REVIEW

Feline leukaemia virus: a review of immunity and vaccination

The availability of feline leukaemia virus (FeLV) vaccines has added a new and important dimension to the control of this infectious agent. FeLV vaccination is a controversial issue, however, partly because of differences in the formulation between the current products, partly because of conflicting claims by vaccine manufacturers and partly because experimental trials have shown that none of the vaccines provides 100 per cent protection against infection. This paper reviews the role of the immune response in determining the outcome following exposure to FeLV and describes the importance of FeLV subgroups. The five commercial FeLV vaccines currently available in the USA and Europe are described and the published literature on efficacy studies is summarised. However, these efficacy studies are often difficult to interpret for various reasons, including the small numbers of animals used; differences in challenge methods, vaccine strains and vaccine dose employed; and differences in postchallenge monitoring protocols.

A. H. SPARKES

Journal of Small Animal Practice (1997) **38**, 187–194

The Feline Centre, Department of Clinical Veterinary Science, University of Bristol, Langford House, Langford, Bristol BS18 7DU

INTRODUCTION

Feline leukaemia virus (FeLV) is a horizontally, and sometimes vertically, transmitted retrovirus, first discovered by Jarrett and others in 1964, and now recognised as a common cause of fatal disease. The recent introduction of FeLV vaccines has great potential for protection of the general pet cat population, but FeLV vaccination has become controversial, partly because the available vaccines are produced in different ways, incorporating different antigens and adjuvants, and partly because of issues relating to vaccine efficacy and safety.

Where a disease is prevalent, the success of vaccination may be clearly apparent through clinical observation. With FeLV, however, the prevalence of infection in the healthy cat population is considerably less than 5 per cent (Hosie and others 1989, Macy 1994), and in such circumstances it is virtually impossible to evaluate vaccine efficacy through clinical experience (Macy 1994). Judgements on FeLV vaccine efficacy are, therefore, generally made on the basis of results of experimental challenge studies, and none of the available vaccines has provided 100 per cent protection in all published trials.

There is no answer to the question 'which is the best FeLV vaccine?', but a knowledge of the issues surrounding FeLV vaccinations, and access to the published efficacy data, provide the best opportunity for reasoned product evaluation. The purpose of this paper, therefore, is to review briefly FeLV infection and naturally acquired immunity; and then to review the literature relating to the efficacy of the five commercial FeLV vaccines currently available, three of which are licensed for use in the UK.

INFECTION AND IMMUNITY

Pathogenesis

Following exposure to FeLV, several potential outcomes are recognised (Rojko and Olsen 1984, Hoover and Mullins 1991, Rojko and Kociba 1991, Rojko and Hardy 1994):

- Acute infection
- Persistent viraemia
- Immunity (latent infection)
- Immunity (extinguished infection)
- Atypical (localised, sequestered) infection.

The outcome in any individual cat depends on many factors including the strain of virus, exposure dose, exposure duration, the age of the cat and also, importantly, the nature of the cat's immune response.

Acute infection

In most cats, acute infection results from oronasal exposure to the virus, with initial replication of the virus in the mononuclear cells (lymphocytes, macrophages) of the tonsils and other regional lymphoid tissue. Within 14 days of exposure, a cell-associated (lymphocytes and monocytes) viraemia develops which allows spread of the virus to distant lymphoreticular tissues,

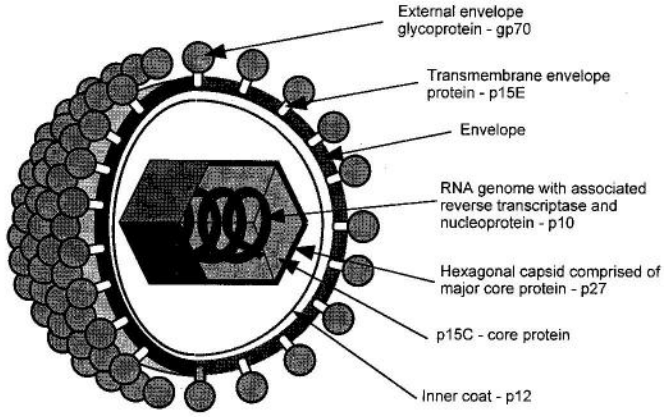

FIG 1. Diagrammatic representation of the structure of FeLV

the rapidly dividing cells of the intestinal epithelium and also, crucially, the bone marrow.

