the cat grooms away (and thus ingests) vaccine spilled on the skin.

Table 4: Sarcomas reported to the Veterinary Medicines Directorate in the UK

	2003	2004	2005	2006
Sarcomas related to vaccines	32	41	33	38
Sarcomas related to other products (e.g. long-acting penicillin, corticosteroid or lufenuron injections and resorbable s/c sutures)	3	2	1	1

The following measures have been suggested to decrease the likelihood of vaccine reactions in cats:

1. Avoid aerosolising cat vaccines. If vaccine is spilled on the coat, wipe it up with an alcohol / an F10 swab that will also inactivate the antigen.
2. Inject vaccines on the lateral thigh or foreleg so that the affected limb could be amputated with wide margins around the tumour should a vaccine induced sarcoma develop. When sarcomas develop in the dorsal neck they often infiltrate the facial planes between the shoulders, making resection technically challenging. Injecting from mid radius and mid tibia distally should be avoided because blood supply to the distal limb could be compromised should significant local swelling develop at the injection site. Some have recommended injecting different vaccines at prescribed sites (Trivalent vaccine: right shoulder, FeLV: left hind, Rabies: right hind [29]) so that associations with particular antigens can be more clearly established. This may not be practical in more fractious patients.
3. Consider using non-adjuvanted vaccines: compared with adjuvanted vaccines, non-adjuvanted ones were shown to be associated with significantly less inflammation in biopsies collected 1-9 w post vaccination[7]. Note that I could find *no evidence to prove* that non-adjuvanted vaccines are associated with a decreased risk of injection site sarcoma though.
4. Monitor injection site masses closely: Following rabies vaccination, 80-100% of cats will have signs of subcutaneous inflammation on histopathology. In 12 / 10 000 doses a visible and / or palpable nodule will appear about 3 weeks post vaccination. To avoid unnecessary surgery, the American Association of Feline Practitioners developed the 4-2-1 rule [22]

Managing suspected injection site sarcoma:
The 4-2-1 rule says you should biopsy

- injection site lumps persisting for > **4 months** post vaccination
- lumps > **2 cm** in diameter
- and / or lumps increasing in size over a period of **1 month**

Several tru-cuts or a wedge biopsy should be collected, taking care to place the tissue contaminated by biopsy within the area that would need to be resected. Lumpectomies should NOT be performed as this will significantly decrease survival time.

If an injection site sarcoma is confirmed, work-up and treatment includes

- tumour staging: MRI to define extent of lesions, aspiration of draining lymph nodes, thoracic radiography and abdominal ultrasound. 22% of these sarcoma metastasise.
- wide resection (3 cm margins). Ideally this should be performed by a specialist surgeon as this significantly increases the remission time (median of 66d when general practitioners performed the surgery vs 276d when specialist surgeons did)[16]. Edges of the mass should be identified and the whole mass submitted for histopathology.
- If tumour cells are evident at the margins, radiotherapy has increased remission and survival times
- The response to chemotherapy appears poor

Suspected injection site sarcomas (and any other vaccine reactions) should be reported to the vaccine company involved (if this is known) as well as the registrar of Act 36 MalutaM@nda.agric.za. The form is available on the Act 36 website http://www.nda.agric.za/Act36/Stock%20Remedies.htm under 'form for reporting suspected adverse drug reactions'.

Now that we've dealt with potential vaccine side effects, let's consider what evidence there is to support the extended vaccination intervals. In contrast to the very similar recommendations on canine vaccinations by various bodies [6,31], there are slight differences in the recommendations by a variety of bodies on feline vaccinations, underlining the fact that there is less definitive information about duration of immunity in cats

Table 5: How different bodies vary in their recommendations on feline vaccinations

	SAVC	WSAVA [6]	AAFP [25,38]	ABCD [18,27,35,44]
Last vaccine	typically at 11-13 w	3rd vaccine at 16w	At 16 w	16 w vaccine if interference by maternal antibodies likely
Boosters against FPV, FHV, FCV, Rabies	Every 3 years	Every 3 years	Every 3 years	Every 3 years against FPV Every year against FCV if multicat household / visiting cattery Every year against FHV unless completely indoor singe cat
FIV	Non-core	Not recommended	Non-core, precede by testing and permanent ID	Not recommended as not tested against European strains
FeLV	Non-core, suggest in multicat households	Non-core	All kittens tested and vaccinated. Adults vaccinated only if at risk (going outside)	All kittens and all adult cats unless completely indoors. Boost every 2-3 years once 3-4 years old

