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The protective rate of the feline immunodeficiency virus vaccine: An Australian field study

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ABSTRACT

A case-control field study was undertaken to determine the level of protection conferred to client-owned cats in Australia against feline immunodeficiency virus (FIV) using a commercial vaccine. 440 cats with outdoor access from five Australian states/territories underwent testing, comprising 139 potential cases (complete course of primary FIV vaccinations and annual boosters for three or more years), and 301 potential controls (age, sex and postcode matched FIV-unvaccinated cats). FIV status was determined using a combination of antibody testing (using point-of-care test kits) and nucleic acid amplification, as well as virus isolation in cases where results were discordant and in all suspected FIV-vaccinated/FIV-infected cats ('vaccine breakthroughs'). Stringent inclusion criteria were applied to both 'cases' and 'controls'; 89 FIV-vaccinated cats and 212 FIV-unvaccinated cats ultimately satisfied the inclusion criteria. Five vaccine breakthroughs (5/89; 6%), and 25 FIV-infected controls (25/212; 12%) were identified, giving a vaccine protective rate of 56% (95% CI −20 to 84). The difference in FIV prevalence rates between the two groups was not significant ($P = 0.14$). Findings from this study raise doubt concerning the efficacy of Fel-O-Vax FIV® under field conditions. Screening for FIV infection may be prudent before annual FIV re-vaccination and for sick FIV-vaccinated cats. Owners should not rely on vaccination alone to protect cats against the risk of acquiring FIV infection; other measures such as cat curfews, the use of 'modular pet parks' or keeping cats exclusively indoors, are recommended.

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1. Introduction

Feline immunodeficiency virus (FIV) was discovered in 1986 in a cat colony in California [1]. FIV is a retrovirus of the genus *Lentivirus*. It has a worldwide distribution and is subdivided into seven clades (subtypes) (A, B, C, D, E, F and U-NZenv) [2–5]. An estimated 14.5 million pet cats are infected with FIV worldwide, and 33.5 million if feral cats are included [2], which is similar to the estimated number (35 million) of individuals infected with human immunodeficiency virus (HIV-1) globally [6]. The FIV-cat model is advocated as a 'test-bed' for HIV infection and HIV-1 vaccine development, and Australia, which has one of the highest FIV prevalence rates in the world (8–15% in client-owned cats with outdoor access; 20–25% in feral cats), is an excellent setting to study FIV transmission and its prevention by vaccination [7–9].

The commercial release of a FIV vaccine[1] for use in domestic cats (USA 2002; Australia 2004) was the first time a vaccine had been registered for preventing infection by a *Lentivirus* in either human or veterinary medicine. More than 5000 laboratory cats were used over 14 years to develop a dual-subtype (A and D), inactivated whole cell (IWC) and inactivated whole virus (IWV) vaccine. 689 client-owned cats were used for safety testing in the field before the vaccine was released commercially. The result was a vaccine registered with a 'preventable fraction' (efficacy) of 68%, based on combined results from two laboratory-based efficacy studies involving 105 cats (52 FIV-vaccinated, 53 FIV-unvaccinated) challenged one year after receiving three FIV vaccinations administered three weeks apart (difference in percentage viraemia between the two groups [25% *vs* 79%] $P < 0.01$) [2].

To date, a total of 262 cats (139 FIV-vaccinated, 123 FIV-unvaccinated) have been tested using the current commercial FIV vaccine in laboratory-based efficacy studies (including the 105 cats from the two pre-registration studies), with reported vaccine efficacy of between 0% and 100%, and an overall preventable fraction of 66% [2,10–16] (Table 1). Extremely high challenge doses, intravenous challenge (which avoids innate immunity barriers), and the use of highly pathogenic strains for challenge (e.g. FIV_{UK8}), have been proffered as possible explanations for the variation in

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[1] Fel-O-Vax® FIV, Boehringer Ingelheim, Fort Dodge, IA, USA.