Persistent viraemia

Haemolymphatic (bone marrow) infection is generally established about two to six weeks following exposure to the virus. If an immune response fails to contain infection at this stage, there is the potential for massive production of virus which will overwhelm the immune response and establish persistent viraemia. Persistent viraemia of bone marrow origin is usually established about four to six weeks following infection. Both free and cell-associated virus is present in the blood, and there is dissemination of infection to multiple glandular and epithelial tissues, including the salivary glands and mucosa of the pharynx and nose, leading to oronasal shedding of the virus and the potential for transmission.

Immune cats

An adequate immune response following infection with FeLV will usually restrict replication and expression of the virus within four to eight weeks of infection. In most cats immunity therefore develops before or during bone marrow infection, and they do not develop marrow-associated viraemia. In a small proportion of cats, however, protective immunity does not develop until shortly after marrow-origin viraemia is established, and in these cats there is a period of transient viraemia, usually lasting only days to weeks (Rojko and Hardy 1994).

Immune cats with extinguished infections are those that have completely eliminated all virus and virus-infected cells from the body, but in a substantial proportion of immune cats (perhaps 30 to 70 per cent) latent infection persists in the form of integrated provirus within the genome of certain cells. These cells (usually in the bone marrow) do not express FeLV but still have the potential for productive infection if the cat is immunosuppressed (Rojko and others 1982, Rojko and Olsen 1984). However, latently infected cats usually progress to extinguished infection over time, and only rarely revert to productive FeLV infection (Rojko and Hardy 1994). The period of latency varies between individuals, usually lasting weeks to months, but occasionally being present for years or even the lifetime of the cat (Hoover and Mullins 1991, Rojko and Hardy 1994).

Atypical infections

Atypical infections affect only a small proportion (less than 5 to 10 per cent) of FeLV-infected cats, and represent infection sequestered at various sites by a partially protective immune response. These cats may exhibit intermittent viraemia or antigenaemia and over time are likely to progress to either extinguished infection or persistent viraemia (Rojko and Hardy 1994).

Importance of FeLV subgroups

Isolates of FeLV are divided into three major subgroups (FeLV-A, B and C) according to the structure of the gp70 protein (Fig 1), which confers differences in viral interference patterns and neutralisation tests (Sarma and Log 1973). FeLV-B and C subgroups are thought to arise from FeLV-A by recombination or mutation of proviral DNA. Within the genome of every domestic cat, there are multiple incomplete DNA proviral sequences of a retrovirus closely related to FeLV, which are referred to as endogenous FeLV-related sequences or enFeLV (Soe and others 1985, Rojko and Hardy 1994). These sequences are incomplete and therefore not capable of transcribing intact virions, but there is strong evidence that FeLV-B isolates arise through recombination between integrated FeLV-A provirus and enFeLV sequences (Stewart and others 1986, Overbaugh and others 1988); FeLV-C may arise in the same way or, perhaps, through mutation of FeLV-A (Vedbrat and others 1983, Rojko and Hardy 1994).

Studies of naturally infected cats have revealed that FeLV-A is the dominant subgroup, being ubiquitous and present in all FeLV-infected cats (Jarrett and others 1978, Stewart and others 1986, Tompkins and others 1988, Hoover and Mullins 1991). Infection with FeLV-B and/or FeLV-C under natural conditions is therefore found only in combination with FeLV-A, and about 50 per cent of viraemic cats are infected with subgroup A alone, about 49 per cent with subgroups A and B, and 1 per cent with subgroups A and C or A, B and C (Jarrett and others 1978, Rojko and Hardy 1994).

Isolates of FeLV-A are essentially monotypic, showing a high degree of genomic conservation (Donahue and others 1988, Hoover and Mullins 1991, Rigby and others 1992). Importantly, this means that the FeLV-A gp70 protein shows antigenic stability, and therefore there is cross-reactivity of neutralising antibodies between different isolates (Russell and Jarrett 1978, Vedbrat and others 1983, Donahue and others 1988). In contrast, isolates of FeLV-B and C show much greater antigenic heterogeneity, and virus neutralising (VN) antibodies to one isolate do not necessarily neutralise other isolates (Russell and Jarrett 1978, Vedbrat and others 1983, Donahue and others 1988, Rigby and others 1992, Rojko and Hardy 1994).

