

**Veterinary Products
Committee (VPC) Working
Group on Feline and Canine
Vaccination**

Final Report to the VPC

**Veterinary Products
Committee (VPC)
Working Group on
Feline and Canine
Vaccination**

Department for Environment, Food & Rural Affairs

May 2001

Department for Environment, Food and Rural Affairs
Nobel House
17 Smith Square
London SW1P 3JR
Telephone 020 7238 6000
Web site www.defra.gov.uk

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This report was written by the Veterinary Products Committee Working Group on Feline and Canine Vaccination: Professor Rosalind Gaskell (Chairman), Professor George Gettinby, Mrs Sheila Graham, and Mr David Skilton.

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Veterinary Products Committee (VPC) Working Group on Feline and Canine Vaccination:

Membership of the Working Group

Professor Rosalind Gaskell BVSc, PhD, MRCVS (Chairman), Department of Veterinary Pathology, Faculty of Veterinary Science, University of Liverpool, Leahurst, Neston, South Wirral, CH64 7TE

Professor George Gettinby BSc, DPhil, CStat, Hon Ass RCVS, FRSE, Department of Statistics and Modelling Science, University of Strathclyde, Glasgow, G1 1XH

Mrs Sheila Graham BSc, Lay member of the Veterinary Products Committee contactable via the Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey KT15 3LS.

Mr David Skilton BVSc, MRCVS, c/o the Veterinary Defence Society Limited, 4 Haig Court, Parkgate Industrial Estate, Knutsford, Cheshire, WA16 8XZ

Working Group Secretariat (Veterinary Medicines Directorate)

Mr Alastair Gray BVetMed, BA, MSc, MRCVS, Head of Suspected Adverse Reaction Surveillance Scheme;

Mrs Samantha Knivett BSc(Hons), Suspected Adverse Reaction Surveillance Scheme;

Miss Amanda Leavey HND, BSc(Hons), Suspected Adverse Reaction Surveillance Scheme;

Dr David Mackay BVetMed, MSc, PhD, MRCVS, Head of Immunological Products Team;

Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey KT15 3LS

Executive Summary

- The Working Group was set up by the Veterinary Products Committee (VPC)* in response to current concern in both the public domain and in the scientific community about possible health risks related to the routine vaccination of cats and dogs. The Working Group concluded that vaccination plays a very valuable role in the prevention and control of the major infectious diseases in cats and dogs. Although adverse reactions to vaccination, including lack of efficacy, occasionally occur, the Working Group concluded that the overall risk/benefit analysis strongly supports their continued use.
- Although for some diseases there is evidence of a longer duration of immunity following vaccination than the one year which is typically recommended on the product literature, there is currently insufficient information to propose revaccination intervals other than those proposed by the manufacturer and approved by the regulatory process.
- Notwithstanding this, in view of the occasional occurrence of adverse reactions, the Working Group recommends that the product literature indicates that the regime for booster vaccinations is based on a minimum duration of immunity rather than a maximum. The Working Group further recommends that the product literature should state that a risk/benefit assessment should be made for each individual animal by the veterinary surgeon in consultation with the owner with respect to the necessity for each vaccine and the frequency of its use.
- The evidence suggests that cats appear to be susceptible to the occasional development of sarcomas at sites of injection and there is some further evidence to suggest that although other products may be involved, this may be more associated with the use of vaccines containing aluminium based adjuvants. The Working Group therefore recommends that a generic warning to this effect should appear on the product literature for all feline vaccines administered by injection. The Working Group also highlighted the need for professional and educational bodies in the UK to bring to the attention of veterinary practitioners appropriate methods for prevention, diagnosis and treatment of this serious condition.
- The Working Group considered in depth the monitoring of adverse reactions including the advantages and disadvantages of surveillance schemes. A range of options for carrying out further epidemiological (analytical) studies was also considered. However the Working Group emphasised that surveillance schemes, and the UK Veterinary Medicines Directorate (VMD) Suspected Adverse Reaction (SAR) Surveillance Scheme in particular, provided a very valuable resource. The large database within the VMD scheme (collected since 1985) was analysed as part of this report. Figures were derived in terms of incidence (reporting rate) of certain clinical signs per 10,000 doses, and risk factors as identified by statistical analysis. However, due to a number of constraints, the analysis was not fully comprehensive and the interaction of possible risk factors was not determined.
- Product-related control charts were developed in order to detect changes in incidence rates of adverse reactions (per 10,000 doses sold) both within and between different vaccines. Such charts provide a powerful way to detect changing trends in incidence and, when used in conjunction with product characteristics, they may identify possible causes. In general, the data showed that the incidence of adverse reactions to cat and dog vaccines per 10,000 doses of

* The Veterinary Products Committee (VPC) is an independent scientific committee established under Section 4 of the Medicines Act to give advice on the safety, quality and efficacy of veterinary medicines to the UK licensing authority (Health and Agriculture Ministers) and to promote the collection of information relating to suspected adverse reactions for the purpose of enabling such advice to be given.

product sold was relatively low. Although under-reporting is a feature of such surveillance schemes, it does appear that, overall, vaccination of cats and dogs should be considered safe and effective.

- Finally, the Working Group was conscious, whilst preparing this report, of the extensive media coverage that has been given to the issue of the safety of human vaccines, in particular the mumps, measles and rubella (MMR) vaccine. The Working Group emphasises that the conclusions and recommendations included in this report relate only to the vaccines used in cats and dogs. The issues identified are specific to the diseases and species examined and no attempt should be made to draw analogous conclusions in relation to vaccines administered to man.

Conclusions and recommendations

The conclusions and recommendations of this report are as follows:

1. A review of the literature and other sources of information* revealed that published quantitative data on suspected adverse reactions (SARs) was limited. An overall annual incidence of 0.004% of feline / canine SARs associated with the use of vaccines, expressed in relation to estimated sales data, was reported in the UK by Gray²¹. In Australia, a similar adverse reaction rate of 0.2 to 0.4 per 10,000 doses of small animal vaccines has been reported²⁶. There are a number of descriptive reports of clinical signs associated with vaccine SARs. These include well-recognised immune-mediated phenomena, such as anaphylaxis and hypersensitivity; local and systemic reactions which may be due to the adjuvant; and problems of residual virulence or contamination of the vaccine.

More recently there is strong evidence, largely from the USA, that fibrosarcomas may occur in cats at the site of vaccination, and more limited, still equivocal evidence that other disorders such as immune-mediated haemolytic anaemia (IMHA) or immune-mediated thrombocytopenia (IMTP) may be associated with vaccination in dogs.

2. In the UK, the Veterinary Medicines Directorate (VMD), which acts on behalf of the UK licensing authority in relation to veterinary medicines, operates the Suspected Adverse Reaction (SAR) Surveillance Scheme (SARSS), which is a national reporting scheme for monitoring both animal and human Suspected Adverse Reactions (SARs) to veterinary medicines. The holders of Marketing Authorisations have a legal obligation to record and submit adverse event reports to the VMD; all other reporting is voluntary. A breakdown of categories of reporters is shown in Figures 1a and 1b.
3. It is acknowledged that the SAR Surveillance Scheme, like all schemes of its type, is passive, but reactive. Such schemes are a valuable method of monitoring trends in a population over time, although they are not entirely satisfactory measures of the incidence or prevalence of reaction rates in a population, unless the surveillance is based on a properly randomised sampling scheme. It is also noted that although the term 'incidence' is used in this report, a more accurate term would be 'reporting rate'. Surveillance schemes are subject to a number of factors (such as media attention, and owner, breeder, or professional concerns) which may influence reporting sources and reporting rates. Under-reporting is also likely to be a feature of such schemes.

Recommendation 1

Since the effectiveness of the SAR Surveillance Scheme largely depends on the level and quality of reporting, the Working Group recommends that ways should be found to improve this. Thus all reporting should be encouraged; more publicity should be generated for the scheme; and there should be more active targeting of reporters and reporting groups. Procedures should be developed to improve the quality of information reported to the scheme, and the response rate to requests for further information. The Working Group also recommends that follow-up action should be taken by contacting reporters that have not responded within the given three week period: telephone responses should also be encouraged.

* information on issues which related to the objectives of the Group was obtained from a variety of sources including the scientific literature; lay articles and those related to consumer concerns; various animal interest groups; academic, trade, and professional bodies both in the UK and overseas; from the Internet; from EU legislation and guidelines; and from similar relevant areas in the human field¹⁻²⁰. (Appendix 1a)

4. There is clear evidence that the SAR Surveillance Scheme has, and will continue to play an increasingly important role in the identification of, and establishing the cause of, adverse reactions. However, surveillance schemes principally address the early detection and cause of adverse reactions occurring at point of treatment. The Working Group recognises that issues of the occurrence of long-term, low incidence, or perhaps unrecognised adverse effects will have to be addressed by epidemiological studies. Although several studies have recently been reported and others are in progress, there are major constraints to identifying such adverse reactions. These include their apparent low rate of occurrence in vaccinated populations, and the need for large representative samples of both vaccinated and unvaccinated control animals to be compared in order to have sufficient statistical power to substantiate any effect that could arise due to vaccination. Identification of unvaccinated control groups is a major challenge to such work.

Recommendation 2

The Working Group identified a number of possible epidemiological approaches to address this issue, and recommends that an appropriate approach would be a prospective cohort study carried out under a national management programme. Such a study would have the advantage of providing better quality information, providing estimates of relative risk and disease incidence rates. Moreover, such a long-term surveillance scheme would provide information on a large number of treatment related problems and it could pioneer the establishment of a national database for small-animal populations that could be used for monitoring the effects of veterinary medicines other than vaccines. Funding and co-ordination would be a major challenge, but if a number of stakeholders were involved, it could become cost effective and also generate information beyond the immediate goals of the present study.

5. Notwithstanding the limitations of surveillance schemes as outlined above, the VMD SARs database is a considerable resource for identifying and establishing the causes of adverse reactions. Indeed, the Working Group concluded that the UK SAR Surveillance Scheme appears to be one of the best developed of all such surveillance schemes for veterinary medicines worldwide. Recent improvements in the design of collection and analysis of the data at the VMD will enhance the value of the SARs data and its potential for early detection of any health risks that may be associated with cat and dog vaccines.

Recommendation 3

The Working Group concludes that the VMD SAR Surveillance Scheme is a valuable initiative and recommends that the recent developments in the scheme should be extended to vaccines for other species and for other types of product. Whilst acknowledging the current resource and information technology limitations within the SAR Surveillance Scheme, the Working Group recommends that a means be found to provide an appropriate level of funding and expertise to support this important area.

Recommendation 4

The Working Group further recommends that a way should be found to allow the data held by the VMD SAR Surveillance Scheme to be analysed in partnership with the wider research community. The Working Group recognises that there are issues of confidentiality and reliability of data that need to be addressed before this can take place. Nevertheless, the Working Group considers that this represents a means whereby there can be expert, independent and ongoing scrutiny of SAR Surveillance Scheme data to identify significant associations and newly emerging trends.

6. Due to a number of constraints, the analysis of the vaccine SARs database undertaken by the Working Group was not fully comprehensive and the effect of confounding was not determined. There were also limitations on the control populations. In addition, the various analyses undertaken involved different numbers of animals according to the information available.

A number of key findings were identified in terms of levels of reporting; the demographic characteristics of the population involved in vaccine reactions; and in terms of potential risk factors. The figures showed that, over the period 1985 to 1999, the level of reporting of vaccine SARs was of the same order for both species, with 1190 vaccine SARs being reported for cats, and 1133 for dogs (Tables 9 and 10). It should be noted that there may be more than one animal involved in an individual SAR report. Although not included in the analysis, figures for the year 2000 indicate a similar level of reporting between the two species (Tables 9 and 10). However, when related to sales figures for 1995–1999 (when more accurate sales figures were available), the incidence per 10,000 doses sold per year was higher for cat vaccines (0.30 – 0.82; mean 0.61) compared to dog vaccines (0.13 – 0.26; mean 0.21), and the incidence for cat vaccines in particular has shown an increase since 1995 (Table 4). The mean incidence for cat and dog vaccines for the past five years is, however, of the same order to that published previously^{21, 26} and does appear to be relatively low, which is interesting in view of increased publicity over this period.

7. Demographic comparisons of the vaccine SARs population with the non-vaccine SARs showed a number of significant differences between the groups, although the effect of confounding was not determined. There appeared to be significantly more males than females in the vaccine SARs group compared to non-vaccine SARs for both cats and dogs (Table 5) (Appendix 1d). Analysis of breed distributions showed a higher proportion of pedigree cats in the vaccine SARs compared to the non-vaccine SARs, and proportionately fewer non-pedigree animals (Table 6) (Appendix 1e). In dogs, there was a higher proportion of the Toy, and to a lesser extent, the Utility breed groups in the vaccine SARs compared to non-vaccine SARs (Table 7)(Appendix 1e). Comparison of the age distributions in both cats and dogs showed a higher proportion of 0–6 month old animals in the vaccine SARs compared to non-vaccine SARs and proportionately fewer animals over the age of one year (Table 8) (Appendix 1f). Data on the proportion of vaccines used in a primary course as opposed to boosters supported the observation that young animals may be over-represented with respect to vaccine SARs.
8. The most common clinical signs recorded for vaccine SARs in cats were categorised as systemic, general, neurological and behavioural: in dogs the commonest clinical signs were systemic, digestive, neurological and skin disorders. The incidence per 10,000 doses of vaccine sold for specific clinical signs identified in the literature review as being of possible importance was determined for the period 1995–1999 (Tables 9 and 10). This included figures

of 0.026 and 0.018 for anaphylaxis for cats and dogs respectively, and 0.022 and 0.028 for hypersensitivity. Local injection site reactions were more common in cats than dogs (incidences of 0.099 and 0.012 respectively): this may be because, unlike dogs, adjuvanted vaccines are widely used in cats. Indeed following analysis of the frequency of the occurrence of local reactions in cats by vaccine therapeutic group, a significant association was found with the use of vaccines which contained adjuvants as opposed to live vaccines alone.