WSAVA: World Small Animal Veterinary Association
AAFP: American Association of Feline Practitioners
ABCD: The European Advisory Board on Cat Diseases – see also http://www.abcd-vets.org/

Some reminders before we discuss the differences:

Table 6: The differences between modified live and attenuated vaccines

Modified live / attenuated	Killed
Correct handling is essential to avoid killing vaccine virus	More stable than MLV
Incomplete attenuation of vaccine virus may cause the disease against which the vaccine is designed to protect	Cannot replicate in host, so it cannot cause the disease you're vaccinating against. (This is why all small animal rabies vaccines on the market in South Africa are killed vaccines)
May cause disease in foetuses or immunosuppressed patients	safe in immunosuppressed / pregnant animals
Generally result in higher titres of antibodies	Lower than MLV vaccine against the same antigen
Better at stimulating cell mediated immunity	Primarily stimulate antibody synthesis
Generally longer lasting immunity	Generally shorter duration of immunity than MLV vaccine against same antigen
No need to use adjuvants	Usually need adjuvants to stimulate reasonable immunity. Adjuvanted vaccines are thought more likely to result in - Allergic reactions - injection site sarcoma - pain at injection site

Vaccine frequency in kittens

Neonates absorb antibodies from colostrum. The amount of antigen available in colostrum depends on the immune status and disease history of the mother. The amount absorbed varies

between individuals in the litter according to how much colostrum is taken in. Maternal derived antibody (MDA) half-life varies according to antigen (7-18 days)[12]. Because vaccine virus is attenuated, it is also less infective than wild virus. Thus all neonates that have any MDA go through a stage where they have enough antibody to block effective vaccination, but not enough to prevent infection with more virulent field strains of the virus. This is the window of susceptibility.

A single good quality modified live virus vaccine (eg FPV) will trigger a protective immunity IF given at the correct time – when MDA have fallen low enough. There are killed (inactivated) FPV vaccines on the market for cats, so it's important that you know which type you are using. Only repeated serology will determine when a kitten will first be able to seroconvert. This is not practical in the majority of cases. Thus vaccine interval will be determined mainly by the chance of exposure of the kitten to infectious diseases, but should be no less than every 2 weeks. If given more frequently, interferon mounted in response to the first vaccine will inhibit antibody synthesis triggered by the second [12]. The prescribed interval between killed vaccines should not be exceeded as the second vaccine usually builds on a priming effect of the first. These are generalisations and the manufacturer's recommendations on the use of a specific product should be adhered to. (NB FHV and FCV are inherently poorer antigen so 2 initial doses are recommended even if the MLV vaccine is used in adult cats.)

16 week vaccine: The recommendation for a further dose at 16 weeks is based on studies that showed that even in relatively small groups not all kittens seroconverted after vaccination at 12 weeks [5,33]. It may also have been supported by the recent increase in CPV in dogs on the UK that followed after vets changed to an early finish (last vaccine at 10 weeks) protocol[46]. **All the bodies agree that the booster at 12-15 months is essential. It seroconverts those individuals that for some reason did not respond to the initial vaccination course.**

Feline leukaemia virus vaccines

Background: Kittens less than 3 months old are most susceptible to infection – 90% become infected if exposed. Once cats reach 1 year of age, < 15% will become persistently infected. Of the remainder, about half clear the infection immediately and half become transiently infected but later clear the virus. This is one of the reasons why a positive FeLV antigen test in a healthy animal should be repeated 3-4 months later to confirm persistent infection.

All cats should be tested before their first vaccination unless they come from a closed breeding colony where cats are known to be FeLV negative. Vaccination of a FeLV positive cat does not change the outcome of infection, but is a waste of money in that individual and risks side effects for no benefit. If vaccination is performed instead of testing, infectious individuals may be left in contact with potentially susceptible cats. This is a risk because vaccination does not prevent clinical disease in all cases.