The different subgroups also vary in their pathogenicity for cats. FeLV-A is, in general, the least pathogenic, being slow to cause disease in comparison with FeLV-B and C (Jarrett and others 1978, Hoover and Mullins 1991, Rojko and Hardy 1994), but it is the subgroup most commonly associated with latent infections (Rojko and Kociba 1991, Rojko and Hardy 1994). Although more pathogenic, viruses of subgroups B and C are considered to be relatively or absolutely replication defective (Tompkins and others 1988). The altered structure of the gp70 molecule on FeLV-B and C isolates restricts their cell tropism and, therefore, prevents them replicating to high titres.

This helps to explain why these subgroups are always found in association with FeLV-A. The presence of FeLV-A probably leads to phenotypic mixing whereby an FeLV-B (or C) genome can be encased in an FeLV-A envelope, allowing productive infection of cells not normally available to the FeLV-B (or C) isolate (Jarrett and others 1973, 1984, Rigby and others 1992, Rojko and Hardy 1994). Because of the way in which viruses of subgroups B and C are formed, and because of their dependence on FeLV-A for replication, most of these isolates are thought to arise de novo in cats with pre-existing persistent viraemia with FeLV-A (Rojko and Hardy 1994). Horizontal transmission of FeLV-B or C isolates is theoretically possible, but has not been documented under natural conditions while experimental studies have demonstrated that it would inevitably require the concomitant transmission of FeLV-A to enable these viruses to replicate (Jarrett and Russell 1978, Jarrett and others 1984, Hoover and Mullins 1991).

Immune response

The immune response is one of the crucial factors determining the outcome of infection with FeLV, but the mechanisms of naturally acquired immunity to FeLV are incompletely understood. Many investigations of the protective immune response have focused on the importance of VN antibodies and anti-FOCMA (feline oncornavirus-associated cell membrane antigen) antibodies.

Virus neutralising antibodies

FeLV infects cells through the binding of the major envelope glycoprotein (gp70) to specific cell receptors. VN antibodies are directed against epitopes on this glycoprotein which, when bound to the virus, prevent the virus attaching and gaining entry to the cell and assist in clearing the virus from the blood (Rojko and Olsen 1984, Rojko and Kociba 1991).

The importance of VN antibodies has been established through numerous sero-epidemiological and experimental studies. In cats both naturally and experimentally exposed to the virus, persistent viraemia is almost invariably associated with very low or zero VN antibody titres, whereas a high prevalence of high antibody titres is found in cats that have been exposed and resist infection or experience only transient viraemia (Hardy and others 1976, Charreyre and Pedersen 1991, Rojko and Hardy 1994). Furthermore, and important for vaccination, passive transfer of VN antibodies (either artificially, or naturally via colostrum to kittens) has also been shown to protect against viraemia following subsequent challenge with FeLV (Rojko and Olsen 1984).

Antibodies to other viral antigens and cell-mediated immunity

Although many studies have confirmed the very important role of VN antibodies in protection against viraemia, there is evidence that they are not always required for protection (some cats resistant to infection do not develop VN antibodies), and appreciable VN antibody titres are occasionally found in viraemic cats (Charreyre and Pedersen 1991, Hawks and others 1991, Rojko and Hardy 1994). This has led many investigators to question the role of antibodies to other viral antigens and also the possible importance of cell-mediated immunity (CMI).

Using a variety of techniques, investigators have found that FeLV-infected cats develop antibodies to a wide range of FeLV proteins including envelope proteins (p15E, gp70), core antigens (p10, p12, p15, p27) and the FeLV reverse transcriptase (Lutz and others 1980, Snyder and others 1985, Charreyre and Pedersen 1991, Hawks and others 1991, Rojko and Hardy 1994). Antibody responses to these proteins tend to be higher in cats that resist the development of persistent viraemia, but the pattern (range) of antibodies produced is similar in both persistently viraemic and immune (recovered) cats. Although the development of antibodies and immune complexes may play a role in the pathogenesis of some FeLV-related diseases (Rojko and Hardy 1994), there is speculation that antibodies to determinants other than gp70 may also play a role in protective immunity in at least some individuals (Lutz and others 1980, Charreyre and Pedersen 1991).

The potential role of CMI to FeLV infection has been largely unexplored. Studies have documented CMI responses (natural cytotoxic cells and natural killer cells) to FeLV-transformed cells (Kooistra and Splitter 1985, Tompkins and Tompkins 1985), and there has been speculation of the potential role CMI may have in protective responses to FeLV infection. Although the development of VN antibodies in an infected cat may prevent further spread of infection to susceptible cells, the elimination of those cells already infected with the virus would rely on other means such as antibody-dependent complement-mediated lysis of cells or, quite likely, CMI responses (Charreyre and Pedersen 1991, Rojko and Hardy 1994).