The incidence of immune-mediated haemolytic anaemia (IMHA) and immune-mediated thrombocytopenia (IMTP) in dogs was 0.001 and 0.002 per 10,000 doses respectively, which is lower than the incidence of 0.0001% (i.e. 0.01 per 10,000) estimated by Duval and Giger³⁴. However, this condition may be difficult to detect, as it may occur up to several weeks post vaccination. The incidence between 1995–1999 of corneal oedema ('blue eye') in dogs was 0.002 per 10,000 doses. Interestingly, of the 16 cases of corneal oedema reported between 1985–1999, 15 involved modified live canine adenovirus (CAV) 2 vaccines and one involved neither CAV-1 nor 2. Unlike CAV-1 vaccines, CAV-2 vaccines are not thought likely to induce this syndrome, but although it is probable that some of these dogs were exposed to wildtype CAV-1, the situation with respect to CAV-2 vaccines may also need further evaluation. The incidences of polyarthropathies in cats and dogs were 0.044 and 0.006 respectively, indicating the condition appears to be more common in cats than dogs. Lameness with lethargy, pyrexia or anorexia post vaccination also appears to be relatively common in cats. A significant association in cats was found between the occurrence of upper respiratory disease signs following vaccination and the use of live vaccines compared to inactivated aluminium adjuvanted vaccines or mixed vaccine therapeutic groups: numbers in the inactivated vaccines with other adjuvants group were small for reliable comparison. Sequence analysis has shown that in some cases such vaccine reactions may be due to feline calicivirus originating from vaccines^{60,61}.

Recommendation 5

The Working Group recommends that further investigation of the possible association between feline calicivirus vaccination and upper respiratory tract disease in cats be carried out.

9. There was evidence of a rising incidence of feline vaccine-associated sarcomas: 26 cases were reported between 1996–1999, with a further 24 cases in the year 2000 (Table 9) (Figure 4). This compares with 64 injection-site sarcomas reported to histopathology laboratories in the UK over a one year period between 1998–1999^{108, 109}. This discrepancy in reporting rates between these studies illustrates the differences between active surveillance and the more passive/reactive scheme carried out by the VMD. However it also demonstrates the value of the SAR Surveillance Scheme in that although there may be significant under-reporting, rising trends can be identified which then signal that further investigation and action may be required.

The incidence of sarcomas between 1995–1999 per 10,000 doses of all vaccines used was 0.021 (Table 9), but was higher in the FeLV vaccine group (0.045) compared to non-FeLV vaccines (0.009). Sales figures for 2000 were not available at the time of writing the report, but the incidence per 10,000 doses is likely to be much greater for this period since there was a marked rise in cases during the year 2000. These figures compare with an estimated incidence of 1 to 10 per 10,000 doses FeLV or rabies vaccines used in the USA^{86,91,92,93,94}; it should be noted that rabies vaccines are much more widely used in the USA than in the UK. The vaccine SARs data also showed that there was a significantly higher proportion of

sarcomas in the inactivated aluminium adjuvanted vaccines compared to the live and mixed vaccine therapeutic groups: numbers in the inactivated vaccines with other adjuvants group were small for reliable comparison. As reported by others^{89,90}, sarcomas tended to occur in older cats, the mean age of affected cats in the present report being 7.91 years. Breed analysis showed that there was a significantly higher proportion of non-pedigree cats in the sarcoma group than pedigree cats.

Recommendation 6

The Working Group concluded that the apparently rising incidence of feline vaccine-associated sarcomas in the UK is a cause for concern, especially in view of the estimated incidence of this condition in the USA, and the seriousness of the disease in terms of difficulty in treatment, resulting in high mortality. The Working Group recommend that the apparently higher incidence associated with the use of aluminium adjuvanted, and possibly FeLV vaccines, also noted in other studies^{86,88,94}, warrants further investigation, but the condition does not appear to be exclusively associated with such factors.

Recommendation 7

The Working Group note the existence of the well-organised Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) in the USA, and recommend that the UK and other European regulatory and professional bodies liaise with this organisation which provides information on all aspects of the condition including current research, treatment and prevention.

Recommendation 8

In view of the findings of the Working Group on vaccine-associated feline sarcomas, (see section 2.4.11.7) and the seriousness of the condition, the Working Group recommends that a generic warning should be placed on the product literature for all feline vaccines administered by injection. The proposed warning should state that current knowledge suggests that, very rarely, sarcomas may occur at the site of vaccination, and that although other vaccines may be involved, there is some evidence to suggest that this may be more associated with the use of aluminium adjuvanted vaccines. The situation with respect to the role of FeLV vaccines in general, or the use of other adjuvants, is unclear and should be kept under review. The Working Group further recommends that discussion of such risks should be part of the informed risk/benefit assessment carried out, as in recommendation 13 below, by the veterinary surgeon in consultation with the owner.

It is also suggested that professional and educational bodies in the UK should recommend that good veterinary practice should include the use of standardised vaccination procedures, as recommended by VAFSTF, in terms of sites of vaccination, in order to help identify causes of such reactions and aid treatment. VAFSTF currently recommend that any vaccine site masses that persist for greater than three months following vaccination; that are greater than 2cm in diameter; or that are increasing in size one month after vaccination, should be biopsied, and if malignant, be surgically excised. Advanced diagnostic imaging to identify the full extent of the tumour is suggested before extensive surgical excision is carried out^{99,101}.

10. In order to detect changes in incidence rates both within and between different vaccine products, the Working Group developed product-related control charts for each vaccine for

cats and dogs over the period 1985-1999 showing the incidence of vaccine SARs per 10,000 doses sold. Such charts provide a powerful way to detect changing trends in reaction rates, and when used in conjunction with product characteristics information, they offer the possibility of identifying a likely cause. Illustrations of such control charts showing the individual trends over time for each vaccine, and for all vaccines by year are shown in Figures 5a to 5f.

Recommendation 9

The Working Group notes that the development of such control charts for cat and dog vaccine SARs is likely to have a bearing on non-vaccine products and recommends that at a future date the VMD should give consideration to extending the methods and establish similar datasets for monitoring all SARs.

11. The control limit or “warning line” for incidence figures which signals that further investigation may be required has been set at one or more per 10,000 sold. It is recommended that action will be taken if:
- two out of three consecutive years have incidences of one or more per 10,000 for a particular vaccine;
 - an exceptional incidence of three or more per 10,000 occurs on any one occasion;
 - a consistent rising trend is seen over five years, irrespective of whether or not each incidence figure is above the warning line.

Amongst cat vaccines, four vaccines fulfilled one such criterion once during the 15 year period, but none reached an incidence of 3 or more per 10,000 doses sold. Only one dog vaccine fulfilled one of the criteria once over the fifteen years, but annual incidences for this product over the period in question were very low (less than one per 10,000).

In general, the incidence of vaccine SARs per 10,000 doses sold of each product was relatively low. Thus for 23 cat vaccines, the average annual incidence per 10,000 doses sold for each product per number of years authorised ranged from 0.07 – 1.67; five had zero average annual incidence. Similarly, of 27 dog vaccines, three had zero average annual incidence, and the rest ranged from 0.03 – 0.79.

12. The Working Group noted that the validity of the incidence data generated in this study depends on the integrity of the denominator (sales figures) data, which until 1999, were in some cases averaged, cumulative data, or unobtainable, and this was an area of concern for the Working Group. From 1999 onwards, six-monthly sales figures have been used and thus the validity of the control charts should increase in strength with each six-monthly period. It was noted that figures provided by companies in the form of Periodic Safety Update Reports (PSURs) are not usage figures but sales figures and that products could be held at wholesalers prior to use by veterinary surgeons/owners of animals.

Recommendation 10

As accurate sales data are fundamental to the validity of the control charts, the Working Group strongly recommends that audited sales figures should be provided by the companies.

13. Currently, cross-referencing by the VMD of SARs reported on MLA 252A forms ('yellow form' SARs), and Periodic Safety Update Reports (PSURs) provided by Marketing Authorisation Holders occurs for fatal PSUR incidents only. Therefore, only yellow form SARs data provide a comprehensive source of suspected adverse reactions and these data, together with sales data from PSURs, have been the subject of scrutiny in this report.

Recommendation 11

The Working Group recommends that in the future a system should be developed which enables cross-referencing of all yellow form SARs and PSUR incidents. It is also important that, in order to facilitate cross-referencing in the future, companies encourage reporters also to report directly to the VMD.

14. The Working Group discussed the concept of using a formal risk assessment procedure for evaluating SARs and of determining the relative risk for each product with a view to releasing such information into the public domain. However it was felt that at the present time, notwithstanding the current climate of freedom of information, it was inappropriate to do so, given the variable quality of, and many factors influencing the reporting rates and denominator data. It was also noted that in human medicine, although product information is given out, only medically substantiated SAR reports are used in the MCA report making the data released more reliable.

Recommendation 12

At the present time, the Working Group recommends that if deviations from the normal trend occur for a particular vaccine in the control charts, the company should be approached initially for a possible explanation. Subsequent analysis of the database would then be carried out if appropriate to investigate possible causality. If it was decided that the risk/benefit of the product had altered significantly, then the licensing authority, usually in conjunction with the VPC, would consider what action needed to be taken in terms of the product itself, and the need to inform the veterinary profession and the end-user.

15. With respect to current vaccination programmes and current advice on repeat vaccination, the Working Group concluded that there is some reasonable evidence that duration of protection may be significantly longer than one year for some diseases such as canine distemper, canine parvovirus 2 infection, infectious canine hepatitis, and feline panleucopenia. For other diseases such as feline herpesvirus and feline calicivirus infection, whilst protection may last longer in some animals, it is likely to be incomplete. However, such conclusions are generally based on extrapolation from the natural disease, from serological studies, and from studies on different vaccines within a product category using various challenge systems which may not reflect the field situation.
16. The Working Group recognise that ideally, in the longer term, the true duration of immunity, rather than the minimum duration should be established for each disease and for each vaccine, under normal conditions of use. It is recognised that this may be difficult to achieve, but the Working Group suggested a number of ways in which this may be facilitated:
- (i) undertaking long-term experimental challenge studies – but bearing in mind the cost, time and animal welfare considerations, and the many factors which may influence the validity of such results with respect to the field situation;

- (ii) developing standardised potency tests for each disease and their vaccines, where European Pharmacopoeia monographs are not available;
- (iii) standardising serological assays between veterinary laboratories;
- (iv) where appropriate, developing in vitro correlates of protection, and determining duration of immunity by monitoring vaccinated sentinel groups in the field;
- (v) developing centralised surveillance schemes and carrying out epidemiological studies (including modelling studies) to determine disease incidence and risk factors for a disease;
- (vi) obtaining audited vaccine sales figures and population estimates for dogs and cats such that the level of vaccine coverage in the population can be accurately determined and in the long-term increased.

Recommendation 13

The Working Group concludes that, currently, there is insufficient information to propose re-vaccination intervals on product literature other than those recommended by the manufacturer, and approved by the regulatory process. However, the Working Group recommends that for both cat and dog vaccines, statements be added to the product literature indicating that the regime for booster vaccinations is based on a minimum duration of immunity rather than a maximum, and that a risk/benefit assessment should be made for each individual animal by the veterinary surgeon in consultation with the owner so that, if required, an informed choice may be made by the owner with respect to the necessity for a particular vaccine and the frequency of its use. The assessment should include discussion on the likelihood of exposure, available data on duration of immunity, and the risks related to vaccination. The Working Group also recommends that more information should be provided for veterinary surgeons and owners by Marketing Authorisation Holders in order to facilitate such decision-making.

Recommendation 14

The Working Group recommends that manufacturers and other organisations should be encouraged to obtain data on disease incidence and duration of immunity in the field: epidemiological studies should help identify risk factors for a disease.

Once such information is available it may be possible to alter recommended revaccination intervals, initially on an individual vaccine basis, and perhaps, in the longer term, overall. It is recognised that the current system maximises protection for the individual and that in some cases this may be helpful, since there may be biological variation in response. However, in the longer term, population immunity should be increased such that exposure to infection is reduced.

Recommendation 15

The Working Group recommends that manufacturers are encouraged to market single component as well as multivalent products in order to retain flexibility in their use.

17. It is important that the regulatory authorities distinguish in their guidelines between companion animals and food-producing animals, in view of the longer life expectancy of companion animals and the likelihood of their receiving many repeated vaccinations over their lifetime.

Recommendation 16

The Working Group therefore recommends that the appropriate regulatory authorities (see 18 below) produce clear legislation and guidelines which lead to determination of as long a duration of immunity for each product as possible.

18. The Working Group recognise that changes to the authorisation requirements for cat and dog vaccines can only be applied within the context of veterinary pharmaceutical legislation. Changes that are within the scope of current UK legislation can be applied directly by the Licensing Authority, frequently as a result of advice from the Veterinary Products Committee. Changes that require amendments to legislation, monographs of the European Pharmacopoeia, or European guidelines require agreement at a European level through the Committee for Veterinary Medicinal Products, one of its working groups or, in the case of monographs, through the European Pharmacopoeia.

Recommendation 17

The Working Group, through the VPC, therefore recommends that the contents of this report be brought to the attention of the relevant European bodies and that proposals be put forward by the UK Licensing Authority to implement any recommendations for change that cannot be introduced through national legislation.

Recommendation 18

The Working Group concludes that there is an urgent need for further research into the causes of vaccine-associated feline sarcomas. This research should focus in the first instance on obtaining a better understanding of the association between such tumours and the various constituent components of vaccines and other medicinal products administered by injection to cats. If a causal relationship is established, methods should be developed to screen components for their tumour-inducing potential as part of the pre-authorisation development and registration requirements for medicinal products for cats. The need for such research should be brought to the attention of the veterinary pharmaceutical industry and their trade associations who should be encouraged to sponsor independent research in this area. The Working Group recognises that this research could lead to the need to amend the authorisation requirements for medicinal products for cats.

Recommendation 19

Finally, the Working Group wish to emphasise that vaccination plays a very valuable role in the control of infectious disease in cats and dogs. Although adverse reactions, including lack of efficacy, occasionally occur, the Working Group is convinced that the overall risk/benefit analysis favours the continued use of vaccination to control the major infectious diseases of cats and dogs. There is a need for further improvements in conventional vaccines and for further research into the role that recombinant technology can play in developing safer and more efficacious vaccines. The need to develop vaccines for cats and dogs against additional or emerging diseases should be approached on a case-by-case basis, bearing in mind the importance of keeping unnecessary vaccination to a minimum. The Working Group recommends that a thorough risk/benefit analysis should be the basis of all decisions relating to vaccination, whether in terms of authorising the vaccine itself or in the use of a particular vaccine for an individual animal.

Introduction

The Working Group was set up by the Veterinary Products Committee (VPC)* in 1999 in response to current concern in both the public domain and in the scientific community about possible health risks related to the routine vaccination of cats and dogs. The terms of reference were:

- to review post vaccination reactions, both acute and chronic, in both species,
- to provide guidance for the future identification and analysis of post vaccination reactions, and
- to consider current vaccination programmes and current advice on repeat immunisation.

The particular issues identified by the Working Group were (i) possible links between vaccination and (fibro) sarcomas in cats, (ii) a possible association between repeated vaccination and a suggested increase in the incidence of particular clinical signs in both cats and dogs, and (iii) the scientific basis of the currently recommended re-vaccination schedules, in the light of current knowledge.