Vaccine efficacy is difficult to compare as the technology used in the vaccines varies widely (see table 7) and as adult cats are difficult to infect in challenge studies. For this reason, vaccine efficacy is usually reported as the preventable fraction - which takes into account how many unvaccinated cats became ill. Individual products perform very differently depending on how they're tested and the preventable fraction reported for particular brands often varies dramatically, ranging from 5% and 100% for Leukocell 2 (not licensed in South Africa), for example [43].

Table 7: Feline leukaemia vaccines in South Africa

Vaccine name (manufacturer)	Antigen	Preventable fraction [17,43]
Fel-o-vax LV-K (Fort Dodge)	Killed whole virus (with adjuvant)	44-100% (4 studies)
Leucogen (Virbac)	Recombinant p45 envelope antigen (with	52-87% (3 studies)

	adjuvant)	
Purevax FeLV	recombinant env and gag genes of FeLV A in a canary pox vector (no adjuvant)	78% (1 study)
Eclipse3 +FeLV (FeLV component = Fevaxyn)	Killed whole FeLV A and B (with adjuvant)	90-100% (2 studies)

FIV vaccination

Background: FIV is a retrovirus that has been used as a model to assist HIV vaccine development [48]. It is most commonly transmitted via bite wounds, so is classically a disease of roaming entire tom cats (this is probably an oversimplification as it can also be effectively transmitted in a colony in which there is minimal intercat aggression). FIV strains are divided into 5 subtypes or clades. There is almost as much genetic variation within subtypes (4-14%) as between subtypes (13-38%) [20,47]. As in HIV infection, a particular FIV strain will continue to mutate within its host. This means that viruses of the same subtype can still vary dramatically.

The Fel-o-Vax FIV vaccine is the only FIV vaccine on the market. It contains whole cells infected with 2 FIV strains that belong to subtypes A and D that have then been inactivated. It has been shown to confer protection against infection with high levels of challenge with subtype A and D strains and moderate challenge with a subtype B strain (which may be less pathogenic [42]). Specifically, it was shown to prevent between 54 – 100% of infections depending on the number of cats in the groups, the challenge strain, the dose used and the route of exposure (more effective when challenge was performed with vaccine strains)[47,48]. When natural infection with was mimicked with i/m injection of the challenge virus 1 year after the initial series of vaccines, the preventable fraction was 69% [48]. Protection against subtype C and E infection has not been assessed to date [48]. In a small survey of 31 FIV positive cats in South Africa, subtypes A and C were found. Subtype A was found in 25 of the 31 cats [20].

A significant disadvantage of this vaccine is that it becomes impossible to distinguish infected from vaccinated cats by routine tests - and from the above it becomes clear that an infected vaccinated cat is also a real possibility. The FIV Snap test looks for antibodies to the virus so would be positive in all three situations. PCR was touted as the solution, but recent papers [2,4] showed that different PCRs varied markedly in their accuracy in distinguishing vaccinated from infected cats. A PCR run by a molecular laboratory at UC Davis was about 90% accurate. Two PCRs run by commercial labs identified only 44 – 51% of vaccinated cats correctly [4] – as accurate (but more expensive) than flipping a coin. More recently, a Japanese group claimed to be able to differentiate vaccine induced antibodies from those triggered by natural infection by serology [23,26]. This is not available commercially in South Africa to my knowledge. Virus isolation is the gold standard test but requires a research facility, is extremely expensive and is not routinely run at Onderstepoort.

A second problem is that we know little about the FIV strains that occur in South Africa and even less on whether the vaccine protects against local strains. If FIV vaccination is considered, testing prior to vaccination should be mandatory. Testing should be performed at least 60 days after the last cat bite. All vaccinated cats should be permanently identified. Owners should be aware of the consequences of vaccination.

Core antigens Little is known about duration of immunity to core antigens in cats. The rabies vaccines on the market in South Africa are licensed for use every 3 years so even though there are no duration of immunity studies in the public domain for these vaccines in cats, they will have been submitted to the licensing authorities. There are small studies that show that MLV FPV vaccines will probably result in extended periods of immunity, much like the CPV vaccines. The duration of immunity to the respiratory components is more difficult to assess as vaccination decreases the severity of signs, but does not prevent disease in a proportion of cases. In addition, there is a huge range of FCV strains and the vaccines only protect against

some of these. It becomes difficult to quantify and monitor a decline in such a partial protection. For the really nitty gritty details, see below.