FOCMA and anti-FOCMA antibodies

FOCMA is an antigen expressed on the cell surface of FeLV-transformed cells (Vedbrat and others 1983). The origin of FOCMA has not been entirely resolved but there is some cross-reactivity between anti-FOCMA antibodies and antibodies to FeLV subgroup C gp70 (Vedbrat and

Table 1. FeLV vaccines currently available in the UK and elsewhere*

Vaccine	Manufacturer or distributor	Type of vaccine	FeLV subgroups included	Available in the UK	Inclusion of FOCMA
Leucat/VacSYN	Rhône Mérieux/Synbiotics	Inactivated, non-adjuvanted, whole virus	A, B and C	No	Yes
Leucogen/Genetivac/ Nobivac FeLV	Virbac/Mallinckrodt/ Intervet	Purified, adjuvanted, recombinant, non-glycosylated form of gp70 (p45)	A	Yes	No
Leukocell 2	Pfizer	Inactivated, adjuvanted, mixed sub-unit from FeLV-infected tissue culture filtrate	A, B and C	Yes	Yes
Fel-O-Vax	Fort Dodge	Inactivated, adjuvanted, whole virus	A and B	No	No
Fevaxyn	Solvay-Dulphar/Fort Dodge	Inactivated, adjuvanted, whole virus	A and B	Yes	No

*See Loar 1993

Table 2. Results of studies of commercially available FeLV vaccines

Study	Vaccine(s) studied	Number of cats		Persistent viraemia		Transient viraemia		Preventable fraction against persistent viraemia (per cent)
		Vaccinates	Controls	Vaccinates	Controls	Vaccinates	Controls	
1 Haffer and others 1990	Leukocell 2	25	10	7 (28%)	6 (60%)	9 (36%)	4 (40%)	53·3
2 Clark and others 1991	Genetivac	20	20	3 (15%)	14 (70%)	8 (40%)	6 (30%)	78·6
3 Hines and others 1991	Fevaxyn*	144	45	12 (8%)	39 (87%)	10 (7%)	6 (13%)	90·4
4 Legendre and others 1991	Fel-O-Vax	12	11	0 (0%)		6 (50%)		100·0
	Leukocell 2	12		5 (42%)	7 (64%)	3 (25%)	3 (27%)	34·5
	VacSYN	12		6 (50%)		2 (17%)		21·4
5 Lehmann and others 1991	Genetivac†	18	12	1 (6%)	10 (83%)	2 (11%)	2 (17%)	93·3
6 Pedersen and Johnson 1991	VacSYN†§	18	12	10 (56%)	11 (92%)	NS	NS	39·4
7 Pollock and Haffer 1991	Leukocell 2	148	81	23 (16%)	50 (62%)	NS	NS	74·8
8 Pollock and Haffer 1991	Leukocell 2	14	5	1 (7%)	3 (60%)	NS	NS	88·1
9 Sebring and others 1991	Fel-O-Vax	4	4	0 (0%)		NS		100·0
	Leukocell 2	4		2 (50%)	4 (100%)	NS	NS	50·0
	VacSYN	4		3 (75%)		NS		25·0
10 Sebring and others 1991	Fel-O-Vax*†	90	58	4 (4%)	53 (91%)	NS	NS	95·1
11 Tizzard and Bass 1991	Leukocell 2†	10	18	4 (40%)	13 (72%)	NS	NS	44·6
12 York and York 1991	VacSYN	43	22	2 (5%)	14 (64%)	NS	NS	92·7
13 Pedersen 1993	Fevaxyn	10	10	0 (0%)	10 (100%)	1 (10%)‖	0 (0%)	100,0
14 Lafrado 1994	Leukocell 2	26	26	0 (0%)	1 (4%)	0 (0%)	4 (15%)	100·0
15 Jarrett and Ganiere 1996	Leucat	12	8	12 (100%)		0 (0%)		–14·3
	Leucogen	12		5 (42%)	7 (88%)	0 (0%)	1 (13%)	52·4
	Leukocell 2	12		10 (83%)		0 (0%)		4·8
16 Jarrett and Ganiere 1996	Leucogen	6	6	1 (17%)	5 (83%)	0 (0%)	0 (0%)	80·0