Within the context of the terms of reference, the specific objectives agreed by the Working Group were:

1. To review the scientific literature and other sources of information.
2. To review available data on Suspected Adverse Reactions (SARs) to feline and canine vaccines, and, where appropriate, request further data.
3. To consider the feasibility of conducting a survey of feline and canine post vaccination reactions.
4. To consider current vaccination programmes and current advice on repeat immunisation.
5. To report findings and make recommendations to the VPC.

The Working Group was conscious, whilst preparing this report, of the extensive media coverage that has been given to the issue of the safety of human vaccines, in particular the mumps, measles and rubella (MMR) vaccine. The Working Group emphasises that the conclusions and recommendations included in this report relate only to the vaccines used in cats and dogs. The issues identified are specific to the diseases and species examined and no attempt should be made to draw analogous conclusions in relation to vaccines administered to man.

The types of vaccine authorised for use in cats and dogs in the United Kingdom as at 31/12/99 (i.e. when analysis of the data in this report began) are given in Table 1.

* The Veterinary Products Committee (VPC) is an independent scientific committee established under Section 4 of the Medicines Act to give advice on the safety, quality and efficacy of veterinary medicines to the UK licensing authority (Health and Agriculture Ministers) and to promote the collection of information relating to suspected adverse reactions for the purpose of enabling such advice to be given.

Table 1 Types of vaccine authorised for cats and dogs in the UK at 31/12/99

Cats				
	Vaccine Type			
	Live vaccine	Inactivated vaccine with aluminium adjuvant	Inactivated vaccine with other adjuvants	Mixed vaccine#
Feline panleucopenia virus	Y	Y	Y	Y
Feline calicivirus	Y	N	Y	Y
Feline herpesvirus (rhinotracheitis virus)	Y	N	Y	Y
Feline <i>Chlamydia psittaci</i>	Y	N	Y	N
Feline leukaemia virus	N	Y	Y	Y
Rabies virus	N	Y	N	N

Dogs				
	Vaccine Type			
	Live vaccine	Inactivated vaccine with aluminium adjuvant	Inactivated vaccine with other adjuvants*	Mixed vaccine#
<i>Leptospira canicola</i>	N	N	N*	Y
<i>Leptospira icterohaemorrhagiae</i>	N	N	N*	Y
Canine parvovirus	Y	N	N*	Y
Canine distemper virus	Y	N	N	Y
Canine parainfluenza virus	Y	N	N	Y
<i>Bordetella bronchiseptica</i>	Y	N	N	N
Canine adenovirus	Y	N	N	Y
Rabies virus	N	Y	N	N

Key

Y There is currently a vaccine in this category

N There is **not** currently a vaccine in this category

* Inactivated preparation(s) available without adjuvant

Live plus an inactivated vaccine

Section 1:

Review of Literature and Other Information Sources

1.1. Sources of information

Information on issues which related to the objectives of the Working Group was obtained from a variety of sources including the scientific literature; lay articles and those related to consumer concerns; various animal interest groups; academic, trade, and professional bodies both in the UK and overseas; from the Internet; from EU legislation and guidelines; and from similar relevant areas in the human field^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 and 20}. (Details are given in Appendix 1a).

1.2. Subject areas of the literature review

Information accumulated from 1.1 above was examined under four headings:

- section 1.3. Safety: adverse reactions excluding feline vaccine-associated sarcomas
- section 1.4. Safety: vaccine-associated feline sarcomas
- section 1.5. Consumer concerns
- section 1.6. Efficacy: with particular respect to duration of immunity

1.3. Safety: adverse reactions excluding feline sarcomas

1.3.1. *General data:* published literature on general adverse reactions to cat and dog vaccines is sparse. A published review of UK SAR Surveillance Scheme data between 01/01/95–01/10/98 showed that 971 (30.5%) of 3188 canine / feline reports were associated with the use of vaccines²¹. The overall annual incidence, expressed in relation to estimated annual sales of 6.8 million doses²² was 0.004%. The predominant clinical signs seen in 841 reports examined further were anorexia, malaise, pyrexia, stiffness, lethargy, depression, lameness and joint pain (38.4%); type 1 hypersensitivity (20%); and injection site reactions (11.9%). There were six reports of suspected autoimmunity, all in dogs, giving an incidence of 1.6% of a total of 369 canine reports. In 1999, 38.1% of 333 canine adverse reaction reports in the UK were vaccine-related, and 45.8% of 384 feline reports²³. Information reported recently by a commercial company stated that the incidence of vaccination site reactions, systemic reactions and true anaphylaxis in the UK for all small animals is 0.0019% of doses sold²⁴.

In Sweden, between 1991 and 1995, 47.8% of 318 adverse reaction reports in the dog were associated with the use of vaccines²⁵. The main reactions recorded were oedema of the head region, pruritis and general weakness. Fever, urticaria, vomiting, diarrhoea, ataxia and arthritis were reported in some instances and in a few cases, thrombocytopenia and other signs were observed. In cats, 59% of 61 reports related to vaccine use. Reactions included apathy, fever, vomiting, diarrhoea, ataxia, conjunctivitis, rhinitis and local site reactions. In Australia, an adverse reaction rate of 0.2 to 0.4 per 10,000 doses of small animal vaccine sold has been reported²⁶.

1.3.2. More specific reports of vaccine-associated reactions can be broadly divided into those that are immunologically related, and those that are non-immunologically based^{27, 28}.

1.3.3. *Immune-mediated vaccine-associated reactions*: this section, on immune-mediated vaccine reactions in cats and dogs, is largely based on reviews by Greene^{27, 28} and Day²⁹. Immunological vaccine reactions are generally categorised using the framework of the Gell and Coombs classification of hypersensitivity (Type I-IV). Such vaccine reactions will theoretically be a hypersensitivity response that occurs in an animal previously sensitised by (repeated) exposure to vaccine antigen or other vaccine components. In theory therefore, vaccine reactions should mainly occur on second or subsequent exposure to the vaccine, but this does not necessarily seem to be the case.

1.3.3.1. *Type I hypersensitivity*: type I (immediate) hypersensitivity involves an interaction with antigen-specific IgE (or IgG) on the surface of a mast cell or basophil, with resultant degranulation and release of vasoactive mediators. Such reactions occur within minutes, or sometimes up to 24 hours following antigenic exposure and may manifest as local or generalised (anaphylactic) effects. In the dog, signs are facial oedema, pruritus, hypotensive shock, weakness, dyspnoea and diarrhoea. Cats show facial pruritus, salivation, dyspnoea, collapse and respiratory distress from acute pulmonary oedema. Paul and Wolf³⁰ cite an estimated incidence of severe systemic anaphylaxis of approximately 1: 15,000 vaccinated animals, but also report figures of 2 cases per 3,000 vaccinates in one year. In the USA, Miniature Dachshunds are said to have a disproportionately high anaphylaxis reaction rate²⁷. Anaphylaxis may occur after the use of any vaccine, but is particularly thought to occur following the use of multivalent or adjuvanted products containing large amounts of foreign proteins such as leptospiral vaccines³¹.

1.3.3.2. *Type II hypersensitivity* involves binding of antibody, with or without complement, with subsequent damage to host cells. There are several reports suggesting an association between vaccination in dogs and the cellular damage that occurs in immune-mediated haemolytic anaemia (IMHA) and/or immune-mediated thrombocytopenia (IMTP)^{32, 33, 34, 35}. In a controlled, retrospective study, Duval and Giger³⁴ showed a significant difference in time since vaccination in 58 cases of IMHA compared to 70 randomly selected controls, with fifteen (26%) of the dogs with IMHA having been vaccinated within one month of developing the disease. The nature of the disease also appeared to be significantly different in the vaccine-associated IMHA group, with significantly lower platelet counts and a trend towards increased prevalence of intravascular haemolysis and autoagglutination. Although early reports suggested that IMHA was associated with modified live parvovirus vaccines³² in the Duval and Giger study³⁴, combination vaccines from a variety of manufacturers were used in the recently vaccinated dogs. The authors calculated that the reported prevalence of vaccine-induced IMHA is likely to be less than 0.0001% of vaccinated dogs, although because of possible under reporting, they observe that this may be an underestimate.

Although the Duval and Giger³⁴ study supports an association between IMHA and recent vaccination, the evidence overall is still equivocal. A recent study by Gould et al³⁵ found five (20%) of 25 cases of IMHA had been recently vaccinated. In contrast, a survey of insurance company data by Astrup et al³⁶ found no statistically significant relationship between IMHA and IMTP and recent vaccination, although five (12%) of 41 cases had been vaccinated within 30 days of the onset of clinical signs. The study also found spaniels to be over-represented, and terriers under-represented with respect to these diseases. Other authors have also referred to possible breed predispositions for IMHA^{35, 37}.

IMTP is a well recognised, although rare, complication of vaccination in humans, particularly after vaccination against measles, mumps and rubella vaccine³⁸. In dogs, it mainly appears to be associated with canine distemper vaccination, and interestingly, measles and canine distemper virus are both morbilliviruses^{39, 40, 41, 42}. Possible mechanisms by which vaccines could induce IMHA or IMTP have been reviewed by Duval and Giger³⁴ and Day²⁹. Vaccines have also been associated with other type II autoimmune disorders such as myaesthesia gravis and pemphigus, although the latter reports were largely anecdotal²⁹.

1.3.3.3. *Type III hypersensitivity*, associated with immune complex formation and deposition, classically occurs in the dog following either natural infection (20% cases) or vaccination (0.4% cases) with modified live canine adenovirus 1 (CAV-1)⁴³. Immune-complex of antibody and CAV-1 form in the anterior uveal tract, leading to uveitis and corneal oedema or 'blue eye'. The condition may have a greater prevalence in some breeds such as Afghans⁴⁴ and other sight hounds and Siberian huskies may share a similar predisposition⁴³. However, it is now considered to be rare in dogs because current vaccines in the UK contain CAV-2.

Localised alopecia has been reported in dogs following rabies vaccination, particularly in poodles and appears to be due to an ischaemic vasculopathy^{45, 46}. Rabies antigen has been detected in the walls of dermal blood vessels and follicular epithelium, but the role of immune complexes in the pathogenesis of this condition is not clear. In some cases, multifocal ischaemic dermatopathy affecting peripheral areas may also develop⁴⁷. In addition a cutaneous vasculopathy has been reported in German Shepherd dogs, with a majority of cases following multivalent vaccination⁴⁸.

1.3.3.4. *Type IV hypersensitivity*: an example of cell-mediated, or Type IV hypersensitivity was postvaccinal encephalitis which occurred following the original nervous tissue-derived rabies vaccines, which are no longer used in developed countries. An immune-mediated polyneuritis (polyradiculoneuritis) has been reported following rabies vaccination in the dog⁴⁹. In humans a similar peripheral polyneuropathy (Guillain-Barre syndrome) occurs, also associated with vaccination in some cases³⁸.

1.3.3.5. Vaccination has also been implicated in some cases of polyarthritis in dogs. However the immunological basis of such reactions is unclear, and it is possible that such apparent associations with vaccination may be due to coincident disease development, particularly in young animals. Occasional self-limiting cases of immune-based arthritis in dogs have been reported usually following primary vaccination⁵⁰, and recently, four young adult dogs of different breeds have been reported to develop an idiopathic polyarthritis 3–15 days after multivalent vaccination⁵¹. Immune-mediated polyarthritis and systemic disease including amyloidosis has been reported in Akita dogs following modified live vaccination³⁷. Hypertrophic osteodystrophy, in some cases associated with juvenile cellulitis, has been reported following vaccination, mainly in Weimaraners^{37, 52, 53}, and it has been suggested that canine distemper virus may be involved⁵⁴. There is also some evidence that canine distemper virus (and possibly vaccines) may be involved in canine rheumatoid-like arthritis through the formation of immune complexes⁵⁵.

Administration of modified live feline calicivirus vaccines has been associated with a transient febrile lameness syndrome, with or without respiratory disease, which typically occurs following primary vaccination in young kittens⁵⁶. Some strains of feline calicivirus are known to have a predilection for joints and there is some evidence of immune complex formation in the joints of affected cats^{57, 58, 59}. Sequencing studies have shown that in most cases such signs are due to coincidental infection with field virus: however in other instances, vaccine virus appears to be involved^{60, 61, 62}.

1.3.4. *Non immune-mediated vaccine-associated reactions*

1.3.4.1. *Local and systemic reactions:* local, injection site reactions following vaccination may sometimes occur and include pain, erythema, oedema, swelling and urticaria. These signs can appear within 30 minutes of the injection or may take 10–14 days to manifest, depending on the pathogenesis of the condition. In most cases such reactions are mild and of short duration although in some animals large granulomas may develop following vaccination and persist for up to several weeks. Such reactions tend to occur following the use of adjuvants in inactivated vaccines. Systemic reactions may also occur including pyrexia, depression, anorexia and lethargy.

1.3.4.2. *Contamination:* local and systemic inflammatory reactions have occurred from the inadvertent inclusion or growth of pyrogens in vaccines²⁷. Bacterial contamination may occur, leading to abscess formation at the site of injection, with or without systemic signs. A number of viruses have inadvertently been introduced into vaccines from contaminated cell cultures (e.g. bluetongue virus, which has caused fatal illness in pregnant bitches^{63, 64}). However modern quality control processes have minimised the risk of such events occurring.

1.3.4.3. *Residual virulence:* there have been reports of modified live vaccines causing unexpected disease signs in the dog and cat. For example problems associated with the use of a particular modified live feline panleucopenia vaccine in certain breeds of cat were reported several years ago, although subsequently resolved⁶⁵. Care must also be taken to avoid the use of live panleucopenia vaccines in kittens less than 4 weeks of age because of the possibility of cerebellar hypoplasia. A neurologic syndrome has been associated in the USA with a particular canine coronavirus vaccine which is no longer available^{66, 67}.

Although rare, encephalomyelitis has been reported in dogs after vaccination with non-Onderstepoort strains of distemper vaccine virus⁶⁸. Interactions between canine distemper virus and CAV-1 or 2 are thought to be responsible for a suppression of lymphocyte responsiveness following the use of polyvalent vaccines in dogs, although individual components do not appear to cause this problem⁶⁹.

Overseas, vaccine-induced encephalomyelitis occasionally developed following the use of modified live rabies vaccines in dogs and cats. However, such vaccines have now largely been superseded worldwide by inactivated vaccines.

Clinical signs also tend to occur following the use of intranasal vaccines in the cat or dog. In the UK, intranasal feline herpesvirus and calicivirus vaccines are not currently available, although they are widely used in some other countries, particularly the USA: signs of respiratory disease, generally mild, may sometimes be seen following their use⁷⁰. A similar situation pertains in the dog following the use of intranasal *Bordetella bronchiseptica* and canine parainfluenza vaccines.