1. **Feline panleukopenia**: Immunity against FPV is predominantly antibody mediated so determining antibody levels can reasonably be seen as a surrogate marker for protection. As is the case with canine parvovirus, immunity to this antigen is thought to be long-lasting. Adult cats are also much less likely to show severe clinical signs.

Intervet and Merial have published results of conventional 3 year challenge studies for their trivalent vaccines showing 95-100% protection [11,33] and Schering Plough has done the same 2.5 years after the last booster [24]. Nine cats vaccinated with Fort Dodge's inactivated FPV vaccine were protected against challenge 7.5 years later [41]. The vaccinated cats' antibodies had fallen sharply after 6 years, but they were able to mount a rapid anamnesic response when challenged. In this study, none of the ***control*** *cats showed clinical signs of FPV either (although their WCC decreased more and faecal viral shedding was increased when compared with vaccinated cats). In my mind, this particular study provides better evidence that FPV is not very pathogenic in adult cats. In a serological study using Pfizer vaccines, protective FPV titres (Hemagglutination inhibition titres of 40 or more) were present in 67/71 (94%) cats last vaccinated 3 or more years previously [30].*

2. **Feline calicivirus:** Caliciviruses are genetically unstable and readily mutate. This means that there are many different FCV field strains. Vaccine strains provide variable protection against different field strains. Immunity against FCV is predominantly antibody based [8]. The problem with using antibodies to predict protection against FCV is that it is difficult to relate the protection against the lab virus (reflected by the antibody levels) to the degree of protection against a variety of field strains.

   In the field, FCV vaccine failure may occur because FCV immunity has waned or because the strain used in the vaccine did not cross protect against a field strain the cat met. Thus rotating FCV antigens may be of value. Similarly, if there is an outbreak of FCV in a vaccinated colony, it may be wise to choose a vaccine with a different antigen to see whether protection against the strain involved in the outbreak can be improved.

Different FCV strains are used by different manufacturers. Some companies claim broader cross protection against field strains than their competitors. Most comparative studies are based on cross neutralisation studies where a variety of field isolates of FCV are exposed to serum from vaccinated cats. Results of cross neutralisation studies appear to vary widely [1,32] depending on the cats sampled to collect the strains (clinically healthy ones at cat shows, infected colonies, referral cases) as well as how the test is performed. I am not aware of any information on the relationship between South African FCV field strains and the strains used in the various vaccines.

Intervet showed complete protection against oral ulcers when challenging cats with FCV strain 225 three years post vaccination but some developed a fever or became lethargic [11]. Merial showed a 79% decrease in clinical signs when challenged with heterologous (ie non-vaccine strain) FCV four weeks post vaccination and a 58% decrease when challenged a year following vaccination [33]. The Schering Plough vaccine resulted in a 94% decrease in clinical signs when cats were challenged 36 months after the last injection[24].The relationship between the vaccine and challenge virus was not specified. The Fort Dodge vaccines decreased clinical signs by 63% when cats were challenged with FCV strain 225 (same as in vaccine) 7.5 years post vaccination [41]. When challenged immediately following the primary vaccinations, clinical signs were decreased by 85% in one study [34] and by 64% in another study [41]. The Pfizer study showed that protective FCV titres (Serum

neutralisation titres of 32 or more) were maintained for at least 3 years in 67/71 (94%) cats [30].

Different FCV challenge studies become difficult to compare because it is usually not described how the clinical score is derived. This means it could vary from study to study. If you wanted to make the vaccine look good, you would challenge with a closely related strain for which there is known excellent cross immunity. If you wanted it to look bad, you would do the opposite. Neither scenario will mimic what happens in the field where different individuals will be exposed to a variety of strains. The next tricky question is: at what stage in this gradually waning immunity does the decrease in protection become clinically relevant?

Table 8: Feline calicivirus antigens in vaccines licensed in South Africa

FCV Antigen	Vaccine
F9	Feligen (Virbac); Felocell (Pfizer); Nobivac (Intervet-Schering Plough); Purevax in South Africa (Merial Animal Health)
225 and DD1	Fel-o-vax pct+calicivax (Fort Dodge Animal Health)
894-T	Eclipse (Intervet-Schering-Plough)
G1 and 431	Purevax (Merial) in EUROPE – (but check with them, they may be changing the South African vaccines over in the near future)

3. **Feline herpes virus:** There is only one FHV serotype that infects cats [44]. Cell-mediated and local (serosal) immunity are more important than antibodies in protecting cats against infection [10].