NS Not specified
* Composite figure given for result of several reported trials
† 50 per cent of vaccinates and controls FIV-infected, but FIV status reported not to affect vaccine efficacy
‡ Other (unlicensed) vaccines included in the study
§ Study performed when VacSYN only licensed (under a different name) in one state of the USA
‖ This cat reported as 'suspiciously' positive by the author

others 1983). The expression of FOCMA, however, occurs on all FeLV-transformed cells and not just those associated with FeLV-C infection. It has been speculated that FOCMA may therefore be an antigen expressed through transcription of endogenous FeLV-related sequences in FeLV-infected and transformed cells (Rojko and Kociba 1991, Rojko and Hardy 1994).

Regardless of the exact origin of FOCMA, the development of anti-FOCMA antibodies has been found to confer protection against the development of FeLV-related neoplastic disease (Rojko and Hardy 1994). Large seroepidemiological studies performed over several years have demonstrated that cats which develop lymphoma or leukaemia have low or zero anti-FOCMA antibody titres, whereas high titres are associated with protection against development of these neoplasms, and passive administration of anti-FOCMA antibodies can even result in regression of established lymphomas (Cotter and others 1974, Essex and others 1976, Hardy and others 1976, Rojko and Hardy 1994). There is strong evidence that the protection conferred by anti-FOCMA antibodies is achieved through complement-dependent (antibody-mediated) lysis of the transformed cells (Grant and others 1979).

VACCINES

An understanding of the pathogenesis of, and immune response to, FeLV infection helps to resolve some of the controversies surrounding FeLV vaccination. There are five commercial vaccines marketed in the USA and Europe (Table 1), although

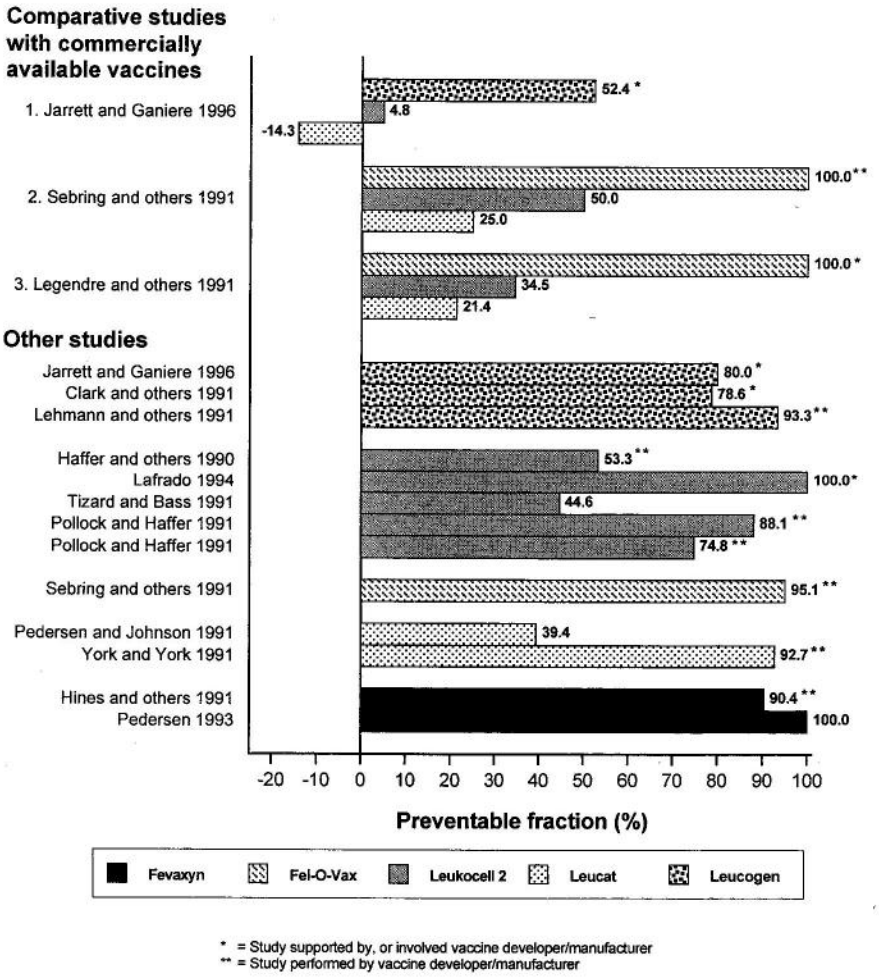

FIG 2. Performance of five FeLV vaccines in different challenge studies

some of these are marketed by different companies (and under different labels) in different countries. The five vaccines are all inactivated, but differ in other respects. Four are adjuvanted (using different products), three are whole virus vaccines and two are subunit (one recombinant), and the vaccines incorporate different sources and subgroups of FeLV (Table 1, Loar 1993).