Subcutaneously administered feline calicivirus and herpesvirus vaccines may also induce respiratory signs if the cat has oro-nasal contact with leaked vaccine at an injection site or from an aerosol created at inoculation⁷⁰. In some cases, subcutaneously administered feline calicivirus vaccine virus may also spread to the oro-pharynx where it may have the potential to induce signs of disease^{58,60,61,70,71}. There is also some recent evidence that vaccine virus may circulate within colonies of cats, and may possibly be associated with disease⁶².

1.3.5. *Lack of efficacy:* lack of efficacy, or vaccine failure, is reportable under the VMD Suspected Adverse Reaction (SAR) Surveillance Scheme. Published data from January 1995 to October 1998 showed that 58 (6.9%) of 841 reported adverse reactions to dog and cat vaccines were related to suspected lack of efficacy²¹.

Stringent testing of vaccines for efficacy is undertaken according to EU guidelines prior to authorisation, and such testing usually involves both laboratory and field trials^{9, 10, 11, 12, 13}. However, because of biological variation, no vaccine is completely effective in all cases even under ideal conditions, and once a product is marketed and more widely used in the field, suspected lack of efficacy may be reported to occur. A number of host factors may contribute to vaccine failure, including age, health and nutritional status (reviewed by Greene²⁷). The animal may have been immunosuppressed, possibly from concurrent infection at the time of vaccination; it may have been incubating the disease or already be a carrier; it may have been vaccinated while maternally-derived antibody was still present which interfered with the development of an active immune response; or the animal may have been infected with another agent which caused similar signs. In some cases, for example with feline calicivirus infection, it is probable that vaccine strains do not protect equally well against all strains of virus^{72, 73}. Human error may play a role – for example the animal may not, in fact, have been vaccinated or the wrong route or product may have been used. Incorrect storage or handling of vaccine, or the use of chemicals to sterilise syringes or the use of skin disinfectants can lead to inactivation of live virus vaccines, rendering the vaccine ineffective⁷⁴.

Some breeds of dogs may be more susceptible to problems with vaccination which may include lack of efficacy. For example, Rottweilers, Dobermann Pinschers and some other breeds were thought to respond poorly to vaccination although it appears this may be a reflection of a greater susceptibility to the disease^{27, 75, 76, 77}. Weimaraners have a breed-related immunoglobulin deficiency and possible neutrophil defect that causes immunodeficiency^{78, 79, 80, 81}. This may lead to systemic effects following the use of modified live vaccines, and possible lack of efficacy.

1.4. Safety: Feline vaccine-associated sarcomas

- 1.4.1. Sarcomas associated with sites where vaccines and other pharmaceuticals have been used in cats have been reported. A number of terms have been used to describe this condition including injection site sarcomas, vaccination-site associated sarcomas and vaccine-associated sarcomas. The last mentioned term will be used in this report
- 1.4.2. The first report proposing a possible association between vaccination and the development of fibrosarcomas in cats was in 1991 from Pennsylvania in the United States, where mandatory rabies vaccination had recently been introduced⁸². An increased prevalence of fibrosarcomas in cats predominantly at sites used for routine vaccination was subsequently noted in various parts of the USA^{83, 84, 85, 86, 87}. The increase apparently paralleled the introduction and widespread use of inactivated, adjuvanted vaccines against rabies and feline leukaemia (FeLV) in the USA in the mid 1980s⁸⁸. Subsequently Kass et al⁸⁶, in a retrospective epidemiological study, showed a highly significant association between FeLV and, to a lesser extent, rabies vaccination and the development of a fibrosarcoma at the injection site within a year following vaccination. Other retrospective studies have shown that vaccine-associated sarcomas tend to be larger and more aggressive, have a higher recurrence rate than fibrosarcomas at other sites, and that they develop in younger cats (mean 8.1 –8.6 years) compared to cats with non-vaccination site tumours (mean 10.2 – 10.5 years)^{89, 90}. No breed or sex predisposition was reported.
- 1.4.3. The prevalence of soft tissue sarcomas at sites of vaccination has been reported in the USA to range from 1 to 10 per 10,000 FeLV or rabies vaccines administered^{86, 91, 92, 93, 94}. A report from an on-going prospective study has found that 5 of 2000 cats have developed sarcomas at the site of rabies vaccination, the average time interval between last vaccination and tumour development being 26 months⁹⁵.

- 1.4.4. Vaccine-associated sarcomas are typically mesenchymal in origin, with fibrosarcomas and malignant fibrous histiocytomas (also referred to as myofibroblastic sarcomas) most frequently reported^{83, 90, 96, 97}. A characteristic inflammatory lesion surrounds the tumours, and the morphology is similar to that of tumours that arise following trauma or foreign bodies. The aetiology of vaccine-associated sarcomas is unclear, although it is thought to be the result of an inappropriate or excessive inflammatory response at the injection site which occurs in some, possibly genetically predisposed cats⁸⁸. There is recent indirect evidence that mutations in the p53 gene (a critical cell cycle regulatory gene) may play a role in the pathogenesis of these tumours^{98, 99}. Interestingly, although feline leukaemia vaccines seem to be epidemiologically more associated with sarcomas than rabies vaccines, rabies vaccines have been reported to induce a greater inflammatory response⁹³.
- 1.4.5. The vaccine component considered most likely to induce such an inflammatory response is the adjuvant. Aluminium-based adjuvants have particularly been implicated, since aluminium has been detected in local macrophages in some injection site sarcomas by electron probe X-ray micro-analysis⁸⁴ and by energy dispersive X-ray spectroscopy⁹⁷. However, aluminium may only be a marker of vaccination and other factors may be involved, since injection site sarcomas have in some cases been associated with the use of vaccines with other adjuvants, with non-adjuvanted vaccines and occasionally following the administration of other pharmaceuticals, for example, antibiotics or lufenuron^{86, 88, 99}. No specific vaccines have been implicated in the development of sarcomas, although there is conflicting evidence as to whether the simultaneous administration of vaccines at the same site may lead to an increase in vaccine-associated sarcoma development^{86, 89, 95}. Although feline sarcoma viruses (which are replication-defective, acute transforming FeLV with one of several cellular oncogenes incorporated) are known to be involved in multicentric fibrosarcomas in cats, no epidemiological association with FeLV or feline immunodeficiency virus infection has been reported with vaccine-associated sarcomas^{85, 86, 89}. In addition, FeLV could not be detected by PCR or immunohistochemical staining in vaccine-associated feline sarcomas¹⁰⁰.
- 1.4.6. Concern in the USA, over the issue of sarcoma formation in cats at commonly used vaccination sites, led to the formation of the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF). The group was set up in 1996 and includes representatives from the American Animal Hospital Association, the American Veterinary Medical Association, the Veterinary Cancer Society, The American Association of Feline Practitioners; the Animal Health Institute and the Cornell Feline Health Center. VAFSTF have made a number of recommendations with regard to treatment and reduction/prevention of the condition which are presented in a report of a Vaccine-Associated Feline Sarcoma Symposium on their web site (www.avma.org/vafst 26/07/00), and by Morrison, Starr et al⁹⁹, and are briefly summarised in 1.4.7. and 1.4.8. below.
- 1.4.7. Treatment of post-vaccinal sarcomas is difficult (reviewed by Couto and Macy⁹⁴ and Morrison, Starr et al⁹⁹). A number of vaccines, particularly adjuvanted vaccines, induce granulomas at the site of injection which may persist for up to two to three months.

VAFSTF currently recommend that any vaccine site masses:

- that persist for greater than 3 months following vaccination;
- that are greater than 2cm in diameter or;
- that are increasing in size 1 month after vaccination;

should be biopsied, and if malignant, be surgically excised. Advanced diagnostic imaging to identify the full extent of the tumour is suggested before extensive surgical excision is carried out^{99, 101}. Radiotherapy and possibly chemotherapy may also have some beneficial effect⁹⁹. However, local recurrence is common, and even wide surgical excision results in a 30–70% failure rate^{94, 102, 103}. Removal of sarcomas by hind limb amputation has a higher rate of success than surgery of a sarcoma in the interscapular space⁹⁴. Although the majority of vaccine-associated sarcomas are only locally invasive, 10–25% metastasise to the lungs or other sites.

- 1.4.8. A number of recommendations have been made to help prevent or decrease the prevalence of vaccine-associated sarcomas, some of which are still being debated. These include changing vaccination site location, decreasing the use of polyvalent vaccines, using non-adjuvanted vaccines, avoiding the use of aluminium-based adjuvants, and perhaps most importantly, avoiding over vaccination⁹⁴.

VAFSTF recommends a standardised approach to vaccination in order to help identify causes of local reactions, and to aid in the treatment of vaccine-associated sarcomas. This is as follows:

- (1) vaccines containing rabies antigen are given as distally as possible in the right rear limb;
- (2) vaccines containing feline leukaemia virus antigen (unless containing rabies antigen as well) are given as distally as possible in the left rear limb;
- (3) vaccines containing any other antigens except rabies or feline leukaemia virus are given on the right shoulder, being careful to avoid the midline or interscapular space.

Subcutaneous vaccination is recommended rather than intramuscular, because of earlier detection of growths⁹⁴.

Other recommendations from the VAFSTF and other bodies concerned with vaccination in the USA (for example, Report from the Advisory Panel on Feline Vaccines from the American Association of Feline Practitioners and the Academy of Feline Medicine^{2, 3, 104}) include:

- the concepts of risk/benefit analysis and the use of ‘core’ and ‘non-core’ vaccines;
- the use of alternative (e.g. intranasal) vaccination routes if available;
- the use of single rather than multidose vials (note: multidose vials are not used in the UK) because of possible uneven concentration of adjuvant;
- ensuring medical records are kept of the date, site, type and serial number, and manufacturer of the vaccine;
- that any adverse reactions are reported to the appropriate authorities.

The question of whether multiple or single antigen vaccines should be used is still the subject of discussion^{2, 30}.

- 1.4.9. It is clear that awareness of feline vaccine-associated sarcomas is high in the USA, and that much has been done to address the issue. In Europe, the problem has received less attention, although a study group has been formed in France^{105, 106} (the Groupe d’Etude Français des Fibrosarcomas (GREFFI)). In the UK, the first reported cases to the Suspected Adverse Reaction (SAR) Surveillance Scheme at the VMD were received in 1996: interestingly, inactivated adjuvanted vaccines for feline leukaemia were first authorised in the UK in 1991. It is also noteworthy that until the recent introduction of the ‘Pet Travel Scheme’ (PETS)¹⁰⁷ in

February 2000, which was extended in January 2001, the only rabies vaccination allowed in the UK for cats and dogs was for animals in quarantine or going abroad.

- 1.4.10. A recent study conducted by the British Small Animal Veterinary Association (BSAVA)^{108, 109} on 64 injection site sarcomas and 19 non-injection site sarcomas reported from April 1998 – March 1999 to histopathology laboratories in the UK found that the injection site sarcomas tended to occur in younger cats compared to non-injection site sarcomas, and there was an apparent bias towards females. Breed distribution was said to reflect the general population, and the product used was thought to reflect the manufacturers' market share. A higher proportion of the injection site sarcoma group had received an FeLV vaccine component than the non-injection site group, although it was suggested that differences in the age distribution of the two groups may have accounted for this. Numbers were small in this study, however, and only limited statistical analysis was possible. Information reported recently from a commercial source indicated an incidence of feline injection-site sarcomas in the UK of one per 265,000 vaccine doses (i.e. 0.038 per 10,000 doses)²⁴. On-going surveillance is required to determine if the incidence is rising in the UK: the BSAVA are continuing with this study, in parallel with a large epidemiological survey of disease prevalence¹¹⁰.

1.5 Consumer-related literature

The issue of vaccination in cats and dogs has been raised in recent years, nationally and internationally, by a number of specialist journals for cat and dog owners and breeders, on Internet advice lines and also in non-specialist publications such as national newspapers^{111, 112, 113, 114, 115, 116, 117, 118, 119}.

In relation to the dog, a major part of the non-technical literature in the UK is related to Canine Health Concern (CHC)^{120, 121}. This organisation has stimulated considerable interest and comment from both scientists and lay people, some of whom support the views of CHC, and some of whom do not. CHC have raised the issue of possible over vaccination of dogs, and that there may be significant under reporting of vaccine reactions as assessed by surveillance schemes. CHC therefore carried out a retrospective survey involving 523 dog owners and involving 3,800 dogs, to test whether or not there was a temporal link between vaccination and the start of an illness¹²⁰. Although some interesting observations were made, the study was difficult to interpret due to a number of shortcomings in the statistical analysis and study design.

Concern over feline vaccination in the UK has mainly focussed on vaccine-associated sarcomas. The condition has been highlighted for example by the Feline Advisory Bureau, which has published informed articles on the benefits and risks of vaccination, and on vaccine-associated sarcomas^{122, 123, 124}.

1.6 Efficacy: with particular respect to duration of immunity

- 1.6.1. Definition: duration of immunity and duration of protection. These terms are often used interchangeably. However, duration of immunity generally refers to the duration of a detectable humoral or cell-mediated immune response, whereas duration of protection is the length of time following vaccination that an animal is protected against challenge. In this review, duration of protection will be used where specific reference is being made to protection following challenge, otherwise the more general term duration of immunity will be used.
- 1.6.2. In the UK, all claims on the efficacy of vaccines, including the duration of protection, have to be fully supported by data from specific laboratory trials and usually supported by field

studies⁹. The European Pharmacopoeia also states that any claim regarding duration of protection shall be supported by data from trials. Guidance is given in the 'Requirements for immunological veterinary medicinal products'¹⁰ and the European Pharmacopoeia 1997¹¹. More specific guidance is given in the CVMP guideline III/5736/94 'Specific requirements for the production and control of live and inactivated viral and bacterial vaccines for cats and dogs'¹². Essentially, specific claims for the efficacy and duration of immunity of a vaccine must be demonstrated for each component by means of controlled laboratory challenge trials, and in general, supported by field trials, in both cases including untreated control animals. However, where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.

- 1.6.3. More recently, a Note for Guidance¹³ has been issued on the 'Duration of protection achieved by veterinary vaccines' finalised in October 2000 and which comes in to effect on 1st May 2001. This recognises that in order to avoid frequent vaccinations, it is recommended that vaccines are studied in a manner which demonstrates the actual duration of protection provided and that products are developed that provide as long a duration of protection as possible. The Note for Guidance¹³ does not specify the duration of protection that should be expected from a vaccine against a particular disease but states that, in all cases, the duration of protection demonstrated should be justified in relation to the length of time for which an animal is likely to be at risk. Because of the expense, time and animal welfare considerations involved in vaccination-challenge trials, the paper also considers (1) that a more limited number of animals may be used for challenge studies and (2) that protection may be measured using suitable indicators other than challenge (such as antibodies or other markers of protection) as long as there is a qualitative and quantitative correlation shown between the indicator and protection in the target species, and the indicator plays a substantial role in protection.