In the Intervet study, clinical signs of cats challenged with FHV three years after vaccination were reduced by 30% when compared with unvaccinated controls - but they were not compared with cats challenged immediately after vaccination [11]. The Merial study showed that vaccine protection against FHV decreased from a 74% reduction in clinical signs 4 weeks post vaccination to a 50% reduction in clinical signs 1 year after vaccination [33]. The Schering Plough vaccine resulted in a 67% decrease in clinical signs when cats were challenged 31 months after the last injection [24]. The Fort Dodge vaccine resulted in a 95% decrease in clinical signs 3 weeks after completion of the primary course [34]. A different group showed a 52% reduction in signs 7.5 years after vaccination [41]. The Pfizer serological study showed that FHV antibodies were maintained for at least 3 years in 61/71 (86%) cats [30]. Apart from the fact that the relevance of serology in assessing FHV immunity has been questioned [3], a limitation of the serological study was that all cats that had shown clinical signs of URT infection since initial vaccination were excluded. As the URT viruses are ubiquitous, animals with poor protection would have had ample opportunity to become infected. Thus the study would have selected for well protected individuals.

Recent developments

1. Feline panleukopenia: It has recently been shown that cats may become infected with canine parvovirus (CPV) 2a and CPV 2b. Certain strains of CPV 2b may cause signs of panleukopenia in cats. Conventional FPV vaccines have shown to protect against these canine parvoviruses [9].

2. Feline calicivirus: new virulent strains

Over the last few years, several outbreaks of disease caused by virulent systemic feline caliciviruses have been reported in the USA, the UK and in Germany [19,39,40]. Vaccination did not protect cats from infection. Adults were more severely affected than kittens. Mortality varied between 32 and 67%. Clinical signs included upper respiratory signs and oral ulcers, acute interstitial pneumonia, subcutanous oedema, ulceration of foot pads, pleural and peritoneal effusions, pancreatitis and hepatic necrosis (resulting in icterus) and rarely disseminated intravascular coagulation resulting in petechial haemorrhages, epistaxis and thrombosis. Caliciviruses are genetically unstable [36] and it is thought that new mutations were responsible for the increased virulence during each outbreak. Isolates within outbreaks were not identical, suggesting continued mutation. Continued mutation and the death of many hosts may explain why outbreaks all appeared to die out despite the virus being highly infectious. This continued mutation also means that it's pointless to chose a vaccine based on whether it protects cats against *previous* virulent strains – there is no way to predict that they will protect against new mutations that cause virulent disease.

In summary, there is reasonable evidence to support triannual vaccination against FPV. The evidence supporting extended duration of immunity following vaccination against URT viruses (at least that available in the public domain) is more tenuous, particularly in the case of FHV. This does not mean that triannual vaccination against the respiratory viruses will definitely result in a significant decrease in immunity / increase in clinical snuffles cases. It does highlight that further research in this area needs to be published if we are to make informed decisions for pet cats.

Table 9: Common questions on vaccination:

Vaccination while neutering	Not ideal, but studies in SPF kittens [37] and rescue centres show that animals are still effectively immunised in most cases
Feline immunodeficiency virus / FeLV positive cats	Vaccinate only medically stable cats at high risk of exposure. Vaccinate with killed vaccines. Risk of exposure should be low as retrovirus positive cats should be isolated from other cats.
Should cats previously infected with FCV or FHV be vaccinated against these Ag	Yes [8,45]. Immunity is short-lived [8,10]. In the case of FHV, it is possible (though not certain) that vaccination may decrease frequency of reactivation and thus clinical episodes [10]
Vaccination with a different brand of FeLV vaccine	It is generally accepted that if a different brand is used to boost the FeLV vaccines, it is NOT necessary to restart the course despite the fact that the vaccines vary significantly in the antigens used [43]. There is limited evidence to show that different brands may be used in the primary course [13]
A cat has a vaccine reaction. What do we do next time?	Assess risk vs benefit of continued vaccination for that individual. Give the trivalent vaccine, rabies and/or any other antigen 2 weeks apart so you can determine the offending antigen.

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