Assessment of vaccine efficacy

An ideal vaccine would provide protection against both persistent and transient viraemia and thus also prevent latent infections and the development of FeLV-related diseases (Rojko and Hardy 1994). However, none of the currently available vaccines has been shown to produce sufficient mucosal immunity to routinely prevent transient viraemia following exposure. Table 2 summarises the results of the FeLV vaccine efficacy studies relating to the currently available products that were found during a search of the published veterinary literature. This table lists both studies evaluating a single product and comparative studies but, as indicated, where studies included evaluation of experimental vaccines or vaccines no longer commercially available, those results have been omitted.

An important concept in the evaluation of FeLV vaccine efficacy is that of the 'preventable fraction' (PF). This is designed to give a more accurate reflection of vaccine efficacy than simply looking at the proportion of vaccinated cats that were protected against viraemia, as it takes into account that often considerably less than 100 per cent of control (non- or sham-vaccinated) cats develop persistent viraemia (PV). The PF is therefore defined as the proportion of cats protected by vaccination in excess of that protected by natural resistance (Loar 1993) and is calculated as:

$$PF(\%) = \frac{\%\text{ controls with PV} - \%\text{ vaccinates with PV}}{\%\text{ controls with PV}} \times 100$$

The calculated PFs from the various studies cited are shown in Table 2 and Fig 2. Although assessment of the PF is the recommended way of evaluating vaccine efficacy (Loar 1993), it is important that other factors are also considered, in particular the number of cats used for the study and the number of controls developing persistent viraemia. For example, in the study reported by Sebring and others (1991) comparing the efficacy of Fel-O-Vax, Leukocell 2 and VacSYN (study 9 in Table 2), there were only four cats in each group (vaccinates and controls), thus a 25 per cent difference in the reported PF was accounted for by a single cat developing or resisting persistent viraemia. Also in the study reported by Lafrado (1994) evaluating Leukocell 2 (14 in Table 2), the PF was calculated as 100 per cent but this reflected the development of persistent viraemia in only one of the 26 control cats and none of the vaccinates. This emphasises the need to examine other factors in addition to the PF to evaluate fully FeLV vaccine studies.

From the limited data available (Table 2 and Fig 2), the whole cell vaccines (Fel-O-Vax and Fevaxyn) appear to show most consistent protection against FeLV challenge. However, it can be seen from Table 2 and Fig 2 that the reported efficacy for any individual product varies, sometimes greatly, between different studies.

Several factors help to explain this and also make direct comparison between studies very difficult. Some of the important differences between the studies are outlined in Table 3. It can be seen that the method of viral challenge, the strain of virus used for the challenge and the age of cats at the time of challenge varies considerably between studies. Although studies involving 'natural exposure' of cats (ie, control and vaccinated cats housed together with persistently viraemic cats) will mimic field exposure to the virus most closely, many studies employ an artificial challenge system. This usually involves the administration of virus via the intraperitoneal or the oronasal route, frequently with concurrent immunosuppression provided by administration of corticosteroids. These changes produce a much higher proportion of infected control cats, reducing the overall number of cats needed for efficacy studies. However,

they leave open the question of whether such studies truly reflect the efficacy of a product under natural conditions where the virus is usually spread by prolonged close contact between cats (Hoover and Mullins 1991, Rojko and Hardy 1994). Furthermore, it is obviously difficult to compare studies using different challenge protocols, and even where the same virus and challenge route were used for different studies (Table 3) there were often other differences such as in the dose of challenge virus, the frequency of virus administration or the protocol for inducing immunosuppression.