It is also noted that a number of factors influence the duration of protection such as the causal agent(s) of the disease, the epizootiology of the infection, the immunogenicity of the active substances of the vaccines and the nature of the immune responses of the target animals. The duration of protection may also be different under laboratory conditions compared to field conditions of use where other factors, such as exposure to the infectious agent and the health, condition and immunological status of the animals may vary.

- 1.6.4. As in other species, for cat and dog vaccines, laboratory challenge studies carried out to support the claims for duration of protection are typically of short duration, and generally use relatively few animals, due to the cost and welfare implications of keeping such animals for long periods in isolation. Thus they are designed to demonstrate a minimal, rather than a maximal duration of protection and as a consequence, annual revaccination is recommended for the majority of cat and dog vaccines currently authorised in the UK¹²⁵. In addition, for multivalent products the claim for duration of protection has to reflect the claim for the component with the shortest duration shown.
- 1.6.5. Although claims for duration of protection should be supported by field data, in practice, for cat and dog vaccines, these may be difficult to carry out. Owner compliance is required, and the design of appropriate studies may be compromised by the necessity of using convenience-based sampling strategies. In many diseases, there is uncertainty as to exposure, and where disease incidence is low, there may be difficulty in obtaining a sufficiently large sample size.
- 1.6.6. In some other countries, such as the USA, manufacturers are not required to demonstrate duration of protection as part of the authorisation requirements of individual products,

except in the case of rabies vaccines, and more recently, for vaccines containing 'novel' antigens for which no other products are available^{27, 99, 126}. Recommendations for one-year revaccination intervals, which were originally established on the basis of relatively limited scientific evidence, were applied by the United States Department of Agriculture (USDA) to label directions as a standard in order to give vaccines users some guidelines¹²⁷, although a duration of immunity study may be done to show efficacy beyond one year⁹⁹.

In the light of increasing knowledge, an increasing number of products, and concerns about possible adverse reactions following vaccination^{128, 129}, other guidelines for USA practitioners have been, or are being developed by professional and academic bodies such as The Advisory Panel on Feline Vaccines from the American Association of Feline Practitioners (AAFP) and the Academy of Feline Medicine^{2, 3, 104}; Colorado State University's Small Animal Vaccination Protocol¹³⁰; and the AVMA's Council on Biologic and Therapeutic Agents^{4, 127}. The use of both canine and feline vaccines are under review in the USA by the AVMA Council for Biologics and Therapeutics. The council anticipates collecting information during 2001. The AVMA plans to produce new canine and feline vaccination protocols in July 2001. The disadvantage of a system where guidelines are produced from information available for each disease, rather than from specific data generated for each particular product, is that individual vaccines may vary in their content and formulation, and therefore efficacy and duration of immunity may also vary between products.

- 1.6.7. The USA recommendations for a change in vaccination protocols for cats and dogs have been based largely on the concept of 'core' versus 'non-core' vaccines. Such guidelines, which affect both the number of vaccine components administered, and the frequency, obviously have implications for the use of multivalent products. However, in the USA, vaccines against many more diseases are available, and rabies vaccination is also mandatory.

For cats, core vaccines in the USA are chosen on the basis of the following criteria: the consequences of infection are particularly severe (feline panleucopenia); infection poses a substantial zoonotic potential (rabies); prevalence of the disease is high and the disease is easily transmitted so that it poses a substantial risk to the population at large (feline herpesvirus and calicivirus infections); and vaccines selected are safe and efficacious. It has been proposed that all animals should undergo primary vaccination with the core vaccines as indicated by the manufacturer, followed by revaccination one year later (which is important because maternally derived antibody in young animals may interfere with the primary vaccination course). Revaccination is then recommended every three years: an exception to this may be rabies where, in some states, vaccines are legally required to be given more frequently – in this case, the use of non-adjuvanted canarypox-rabies recombinant vaccine may also be considered¹⁰⁴. Non-core vaccines should only be used following an individual risk/benefit assessment. Such vaccines include those against feline leukaemia and *Chlamydia psittaci*, and also others such as those for feline infectious peritonitis, *Microsporium canis*, *Giardia lamblia*, and *Bordetella bronchiseptica* which are not currently available for cats in the UK.

For dogs, recommended core vaccines in the USA include canine distemper, canine parvovirus, canine adenovirus, and rabies vaccines. Again, after a primary course and the first annual booster, three-yearly vaccination is recommended except where rabies vaccines are legally required to be given more frequently. Non-core vaccines are considered to be those against canine parainfluenza, *Bordetella bronchiseptica*, and *Leptospira spp.*, and also others such as vaccines for *Borrelia burgdorferi* and canine coronavirus which are not available in the UK²⁷.

- 1.6.8. Although many authorities in the USA propound less frequent and in some cases, more targeted vaccination, others, both in the USA and elsewhere, consider there is insufficient information and that other factors such as legal issues, client perceptions and preventative health-care implications should be considered¹³¹. After reviewing the evidence, an expert panel in Canada representing the Canadian Veterinary Medical Association (CVMA), produced a statement in 1998 concluding that current scientific data was insufficient to justify a change in vaccine protocols¹³². However, although the Canadian Animal Health Institute (CAHI) and the Veterinary Biologics and Biotechnology Section of the Canadian Food Inspection Agency (CFIA) endorsed the CVMA statement on vaccines it added a short statement indicating that the protocol should be tailored by the veterinarian to reflect the needs of the individual animal¹³³.
- 1.6.9. It should be emphasised that whilst the Working Group took full account of the considerable body of research and experience relating to vaccination of cats and dogs in other countries such as the USA, care must be taken in extrapolating directly to the UK situation. Although the core diseases for cats and dogs are essentially similar, there are some additional diseases in the USA against which vaccines are available. For core diseases there are also a greater number of manufacturers producing vaccines in the USA, although in general a similar range of vaccine types is represented. However, although difficult to quantify, there is an impression that more adjuvanted vaccines may be used in the USA for both species. In part this is due to the greater use of rabies vaccines which are mandatory in many states of the USA and all inactivated vaccines against rabies contain adjuvants. Finally, accessibility to cat and dog vaccines and their consequent frequency of use may be different in the USA, where some may be available to the general public without prescription. In contrast in the UK they are only available as Prescription Only Medicines (POMs) through a veterinary surgeon.
- 1.6.10. In human medicine, duration of immunity is assessed in a number of ways^{134, 135}. In some diseases (e.g. rabies, tetanus, hepatitis B), where protective antibody levels are known, duration of immunity is assessed by monitoring the decline in antibody levels over time in vaccinated sentinel groups. Serological monitoring and interpretation in human medicine are greatly facilitated by the fact that assays for *in vitro* correlates of protection, such as neutralising antibody, are standardised using accepted methodology usually in the form of commercially available kits: human vaccines are also generally of standard potency.

In other human diseases, (e.g. measles, pertussis, rubella), duration of immunity is assessed by epidemiological surveillance of disease incidence, or serological surveillance of vaccinated populations, which in some instances (e.g. measles) has been used in conjunction with mathematical modelling^{136, 137, 138}. Vaccine failures may be detected by breakthrough outbreaks of disease, at which point, vaccination campaigns are re-introduced. Monitoring disease incidence in human medicine is greatly facilitated by centralised national disease surveillance schemes. In the UK there is the Communicable Disease Surveillance Centre (CDSC) of the Public Health Laboratory Service (PHLS), and for specific projects, the British Paediatric Surveillance Unit (BPSU). In other European countries, similar organisations exist; in the USA there are the Centers for Disease Control and Prevention¹³⁹ and there are also world surveillance data collated by the World Health Organisation (WHO)¹⁴⁰.

In general, the recommended duration of immunity for many human vaccines is considerably longer than that for veterinary products – indeed for some diseases, such as tetanus, there are also limitations on the recommended frequency of revaccination¹³⁶. However, for many important human infections a greater proportion of the population is vaccinated and when coverage is high (e.g. more than 90% for diseases such as measles and pertussis) disease incidence becomes very low. In contrast, proportionately fewer cats and dogs are vaccinated

(see section 2.4.1 for figures) and population immunity therefore tends to be much lower with many diseases still prevalent. This has two effects: first, in some situations it allows natural boosting of immunity to occur, but the corollary is that both vaccinated and unvaccinated animals may have to withstand higher levels of challenge in the environment.

- 1.6.11. In some diseases in cats and dogs (such as feline panleucopenia, canine distemper virus, canine parvovirus infection, canine adenovirus infection and rabies), *in vitro* assessments of, for example, neutralising antibody appear to correlate well with protection, although in most diseases it is likely that other immune mechanisms are also involved. In some cases, such as feline herpesvirus infection, cell-mediated immune responses are probably more important than the humoral antibody response¹⁴¹. In addition, animals may still be protected even in the absence of a detectable immune response because of immunological memory. However, before neutralising or other antibody responses can be reliably used in some diseases as a marker for revaccination, assay standardisation between veterinary laboratories is required.
- 1.6.12. The following section summarises available information on the duration of immunity for the major cat and dog diseases following natural infections or vaccination. Serological responses are also reviewed where appropriate, although the limitations in interpretation of serological data (section 1.6.5 and 1.6.11 above) should be noted. Other variables which may affect duration of immunity include biological variation in responses in the host, differences between vaccines (e.g. live versus inactivated, adjuvant, strain, dose, route), environmental factors, and differences in challenge/exposure conditions. The importance of the first annual vaccine boosters should be noted for all vaccines, since failure of the primary course may occur due to residual maternally derived immunity.

1.6.13.1. *Canine distemper*. Natural immunity to distemper in dogs is probably long-lasting. Recovered dogs surviving virulent canine distemper virus (CDV) infection have been reported to resist challenge exposure after 7 years in isolation¹⁴². Long-term protection against challenge following modified live vaccination has been shown to last for at least 12–30 months^{143, 144}. It is generally accepted that there is a correlation between virus neutralising (VN) antibodies and protection: levels of $\geq 1/16$ or $1/20$ are considered to be satisfactory^{145, 146, 147, 148}, although in some laboratories higher cut-offs are used^{37, 149}. Serological studies on dogs kept in isolation indicate that protection may persist for more than 6 years¹⁵⁰, and, in field studies on vaccinated dogs in countries such as Iceland and Sweden that are considered distemper free, 73% and 83% of dogs vaccinated more than four years previously had titres of $\geq 1/16$ ^{148, 151}. In the USA, recent field studies have shown that approximately 79 – 98% of dogs with variable or unknown vaccination histories had protective antibody titres to CDV, depending on the cut-off point selected and the antibody test used^{149, 152}. However the level of field challenge such dogs had experienced is not known.

1.6.13.2. *Canine parvovirus 2 (CPV-2) infection*. The duration of immunity to natural canine parvovirus 2 infection has been shown to persist for up to 20 months¹⁵³, although it is likely to be longer. Challenge trials following vaccination with a modified live and inactivated vaccines have also demonstrated protection for up to two years and 15 months respectively^{143, 154, 155, 156}. Immunity to CPV-2 infection is thought to be mainly antibody mediated and a good correlation has been shown between the presence of haemagglutination inhibition (HI) antibody titres of $\geq 1/80$ and protection^{37, 150, 153, 156, 157}. Such titres are largely based on maternally derived antibody levels in puppies however, and it is likely that, after active immunisation, lower titres may still be protective¹⁵⁸. Although some variation in efficacy between modified live CPV-2 vaccines has been reported¹⁵⁹, most vaccines now induce high levels of antibody which may persist for as long as six years¹⁵⁰. In contrast, in a field study using an inactivated vaccine, less than 40% of dogs had protective antibody titres

by two years post-vaccination¹⁶⁰. In two recent field studies in the USA, 73-95% of dogs with variable or unknown vaccination status had a protective antibody titre to CPV^{149, 152}. However the level of field challenge such dogs had experienced is not known.

1.6.13.3. *Canine adenovirus (CAV) infection*. There are two serotypes of canine adenovirus: CAV-1 predominantly induces infectious canine hepatitis and CAV-2 induces respiratory disease but cross-protection is seen between the two. Because of complications associated with the use of modified live CAV-1 vaccines (see section 1.3.3.3), all vaccines available in the UK now contain modified live CAV-2. Immunity to natural CAV-1 infection is thought to be life-long: recovered dogs kept in isolation for 5 years have been shown to be resistant to virulent CAV -1 challenge¹⁵⁸.

The duration of immunity to CAV-2 infection is unclear. VN antibody titres of $\geq 1/30$ are thought to equate with protection¹⁶¹. Long-term protection of at least a year following modified live vaccination has been demonstrated by experimental challenge and by persistence of antibody titres^{143, 162}. Olson et al¹⁶⁰ has shown in field studies that approximately 80% of dogs had titres of $\geq 1/16$ up to one year after modified live vaccination, declining to 70% by 30 months.

1.6.13.4. *Other canine diseases*. Vaccination is also available in the UK against two causes of infectious tracheobronchitis (kennel cough), canine parainfluenza and *Bordetella bronchiseptica*. In both of these diseases, both natural and vaccine-induced immunity is considered to be relatively short-lived: local immunity is important in protection^{163, 164}. Vaccines against leptospirosis, which contain inactivated bacterins of *L. canicola* and *L. icterohaemorrhagiae*, also induce only short-lived protection²⁷.

1.6.13.5. *Feline panleucopenia*. Natural immunity to feline panleucopenia is considered to be long-lived. There is good correlation between VN antibody and protection, with levels of between 1/8 and 1/30 being considered to be protective^{165, 166, 167}. High levels of antibody have been shown to develop and persist for at least four years following the use of a modified live vaccine¹⁶⁸ and for six years following the use of an inactivated vaccine^{167, 169}. Two year duration of protection following use of an inactivated feline panleucopenia vaccine and experimental challenge has been shown¹⁷⁰. In a recent study, protection against challenge was seen in cats vaccinated 7.5 years previously, although only minimal signs were seen in the unvaccinated controls, making comparison difficult¹⁶⁹.