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Table 1
Summary of laboratory-based efficacy studies in which Fel-O-Vax FIV® was given according to the manufacturer's guidelines (three subcutaneous injections 2–4 weeks apart, followed by a single annual booster in the long-term studies). Experimental vaccine efficacy (preventable fraction) = ([percentage viraemia in controls − percentage viraemia in vaccinates]/percentage viraemia in controls) [2]. Fel-O-Vax FIV® used in the first trial for USDA (United States Department of Agriculture) approval was a slightly different version to what was eventually registered and released commercially[a] [14,37]. Otherwise, studies where Fel-O-Vax FIV® was modified before administration, where Fel-O-Vax FIV® was administered via non-registered routes (e.g. intranasally) and where non-commercial vaccines (e.g. single- subtype FIV vaccines) were trialed are excluded. FDAH = Fort Dodge Animal Health, the parent company that developed and registered Fel-O-Vax FIV® (the FDAH vaccine range has since been acquired in Australia by Boehringer Ingelheim). CID_{50} = cat infectious dose 50, which is equivalent to the amount of virus required to cause infection in half of susceptible subjects. Conflicting CID_{50} doses are both presented[b] [12,15]. IM = intramuscular, IV = intravenous. Origins of homologous challenges: FIV_{Pet} (A) = California, USA; FIV_{Shi} (D) = Shizuoka, Japan, FIV_{UK8} (A) = Glasgow, UK. Origins of heterologous challenges: $FIV_{FD/US}$ (A) = California, USA; FIV_{FC1} (B) = Florida, USA; FIV_{Ao2} (B) (Aomori) = Aomori, Japan; FIV_{NZ1} (F′/C) = Auckland, New Zealand (prime sign represents that a full sequence of subtype F has yet to be identified) [15]; $FIV_{FD/DutA}$ (A) = Netherlands; FIV_{Bang} (A/B) = Massachusetts, USA. NA = not available.

Author	Challenge virus, clade, % difference from vaccine *env* sequence (FIV_{Pet} and FIV_{Shi})	Source	Dose ($\times CID_{50}$), route	Time after final vaccination	Viraemia in FIV-vaccinated cats	Viraemia in placebo controls	Vaccine efficacy (Preventable fraction, %)
FDAH (Study 1 for USDA license approval)[a] [10,15]	$FIV_{FD/US}$, A, 9% and 20%	*In vitro*	×1.47, IM	1 year	9/27 (PCR)	25/34 (PCR)	55
Huang (Study 2 for USDA license approval) [12,15]	$FIV_{FD/US}$, A, 9% and 20% (overall 11% difference in sequence)	*In vitro*	×1.79/11[b], IM	375 days	4/25 (PCR)	17/19 (PCR)	82
Pu [10]	FIV_{FC1}, B, 19% and 19.2%	*In vivo*	×15, IV	21 days	0/8 (VI)	9/9 (VI)	100
Kusuhara [14]	FIV_{Ao2}, B, 18.5% and 19.6%	*In vitro*	Natural, biting	21 days-19 months	0/6 (nested PCR)	4/8 (nested PCR)	100
Dunham [11]	FIV_{UK8}, A, NA	NA	×10, IM	28 days	5/5 (VI, RT-PCR)	6/6 (VI, RT-PCR)	0
Yamamoto [2,10]	FIV_{FC1}, B, 19% and 19.2%	NA	×100, IV	3–4 weeks	3/4	4/4	25
Yamamoto [15]	$FIV_{FD/DutA}$, A, NA	NA	×1.73, IM	NA	3/24	13/15	86
Huang [10,13]	FIV_{FC1}, B, 19% and 19.2%	*In vivo*	×1000 PMBC, IV	54 weeks	4/14 (PCR, RT-PCR)	5/5 (PCR, RT-PCR)	71
Coleman [10,16]	(i) FIV_{Bang}, A/B, NA	*In vivo*	NA, IV	3–4 weeks	3/4 (VI, PCR)	4/4 (VI, PCR)	25
	(ii) FIV_{FC1}, B, 19% and 19.2%	*In vivo*	NA, IV	3–4 weeks	0/8 (VI, PCR)	4/4 (VI, PCR)	100
	(iii) FIV_{FC1}, B, 19% and 19.2%	*In vivo*	NA (higher than [iii]), IV	3 weeks	7/9 (VI, PCR)	5/5 (VI, PCR)	22
	(iv) FIV_{NZ1}, F′/C, NA	*In vivo*	NA, IV	3–4 weeks	3/5 (VI, PCR)	10/10 (VI, PCR)	40
Total					41/139	106/123	66%