Another important difference between the studies is the sampling protocol following the challenge and the definition of persistent viraemia (Table 3), which may have an important impact on the final results. All this serves to emphasise the difficulties in comparing results from the reported studies, and the importance of trying to standardise an approach to FeLV vaccine efficacy trials. Single comparative trials involving several (or all) of the available vaccines are preferable for assessing efficacy, but no one study would be able to address all the variables that could have an impact on the results. It can also be seen from Fig 2 and Table 3 that most of the vaccine efficacy studies have been either supported or performed by vaccine manufacturers or distributors. This does not imply criticism of these particular studies – and if adequate details of the study design are provided they can be judged on their own merit – but fully independent trials are clearly preferable (Loar 1993). Although independent, natural-challenge studies, where several, or all of the vaccines are compared simultaneously, are likely to provide the most convincing efficacy data, such trials are expensive to undertake, and this also raises the issue of how such studies can be funded.

As shown in Table 2, some studies report the prevalence of transient viraemia in vaccinates and controls, and these results clearly suggest that none of the vaccines provides 100 per cent protection against transient viraemia, but again comparison between studies is extremely difficult due, particularly, to the different

Table 3. Details of studies of commercially available FeLV vaccines

Study	Cats used (source, and age at challenge)	Challenge virus (group and strain)	Challenge method	Frequency of sampling (weeks postchallenge)	Definition of persistent viraemia
1 Haffer and others 1990*	SPF: 17–25 w	FeLV-A/Rickard	ON + CS	Every 2 weeks (duration 12 weeks)	Antigenaemia at week 12 and present for at least 6 weeks
2 Clark and others 1991*	SPF: 16–19 w	FeLV-A/Glasgow	IP	1, 2, 4, 8, 12, 16, 20, 24, 28, 39, 52	Viraemia at week 12 and beyond
3 Hines and others 1991*	SPF: 14–19 w	FeLV-A/Rickard	ON + CS	Every 2 weeks (duration 12 weeks)	Antigenaemia at week 12
4 Legendre and others 1991*	SPF: 4 m	FeLV-A/1161, FeLV-A/CT600 and two FeLV-A field isolates	NE	2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 23, 31	Viraemia at week 31 and for at least 2 months prior to this
5 Lehmann and others 1991*	SPF: 14–15 m	FeLV-A/Glasgow	IP	1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24	Persistently positive prior to and at week 24
6 Pedersen and Johnson 1991	SPF: 15–28 w	FeLV-A/CT600 FeLV-A/Rickard	ON + CS	NS, followed to 16 weeks	Antigenaemia for more than 4 weeks and at 16 weeks
7 Pollock and Haffer 1991*	SPF cats (NS)	FeLV-A/Rickard	ON + CS	Every 2 weeks (duration NS)	Antigenaemia beyond 8 weeks
8 Pollock and Haffer 1991*	SPF cats (NS)	FeLV/NCE	SC	Every 2 weeks (duration NS)	Antigenaemia beyond 8 weeks
9 Sebring and others 1991*	NS	NS	IP + CS	NS	NS
10 Sebring and others 1991*	NS	NS	IP + CS	NS	NS
11 Tizzard and Bass 1991*	SPF: 15 w	FeLV-A/Rickard	ON + CS	NS	NS
12 York and York 1991*	Rural source: 16–18 w	FeLV-A/Richard	ON & IM + CS	NS	Antigenaemia of >1 month duration
13 Pedersen 1993	SPF: 9-10 m	FeLV-A/CT600	ON + CS	1·5, 2, 3, 4, 5, 6, 8, 10, 12	Antigenaemia at week 12
14 Lafrado 1994*	SPF 13 w	FeLV-A/Rickard	NE	Every 2 weeks (duration 26 weeks)	Antigenaemia at week 12, and beyond
15 Jarrett and Ganiere 1996*	SPF 14 w	FeLV-A/Glasgow-1	IP	Every 3 weeks (duration 12 weeks)	Antigenaemia at week 12, and present for at least 6 weeks
16 Jarrett and Ganiere 1996*	SPF 14 w	FeLV-A/Glasgow-1, FeLV-B/Sarma and FeLV-C/Sarma	ON	Every 3 weeks (duration 12 weeks)	Antigenaemia at week 12, and present for at least 6 weeks

SPF Specific pathogen free, w Weeks old, m Months old, ON Oronasal, IM Intramuscular, SC Subcutaneous, IP Intraperitoneal, + CS With corticosteroid-induced immunosuppression, NE Natural exposure, NS Not specified

* Study supported or performed by a vaccine manufacturer

postchallenge sampling protocols and the definitions of persistent (and therefore transient) viraemia (Table 3). As transient viraemia has been detected in a proportion of vaccinated cats, it is not surprising that latent infections have also been identified in a variable proportion of vaccinated cats in some studies (Legendre and others 1991, Hines and others 1991).