1.6.13.6. *Feline herpesvirus (FHV) infection*. Although natural immunity develops following feline herpesvirus infection, it is not necessarily complete in all animals and may only be of relatively short duration¹⁷¹. After primary infection, cats become latent carriers of virus which may periodically reactivate and induce recrudescence disease¹⁷². Only low levels of VN antibody develop following initial infection, and there is little correlation with protection¹⁷³. It is likely that, as with other alphaherpesviruses, cell-mediated and local immunity play a significant role¹⁴¹. Similarly, although reasonable immunity develops following the use of modified live or inactivated vaccines, this may be incomplete in some animals, even if challenge takes place within three months of initial vaccination^{174, 175, 176}. Nevertheless, similar levels of protection have been reported after a year¹⁷⁷. A recent study has shown that the relative efficacy of an inactivated vaccine decreased from 83% shortly after the primary vaccination to 52% after 7.5 years¹⁶⁹.

1.6.13.7. *Feline calicivirus (FCV) infection*. As with FHV, although immunity develops following natural feline calicivirus infection it may not be complete in all animals, and again, tends not to be of very long duration. In addition, there are a number of strains of FCV,

which show varying degrees of cross-protection^{178, 179}. Similarly, although reasonable immunity develops following the use of modified live or inactivated vaccines, in some cases this is incomplete, even shortly after vaccination, though this may depend on the strains and challenge system used^{71, 166, 174, 180}. However, protection has also been stated to occur 10 – 12 months after vaccination¹⁸¹. VN antibody levels tend to be higher than with FHV, and in general there is a better correlation with protection: levels of 1/16 are said to be protective¹⁷⁹. However, some protection has also been seen with lower or undetectable levels of VN antibody¹⁸², suggesting cell mediated and possibly local immunity may also play a role^{71, 183}. In recent studies, moderate levels of VN antibody have been shown to persist in a group of vaccinated cats for at least four years, although after 7.5 years titres had declined to low or non-detectable levels^{167, 169}. Protection against challenge decreased from 85% three weeks after vaccination to 63% after 7.5 years.

1.6.13.8. *Other feline diseases.* Vaccines against feline leukaemia virus infection vary in the degree to which they induce protection against persistent viraemia (reviewed by Sparkes¹⁸⁴), although current EU authorisation requirements require at least 80% of vaccinated animals to be protected in experimental challenge studies where at least 80% of the controls develop persistent infection¹⁸⁵. Protection against natural challenge following vaccination is more difficult to demonstrate, but there is limited evidence that some protection may last at least two years, but with a one year booster¹⁸⁶, and in another study (without a booster) up to three years¹⁸⁷. Long term challenge studies are difficult to carry out with feline leukaemia due in part to an age-related immunity to infection.

As with the natural disease, immunity following the use of feline *Chlamydia psittaci* (recently renamed *Chlamydophila felis*) vaccines is incomplete, but some protection has been shown for up to a year^{188, 189}. Other vaccines, such as feline infectious peritonitis and *Bordetella bronchiseptica* vaccines, are not currently available in the UK.

1.6.13.9. *Rabies.* The duration of immunity in cats and dogs following natural or experimentally-induced rabies is unknown since few animals survive challenge. In both species, information on duration of immunity following vaccination is based on experimental challenge studies and serological data. Serum neutralising titres of 0.5 IU/ml following vaccination have been designated as protective by PETS and, in general, there is good correlation between circulating antibody levels and protection. However a small proportion of dogs with antibody titres are not protected in experimental challenge studies, and some seronegative but vaccinated animals may survive challenge^{190, 191}. Indeed EU current authorisation requirements stipulate that a minimum of 80% of vaccinated animals should be protected against a challenge in which at least 80% of the controls die.

Because of safety issues (see section 1.3.4.3) inactivated adjuvanted rabies vaccines are now used in all developed countries for cats and dogs and more recently a canarypox recombinant rabies vaccine has been marketed. In dogs, protection has been demonstrated with such vaccines for at least 22–36 months post vaccination in experimental challenge studies^{143, 190, 192, 193, 194}, and in serological studies, antibody titres have been shown to persist in most cases for at least 12–39 months^{143, 190, 193, 195, 196, 197, 198, 199}. In cats, protection has been demonstrated from at least 7 and 44 months post vaccination in experimental challenge studies^{194, 200}, and for at least 44 months in serological studies¹⁹⁴. Field studies have shown persistence of protective antibody levels in a majority of dogs for one to three years following the use of inactivated adjuvanted vaccines^{195, 196, 197, 198}.

Section 2:

The Suspected Adverse Reaction (SAR) Surveillance Scheme (SARSS) and Review of Suspected Adverse Reactions data

2.1. Background and definitions

- 2.1.1. The Veterinary Medicines Directorate (VMD), which acts on behalf of the UK licensing authority in relation to veterinary medicines, operates the Suspected Adverse Reaction (SAR) Surveillance Scheme (SARSS), which is a national reporting scheme for monitoring both animal and human Suspected Adverse Reactions (SARs) to veterinary medicines. The holders of Marketing Authorisations have a legal obligation to record and submit adverse event reports to the VMD; all other reporting is voluntary.
- 2.1.2. Similar schemes exist in other countries, but in general, these are not as developed as in the UK. In the EU, Member States are required to have a similar scheme under Directive 81/851⁵ but the development in individual Member States varies considerably. The European Medicines Evaluation Agency (EMA) also operates a centralised, EU wide system including a Rapid Alert System. However, the EMA scheme is currently not as advanced as that in the UK, or some other Member States. The VMD forwards reports to the EMA every two weeks on human and animal SARs which have been coded as serious reactions (A and B category), and also all reports received on products holding a community-wide Marketing Authorisation (termed centrally authorised). The International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is currently seeking to harmonise the pharmacovigilance systems in the European Union, Japan and the USA and has produced a draft guideline⁷. The draft guidelines are currently at stage four and are therefore undergoing a consultation process. Ultimately it is intended that they will be recommended for adoption to the regulatory bodies of the European Union, Japan, and the USA, and possibly by other countries which have observer status in the VICH.

In the USA there are three regulatory bodies with responsibilities for veterinary medicines; the Food and Drug Administration Center for Veterinary Medicines (FDA CVM); The United States Department of Agriculture Center for Veterinary Biologics (USDA CVB); and the Environmental Protection Agency (EPA). They are responsible for pharmaceutical, biological and pesticide products respectively. It is mandatory for companies to report SARs to the FDA CVM and the EPA, but not to the USDA CVB, which has no formal pharmacovigilance programme or database. The US Pharmacopoeia (USP) is a non-governmental, non-profit making organisation that runs a voluntary adverse reaction reporting scheme for veterinarians called the Veterinary Practitioners Reporting (VPR) Program. It has no regulatory powers. The reports received are shared with the manufacturer, the appropriate regulatory authority and the American Veterinary Medical Association (AVMA). Recent reports suggest the USDA may develop a central monitoring scheme for vaccinovigilance to provide analysis and to distribute information from this analysis to the user of the product^{127, 201}.

2.1.3. There are a number of possible definitions for a suspected adverse reaction. For the purpose of this report, the definition in Article 42b of EU Directive 81/851⁵ is adopted, which is also used in the CVMP Note for Guidance (NfG): Pharmacovigilance of Veterinary Medicinal Products⁶; Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs) VICH GL24 CVMP/547/00⁷ and the VMD guidance note Animal Medicines European Licensing Information and Advice (AMELIA) 12⁸. The definition agreed by the Working Group includes the concepts of lack of efficacy and causal relationship and is as follows:

“A reaction (to a veterinary product) which is harmful and unintended, and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or modification of physiological function. This includes significant failure of expected efficacy, and indicates that a causal relationship between product and undesirable event is at least a reasonable possibility.”

2.1.4. Lack of efficacy is defined as “lack of expected efficacy of a veterinary medicinal product according to the indications claimed” (CVMP Note for Guidance (NfG): Pharmacovigilance of Veterinary Medicinal Products⁶; Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs) VICH GL24 CVMP/547/00⁷ and the VMD guidance note AMELIA 12⁸). Lack of efficacy is included in the SAR definition (see 2.1.3.).

2.1.5. Suspected serious adverse reactions are defined in Article 42b of Directive 81/851⁵, CVMP Note for Guidance (NfG): Pharmacovigilance of Veterinary Medicinal Products (CVMP/183/96)⁶; Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs) VICH GL24 CVMP/547/00⁷ and VMD guidance note AMELIA 12⁸.

“A suspected serious adverse reaction is one defined in paragraph 7 (i.e. as for an adverse reaction) which is also fatal, life threatening, lesion producing, disabling, incapacitating or which results in permanent or prolonged symptoms (signs) in animals treated (Article 42b of Directive 81/851)”.

From the above definition it is evident that judgement is needed in individual cases to decide whether or not the adverse event is a serious reaction and guidance on this is given in VMD Guidance note AMELIA 12⁸. The Working Group suggests that classification of serious/non-serious SARs needs continual monitoring and the guidelines should be amended as appropriate. For example, since 1/1/00 companies have been requested to report injection site sarcomas in cats as serious reactions.

2.2 Collection of data

2.2.1. SARs data are obtained by the VMD from two sources:

- (i) *Yellow forms (MLA 252A)*²⁰² (Appendix 1b) These forms were updated in January 1999. They include voluntary reports from veterinary surgeons, the general public and other interested parties. In addition, yellow forms or their equivalent are received from pharmaceutical companies according to their legal obligations (see (ii) below). A breakdown of reporting sources for vaccine and non-vaccine SARs for cats and dogs, over the period 1/1/95 to 31/12/99, showing that veterinary surgeons and companies are the main reporters, is given in Figures 1a and 1b.

Figure 1a. Number and percentage of reporting sources of vaccine SARs compared to non-vaccine SARs for cats between 1995–1999

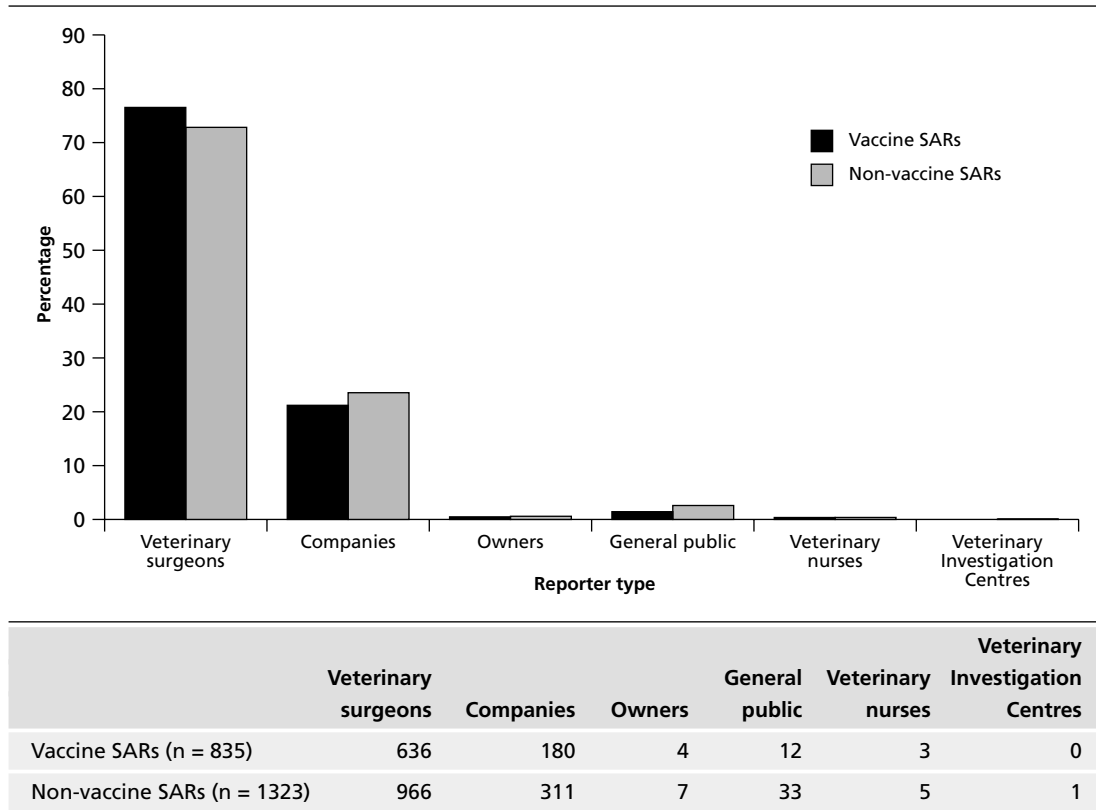
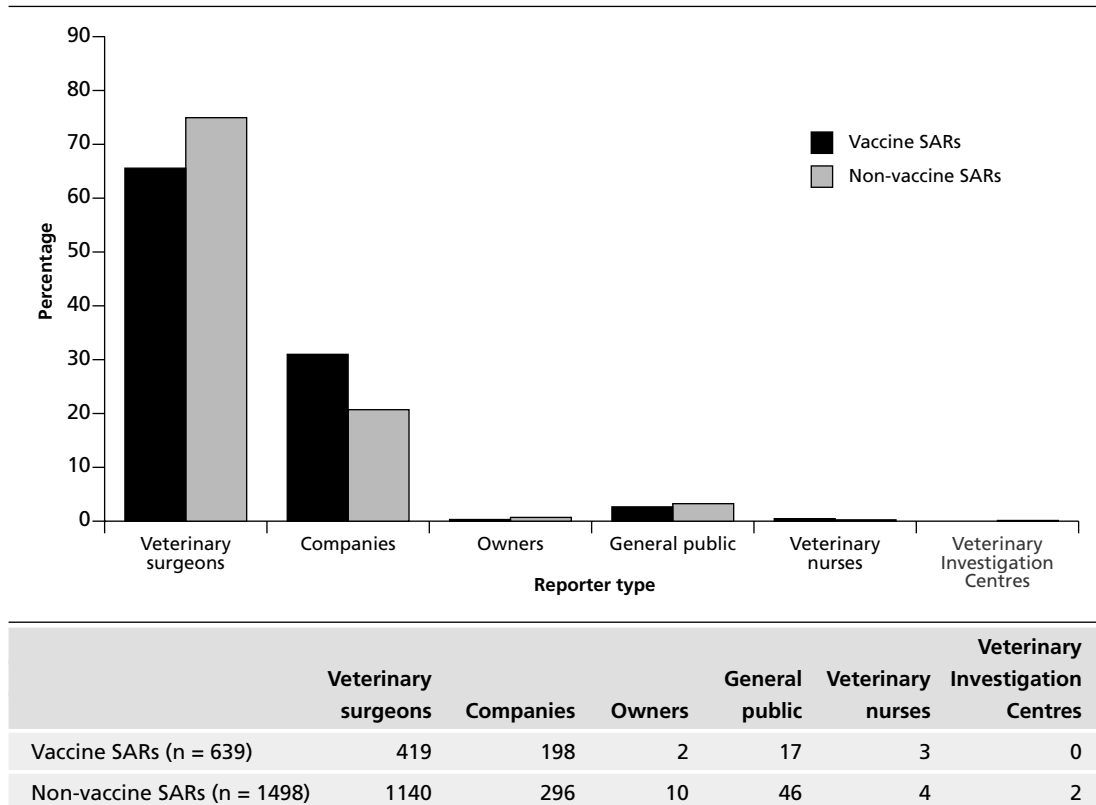


Figure 1b. Number and percentage of reporting sources of vaccine SARs compared to non-vaccine SARs for dogs between 1995–1999



Each report form is checked to ascertain whether or not it has already been received from another source, before being added to the SAR Surveillance Scheme database. The report is then assessed, and a summary of the reaction completed using veterinary clinical terms from the Veterinary Dictionary for Drug Regulatory Authorities (VeDDRA). An assessor assigns a causality code of A, B, O, or N (see 2.3.6 for explanation of ABON causality code system). If necessary, further questions may be asked of the reporter to complete the information on the reaction.