reported protection rates [2,17]. It has therefore been suggested that Fel-O-Vax FIV® efficacy may have been underestimated and there has been speculation that field trials involving natural challenge might report a preventable fraction higher than 66–68% [15,17]. Despite uncertain efficacy, millions of FIV vaccine doses have been sold worldwide, with no unequivocal 'vaccine breakthroughs' reported following in-field use in Australia (personal communication, Dr. Phillip McDonagh [Head of Regulatory Affairs for Animal Health, Boehringer Ingelheim Australia] and Dr. Elvira Currie [Australian Pesticides and Veterinary Medicines Authority]) or elsewhere [2,15].

The aim of this study was to determine the 'protective rate' (effectiveness) for the Fel-O-Vax FIV® vaccine in the field in Australia.

2. Material and methods

2.1. Sample population

Criteria for recruitment have been described previously [18]. Briefly, client-owned cats were recruited through veterinary clinics in Australia during 2013–15, most commonly at the same time as an annual health check or routine procedure (e.g. dental procedures). Two groups of cats were recruited: a FIV-vaccinated group ('cases') and a FIV-unvaccinated group matched to cases for age, sex and postcode ('controls'). Cats in the FIV-vaccinated group had been FIV antibody-tested before FIV vaccination was commenced (unless younger than six months-of-age when first vaccinated, due to the low risk of FIV infection and the possibility of false-positive antibody results from maternal antibodies) [19], given a primary course of three FIV vaccinations 2–4 weeks apart, and vaccinated annually against FIV for at least three years. Cats were excluded from the FIV-vaccinated group if FIV nucleic acid amplification (PCR) testing had been performed instead of FIV antibody-testing before FIV vaccination was commenced (due to the PCR assay's lower sensitivity) [18,20,21], if any primary FIV vaccinations were more than two weeks overdue (i.e. greater than 6 weeks interval between vaccinations), and if any of the annual FIV vaccinations were more than three months overdue (i.e. greater than 15 months interval between vaccinations). Cats included in the FIV-unvaccinated group had never been given the FIV vaccine. Outdoor access was a requirement for cats in both groups. Information pertaining to outdoor access, as well as number of suspected cat fights based on medical records and owner recollection, was collected at the time of sampling via a questionnaire. Owners of cats meeting the criteria of either group were offered free FIV testing in return for enrolling their cat in the study, and participating clinics were given free vaccines (FIV and/or non-FIV core vaccines) as an inducement, in return for their assistance recruiting cats.

Animal ethics approval was granted by the University of Sydney (Approval number N00/1-2013/3/5920).

2.2. Blood collection and determining FIV infection status

Procedures for venipuncture, FIV antibody testing of EDTA blood using point-of-care test kits (SNAP FIV/FeLV Combo[2], Witness FeLV/FIV[3] and Anigen Rapid FIV/FeLV[4] concurrently), nucleic acid amplification of blood using a commercial PCR assay that detects proviral DNA and viral RNA by targeting a conserved region

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[3] Zoetis Animal Health, Lyon, France.
[4] BioNote, Gyeonggi-do, Korea.

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