Other questions relating to vaccines

Subgroups and vaccination

Of the five commercial vaccines, one (Leucogen; Virbac) contains antigens derived from FeLV subgroup A alone and the remainder contain mixtures of FeLV-A with B, or with B and C (Loar 1993, Table 1). While obviously not deleterious, there is no evidence that inclusion of subgroups B and C in a vaccine is of any benefit. As noted previously, there is no evidence of natural horizontal spread of FeLV-B or C between cats and, even if it were to occur, it would require the concomitant transmission of FeLV-A (Jarrett and Russell 1978, Jarrett and others 1984). Protection (primarily through the induction of VN antibodies) against FeLV-A should therefore be all that is required of a vaccine. Furthermore, the heterogeneity of FeLV-B and C isolates means VN antibodies induced by one isolate would not necessarily provide cross-protection against another (Russell and Jarrett 1978, Vedbrat and others 1983, Donahue and others 1988, Rojko and Hardy 1994). The sufficiency of including just FeLV-A derived antigens in a vaccine has also been confirmed in two different studies, where cats immunised with Leucogen (Jarrett and Ganiere 1996) or a prototype vaccine containing just FeLV-A (Hoover and others 1991) were shown to be protected against challenge with a mixture of both FeLV-A and B viruses.

Although FeLV-A strains are monotypic with cross-reacting VN antibodies, other differences between isolates confer altered infectivity and pathogenicity (Rojko and Hardy 1994) and this is one reason why full evaluation of vaccine efficacy requires challenge exposure to different FeLV isolates (Legendre and others 1990, Macy 1994).

Virus neutralising antibodies and vaccination

Although CMI and induction of antibodies to other viral proteins may play a secondary role in the protection of cats, it is the induction of VN antibodies to prevent viraemia that is considered of prime importance to vaccination (Loar 1993). However, vaccine efficacy *cannot* be assessed by examining VN antibody responses after vaccination. It is clear from several studies that while vaccination may confer solid protection to an individual, this is not necessarily reflected in high VN antibody titres. In many cases, vaccination appears to 'prime' the cat and appreciable VN antibody titres may not be observed until after subsequent challenge with FeLV (Pedersen 1993, Clark and others 1991, Lehmann and others 1991).

A practical consequence of the importance of the VN antibody response is that it is generally considered to be possible to give booster vaccinations to a cat using a different vaccine than that used for primary vaccinations (Loar 1993).

Importance of FOCMA in vaccines

Of the five vaccines available, only two contain a claim to incorporate FOCMA (Loar 1993, Table 1), although it has been suggested that, because of the way in which the vaccines are produced, all except Leucogen may contain FOCMA (Loar 1993). However, there is no evidence that the inclusion of FOCMA in the vaccines is of any benefit to the cat. If a vaccine protects against infection with FeLV, it will also protect the cat from the development of FeLV-related disease, and there is no evidence that the inclusion of FOCMA has any role in protecting cats against infection (Loar 1993).

Adverse reactions to vaccines

A low incidence (often less then 1 per cent) of mild adverse reactions are reported with the use of all FeLV vaccines (Clark and others 1991, Hines and others 1991, Pollock and Haffer 1991, York and York 1991, Rojko and Hardy 1994) and these generally take the form of local swelling or pain, or transient lethargy and/or pyrexia. Clinical experience and close observation of vaccinated cats (Clark and others 1991) suggest that the incidence of these adverse reactions is much higher than that reported to the manufacturers, but nevertheless severe reactions are extremely rare.

One potentially severe long-term adverse reaction is the development of vaccine-associated sarcomas. These aggressive fibrosarcomas have been reported to develop at the site of (usually) repeated vaccinations in cats in the USA, particularly, though not exclusively, in association with the use of adjuvanted vaccines such as FeLV and rabies vaccines (Kass and others 1993). The tumours arise with a reported incidence of around one per 10,000 FeLV and rabies vaccines administered (Kass and others 1993). Although the aetiopathogenesis is unclear, they may be associated with chronic inflammation induced at the site of vaccination and/or the aluminium-containing vaccine adjuvants (Hendrick and Brooks 1994). It remains to be seen whether this will become a problem in the UK, where rabies vaccination is not routine and where FeLV vaccines have not been in use for as long.

Acknowledgement

A. H. S. was supported by the Feline Advisory Bureau.

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