It was noted that in the human field in the UK, reports from all sources are collated and recorded by the Medicines Control Agency (MCA), although only medically confirmed cases of adverse reactions (i.e. reported by doctors, dentists, pharmacists and coroners) are used in the analyses carried out for inclusion in official publications of the MCA.

(ii) *Periodic safety update reports (PSURs)*. These are mandatory reports from the Marketing Authorisation Holders (MAH) which contain all adverse reaction reports received by the MAH, with sales figures, over a stated period. The period of the report is laid down in the Marketing Authorisation (MA) and the SAR Surveillance Scheme assessor will select the appropriate paragraph to be included as a condition when the MA is issued. This is selected according to several criteria including issues such as whether the active ingredient is new, whether the active has been used in the species before, and previous SARs performance. The conditions included in the MA will be one of the following;

Unless other requirements have been laid down as a condition of granting authorisation, these records shall be submitted to the competent authorities immediately on request or at least every six months during the first two years following authorisation, and once a year for the following three years. Thereafter the records shall be submitted at five yearly intervals together with the application for renewal of the authorisation, or immediately on request.

On request or every 3 months for the first year, annually for the next four years and then every five years at renewal

On request or annually for five years and then every five years at renewal

On request or every five years at renewal

In order to increase the sensitivity of evaluation, the VMD, on behalf of the Working Group, requested that Marketing Authorisation Holders (MAHs) provide 6-monthly PSURs and sales for all current cat and dog vaccines from January 1999. (see section 2.5.9).

It was noted that the PSURs received by the SAR Surveillance Scheme do not include a scientific evaluation and are abbreviated text in the form of a line listing. The SAR Surveillance Scheme is unable to assess the individual SARs in depth due to the lack of information in a line listing and rely on the Marketing Authorisation Holder's (MAH's) assessment.

Although companies report all adverse reactions as outlined above they are also legally required to report serious SARs, separately, within 15 days of receiving notification (Article 42d Directive 81/85¹⁵; CVMP/183/96 NfG Pharmacovigilance of Veterinary Medicinal Products⁶; and VMD Guidance AMELIA 12⁸).

2.2.2. Currently, cross-referencing by the VMD of SARs reported on MLA 252A forms ('yellow form' SARs) and PSUR incidents occurs for fatal PSUR incidents only. Therefore, only yellow form SARs data provide a comprehensive source of suspected adverse reactions and these data, together with sales data from PSURs, have been the subject of scrutiny in this report.

It was recommended that in the future a system should be developed which enables cross-referencing of all yellow form SARs and PSUR incidents. It is important that, in order to facilitate cross-referencing in the future, companies encourage reporters to also report directly to the VMD.

- 2.2.3. It was recognised that all reporting should be encouraged and ways in which this might be facilitated were considered, including more publicity for the SAR Surveillance Scheme and more active targeting of potential reporters and reporting groups. Yellow forms are currently freely available, for example, in the National Office of Animal Health (NOAH) Compendium of Data Sheets for Veterinary Products¹²⁵, on the World Wide Web²⁰³, the Citizen's Advice Bureau, and the Trading Standards Authority. Other outlets including retailers, pharmacists and libraries may be used. Circulation of the 'Is this medicine suitable for my pet?' leaflet, which makes reference to adverse reactions and is available on request, should be increased. The Working Group also recommends that ways should be found to increase the quality of information reported to the SAR Surveillance Scheme, possibly with a more pro-active approach. The format of the yellow forms, should be reviewed periodically to ensure ease of reporting and compatibility with the database. An interactive Internet reporting system should be developed that is capable of direct uploading of data into the VMD database. Concerns over data protection and security on the Internet were considered, but it was acknowledged that the Government is committed to progressing electronic communication.
- 2.2.4. It was acknowledged that the SAR Surveillance Scheme, like all such surveillance schemes, is passive, but reactive. Such schemes are a valuable method of monitoring trends in a population over time, although they are not entirely satisfactory measures of the incidence or prevalence of reaction rates in a population unless the surveillance is based on a properly randomised sampling scheme. It is also recognised that such schemes principally address the early detection and cause of adverse reactions occurring at point of treatment, with long term, low incidence, or unrecognised adverse events being difficult to detect. Under-reporting is also likely to be a feature of such schemes. In addition, surveillance schemes are subject to a number of factors which may influence reporting sources and reporting rates. Such factors include media attention, and owner, breeder or professional concerns. The effect on reporting rates of developing more active surveillance measures, as outlined in section 2.2.3, above should also be noted. The effectiveness of the individual companies' pharmacovigilance system may also influence the reporting rate of serious SARs. Although the Working Group recognises that the term reporting rate is more accurate the term incidence will be used throughout this report.
- 2.2.5. The efficiency of data collection from the yellow forms is also dependent on response rates for further information requests from the VMD to the reporter. Figures for the calendar year 1999 record follow-up response rates of 59% for feline vaccine SARs and 53% for canine vaccine SARs, with an overall combined response of 57%. The VMD operates a system whereby further information is requested once only: after three weeks a response is considered no longer pending, but will be included if received. It is important that this response rate is improved and the Working Group therefore strongly recommend that ways should be found to improve this low response to requests for further information. The Working Group recommend that follow-up action should be taken by contacting reporters that have not responded within the three week period: reporters could also be made more aware that responses may be made by telephone.
- 2.2.6. It was recognised that there may be differences in interpretation by companies and other reporting sources over the type of reactions that should be reported. It is important that 'expected' reactions (i.e. those noted on the data sheet) should be reported as well as

‘unexpected’ reactions, and that expected reactions at all levels of frequency or severity should be included. The Working Group concluded that all reports should be encouraged, although it was recognised that reliable reporting of mild and/or frequent reactions may not occur, particularly when such reactions are listed in the product literature. It was also recognised that some adverse reactions may be hard to detect particularly if they occur infrequently or a long time after vaccination. (See section 3.2 and 3.3)

2.3. Data management of adverse reactions and product details

- 2.3.1. The Totally Integrated Graphical Relational Electronic Surveillance System (TIGRESS) is an electronic database recently introduced to replace older databases within the VMD. It contains details of all reported adverse reactions, i.e. demography of the animal, clinical signs, time of onset, reporter category, product characteristics, administration details, type of reaction, SAR Surveillance Scheme assessment etc. This database is the principal database that underpins the SAR Surveillance Scheme, providing the necessary information that describes the circumstances under which SARs occur, and is used to investigate possible causality.
- 2.3.2. Clinical signs are classified in the TIGRESS database according to the Veterinary Dictionary for Drug Regulatory Authorities (VeDDRA) system²⁰⁴ with a few minor amendments to general and systemic disorders, and the addition of a System Organ Class (SOC) for Suspected Lack of Efficacy. The VeDDRA is a dictionary of clinical terms originally started in the EU by the Pharmacovigilance VeDDRA Working Group, which has been further developed by the UK for use in their SAR Surveillance Scheme database TIGRESS. It is based on a hierarchical or tree structure beginning at the highest level with a System Organ Class (SOC) which generally refers to the body system affected. e.g. digestive tract disorder. Within these SOCs there are Higher Level Group terms (e.g. defaecation disorders), Higher Level Terms (e.g. emesis), Preferred Terms (e.g. emesis) and Lower Level Terms (e.g. vomiting). The structure of the dictionary allows searching of individual terms at each of the levels as appropriate.
- 2.3.3. Cat and dog breeds are entered into the TIGRESS database and classified according to the Governing Council of the Cat Fancy (GCCF) and UK Kennel Club breed lists (Appendix 1c). Dog breeds were classified for the purpose of analysis according to breed groups rather than individual breeds, which may have masked some specific breed effects. However, details of individual breeds are available on the database and where appropriate, further analysis of some breeds considered at possible risk was undertaken.
- 2.3.4. In most cases, both the date when the incident occurred and the date when the SAR report was received by the VMD are recorded on the TIGRESS system. However, there was a small percentage of SARs (1.2% for cats and 2.3% for dogs of vaccine SARs) seen between 1985 to 1999 for which the incident date was not reported (see section 2.4.2). These cases were not included in the analyses reported here, except where indicated.
- 2.3.5. Except for age, sex, breed and clinical sign comparisons, and the control charts which detailed each individual vaccine, only SARs reported to currently authorised vaccines were included in the analyses. It was felt that little would be gained from investigations into products which are no longer authorised. However, SARs were included to products whose authorisation had expired merely due to a change in the name of the product itself or the Marketing Authorisation Holder. This is because these changes result in a new authorisation being issued and the old authorisation withdrawn whilst the product itself remains unchanged making it appropriate to include the relevant SARs.

2.3.6. An ABON causality code system is used to categorise the SARs within the TIGRESS database. The aims of this system are summarised by Stephens et al²⁰⁵ as:

1. Classification of adverse event.
2. To decide on nature of further enquiries.
3. To satisfy regulatory requirements.
4. To decide whether the drug can cause an Adverse Drug Reaction (ADR).
5. To aid signal recognition (i.e. reviewing cases of particular causality in order to assess emerging trends).
6. To provide a basis for label change (or, in practice, sometimes other changes in the product authorisation).

It should be noted that ABON code allocation is regularly reviewed and as further information is received, or a trend emerges, the coding of an individual SAR may be changed.

The ABON system has been in use in the EU since 1/1/95 and is based on that described in the CVMP/183/96 NfG Pharmacovigilance of Veterinary Medicinal Products⁶ and VMD Guidance AMELIA 12⁸, with some modifications. However for operational UK purposes additional subcodes have been introduced. These subcodes are for internal assessment purposes only. For published reports the standard ABON classification is used. The classification used for this report is as follows:

Table 2. ABON causality codes

A		Reaction probably related to use of the product
B		Reaction possibly related to use of the product
Bm*		Multiple vaccines used concurrently prior to the reaction which is possibly related to use of one or more of the products
O	Bm	Multiple products (vaccines and pharmaceuticals) used concurrently prior to reaction occurring which is possibly related to one or more of the products used (excluding Bm*)
O	B – Opru	A concurrent product is thought to possibly be related to the reaction rather than the product reported
O	B – Factor	Multifactorial aetiology but still a possibility that the product is involved in the reaction
O		Insufficient data to assess whether reaction due to use of the product
N		Reaction not due to use of the product

The Bm, B-Opru, and B-Factor are used by the UK SAR Surveillance Scheme to subdivide Os where there is a possible product reaction but there is insufficient information to be sure. Bm* was a further category used in this report, as it was identified as important where vaccines were involved.

For the purposes of analysis of data in this report, the SARs were grouped into three categories: (1) A, B, Bm*; (2) Total O's, i.e. Bm, B-Opru, B-Factor, and O; and (3) All ABONs, i.e. (1) and (2) plus Ns.

2.3.7. *Ingredients database.* A spreadsheet information system containing detailed information on each vaccine has been constructed, outwith the TIGRESS database. Different spreadsheets are used for feline and canine vaccines and each sheet lists the products and their associated details, i.e. the Marketing Authorisation Holder, alternative presentation, type of vaccine, and

ingredients. For each vaccine, details are recorded on its nature, strain, quantity per dose, adjuvants, excipients etc. The purpose of this data set is to enable the SAR Surveillance Scheme team to carry out detailed examinations of vaccine ingredients to determine if certain products or ingredients may be associated with types of reactions or number of SARs.

- 2.3.8. Non-vaccine SARs were used as a control population for statistical comparison with vaccine SARs for sex, breed, age and clinical signs. In addition sex and age data were obtained from the GfK Home Audit (1999), an external audit commissioned by Pedigree Masterfoods. It was recognised that neither of these sources was ideal in that they were not comparable, unvaccinated, vet-visiting control populations. The use of non-vaccine SARs may have had other limitations particularly with respect to comparison of clinical signs. However, two separate control populations were used for sex and age to check how comparable these samples were of the UK cat and dog populations.

For age, sex, breed and clinical signs, where pre-1995 comparisons were used, not all non-vaccine SARs data were available for logistical reasons. Nevertheless, the comparisons were considered to be based on representative samples. However, the proportionately lower number of non-vaccine SARs in the pre-1995 data may have affected some analyses, for example breed distribution, which may be subject to changing owner preference over time.

- 2.3.9. *Statistical Analysis:* Comparison between the demographic vaccine SARs data and the non-vaccine SARs control population was carried out for a range of risk factors. These comparisons were undertaken using chi-squared analysis, including Yates' corrected chi-squared, and Fishers exact test where appropriate. Those factors which indicated difference between vaccine and non-vaccine SARs groups at the 5% level ($p < 0.05$) were considered significant.

Multifactorial analysis, i.e. analysis of a range of factors within the SARs, using the TIGRESS and ingredients database, was also carried out using chi-squared analysis. This enabled assessment, where appropriate, of possible associations and risk factors for vaccine SARs, the aim being to determine whether or not certain products or particular animal characteristics were contributing to an abnormal number or type of incidents.

The incidences of certain clinical signs (e.g. sarcomas) associated with specific vaccine products and therapeutic types were determined using sales figures as denominator data.

Although follow up information was requested (see 2.2.5) information on the TIGRESS database was not always complete for each SAR. Consequently the various analyses undertaken involved different numbers of reports, according to the information available.

The statistical approaches were effective in screening for potential risk factors, while it was recognised that the data sources were not random samples and, in addition, factors could be confounded.

2.4 Analysis of the SARs database

- 2.4.1. The estimated size of the cat and dog populations of the UK in 1999 were 7.7 and 6.7 million respectively²⁰⁶. PSUR vaccine sales data for 1999 suggests that 35.4%, 35.7% and 14.2% of cats were vaccinated against feline panleucopenia, feline herpesvirus/ feline calicivirus and feline leukaemia respectively. Likewise, 72.0%, 81.7%, 71.9%, 78.2% and 56.1% of dogs were vaccinated against canine distemper, canine parvovirus, canine adenovirus 2, canine parainfluenza virus and leptospirosis respectively. These calculations do not take into account the effect of primary vaccination where two doses may be used in some cases as part of the primary course (see section 2.4.9.). The data compares with other estimates that within the population of cats and dogs approximately one third of cats and half of dogs have up to date vaccinations²⁰⁷.
- 2.4.2. Over the period 1985 to 1999, 1204 vaccine SARs and 1455 non-vaccine SARs were received for cats, and 1160 vaccine SARs and 1651 non-vaccine SARs were received for dogs, with or without an incident date (see sections 2.3.4 and 2.3.8). The corresponding figures for this period with an incident date were 1190 and 1358 vaccine and non-vaccine SARs respectively for cats, and 1133 and 1545 vaccine and non-vaccine SARs respectively for dogs. For analyses of sex, breed and age, 1985–1999, the actual numbers of animals involved were used, with and without an incident date, i.e. 1531 and 1576 cats with vaccine and non-vaccine SARs respectively, and 1332 and 1846 dogs with vaccine and non-vaccine SARs respectively. It should be noted that there may be more than one animal involved in an individual SAR.

The level of reporting of all SARs is in the same order for both species, although there were more non-vaccine compared to vaccine SARs for both cats and dogs. However over the past five years, although the number of biological (vaccine) products in relation to pharmaceutical products with marketing authorisations has decreased for both cats and dogs, the proportion of vaccine SARs reported compared to pharmaceutical (non-vaccine) SARs has risen for both species (Table 3).

Table 3. Number of SARs to biological (vaccine) and pharmaceutical products per year for cats and dogs in relation to the number of marketing authorisations (MAs) (1995–1999)

Cats					
	1995	1996	1997	1998	1999
Number of biological SARs	78	119	179	187	293
Number of biological MAs	57	54	54	38	26
Number of pharmaceutical SARs	184	215	321	295	308
Number of pharmaceutical MAs	512	541	516	493	475
Dogs					
	1995	1996	1997	1998	1999
Number of biological SARs	83	90	148	158	218
Number of biological MAs	103	95	79	52	35
Number of pharmaceutical SARs	217	236	380	314	351
Number of pharmaceutical MAs	745	795	781	744	717

Similarly, the incidence per 10,000 doses sold for cat vaccines has risen over the past five years from 0.30 to 0.82 (mean 0.61), although for dogs it has ranged from 0.13 to 0.26 (mean 0.21) over the same period (Table 4).

Table 4. Number of vaccine SARs and incidence per 10,000 doses sold for cats and dogs (1995 – 1999) for products authorised at 31/12/99

Cats				
Year	Number of Vaccine SARs	Incidence per 10,000 doses sold*	Number of products not included*	Number of SARs not included*
1995	56	0.30	1	17
1996	93	0.55	2	21
1997	173	0.70	1	5
1998	183	0.55	1	3
1999	283	0.82	1	8
Overall	788	0.61	Between 1 and 2	54

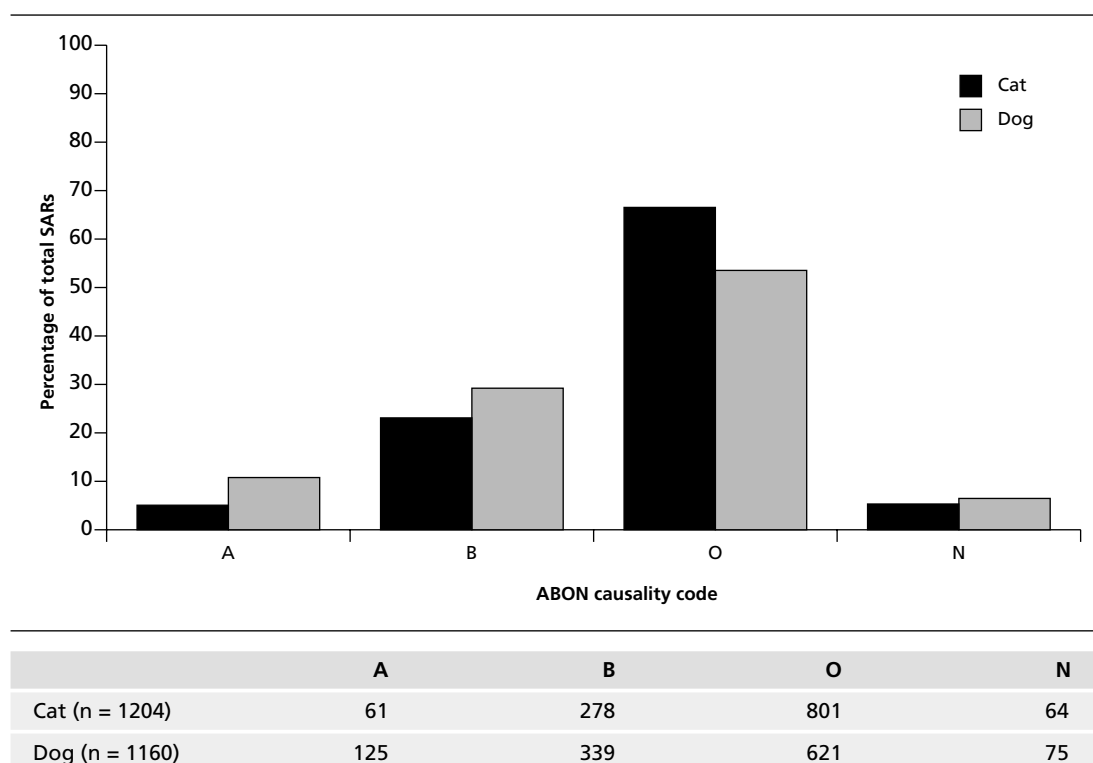
Dogs				
Year	Number of Vaccine SARs	Incidence per 10,000 doses sold*	Number of products not included*	Number of SARs not included*
1995	56	0.13	3	11
1996	68	0.14	1	4
1997	127	0.24	3	6
1998	149	0.26	3	6
1999	207	0.22	1	5
Overall	607	0.21	Between 1 and 3	32

*Any product with SARs for a particular year but no sales figures were not included in the calculations.

Sales data prior to 1995 were insufficiently complete and therefore were excluded from such analyses.

2.4.3. A breakdown of the proportion of vaccine-related SARs for cats and dogs in each of the ABON causality codes is shown for the period 1985 to 1999 in Figure 2. This shows that the majority of vaccine SARs for cats and dogs are classified in the O category i.e. where essentially there is insufficient information to determine causality. However the demographic characteristics and the distribution of clinical signs seen in the O category were broadly similar to that seen in the A and B categories (data not shown) and therefore for the analyses in section 2.4 all ABON categories were analysed together.

Figure 2. Number and percentage of vaccine SARs received* between 1985 – 1999 for cats and dogs in relation to each of the ABON causality codes



Key

- A Reaction probably related to use of the product
- B Reaction possibly related to use of the product
- O Insufficient data to assess whether reaction due to use of the product
- N Reaction not due to use of the product
- * With and without incident date (see section 2.3.4)

2.4.4. When a report is received by the SAR Surveillance Scheme the time of onset of the reaction is recorded if it is known. The length of this onset period for SARs received between 1995 to 1999 is shown in Figures 3a and b. These onset periods were categorised as immediate (within 24 hours), short term (within 3 weeks) and long term (after 3 weeks). The majority of SARs (38% of cats and 41% of dogs) occurred within 24 hours. However an onset time was not reported in 40% of cat and 35% of dog SARs.

Figure 3a. Number and percentage of reaction onset times that were immediate, short term, long term or unknown for feline vaccine SARs between 1995–1999

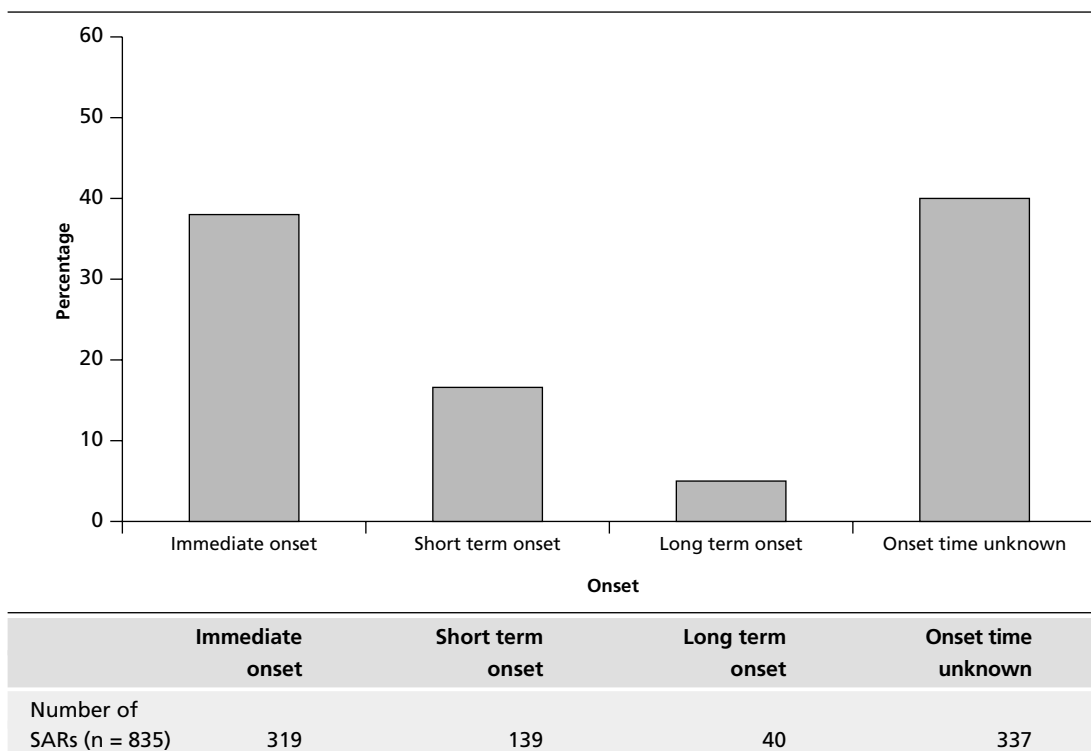
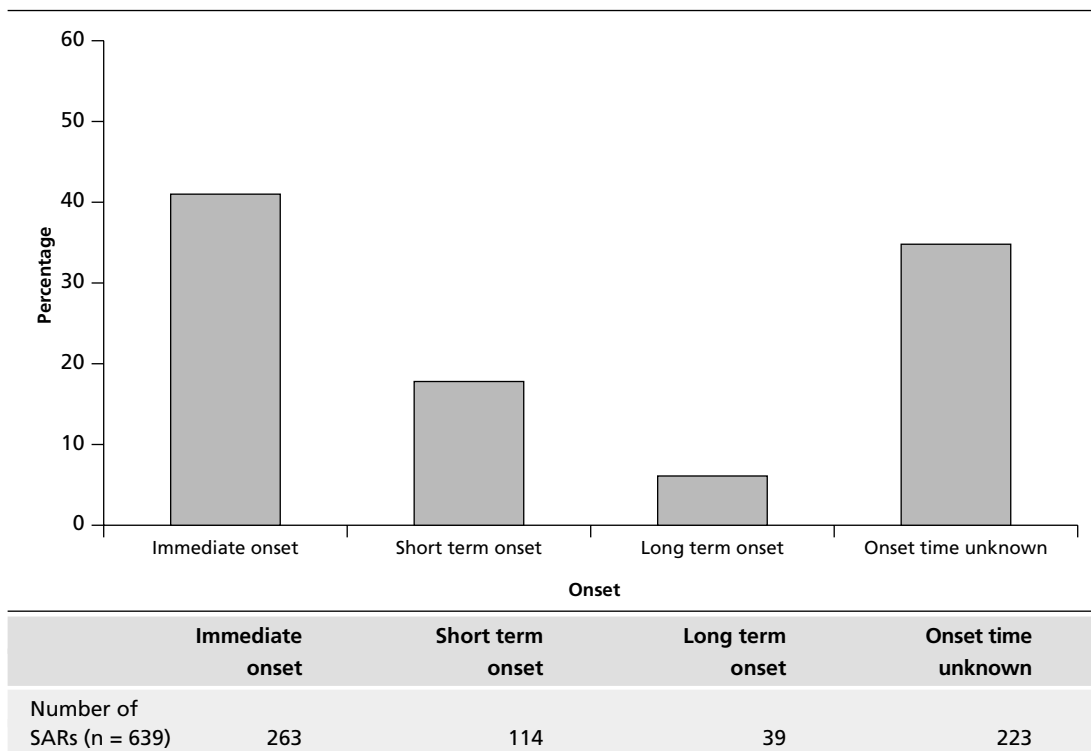


Figure 3b. Number and percentage of reaction onset times that were immediate, short term, long term or unknown for canine vaccine SARs between 1995–1999



Key
 Immediate onset: less than or equal to 24 hours
 Short term onset: less than or equal to 3 weeks
 Long term onset: greater than 3 weeks

- 2.4.5. The sex, breed and age profiles of the number of animals involved in cat and dog vaccine SARs compared with non-vaccine SARs from 1985–1999 are shown in Appendices 1d, 1e and 1f. The sex and age distributions for the GfK population are shown in Appendices 1g and 1h.
- 2.4.6. There appeared to be evidence of a significant difference in sex distribution for cats between vaccine SARs and non-vaccine SARs with the proportion of males being higher in the vaccine SARs (48%) than in the non-vaccine SARs (44%) ($p = 0.044$) (Table 5) (Appendix 1d). For dogs, there is also evidence of a significant difference in distribution of male and female dogs between the vaccine SARs and the non-vaccine SARs with the percentage of males again being higher (52%) in the vaccine SARs than in the non-vaccine SARs (46%) ($p = 0.008$) (Table 5) (Appendix 1d). The GfK sex distribution data are included for comparison, and for cats there is broad agreement with the SARs data (Table 5) (Appendix 1g). For dogs, the GfK ratio of females to males more closely resembles the vaccine SARs data than the non-vaccine SARs controls.

Table 5. Sex distribution: female:male ratios and (percentages) in cats and dogs with vaccine SARs and two control groups (1985–1999)

	Control Populations		
	vaccine SARs	non-vaccine SARs	GfK data (1999 only)
Cats *	1.09: 1 (52%: 48%)	1.29: 1 (56%: 44%)	1.17: 1 (54%: 46%)
Dogs *	0.93: 1 (48%: 52%)	1.16: 1 (54%: 46%)	1.00: 1 (50%: 50%)

*Cats: vaccine SARs: number of animals = 1073; non-vaccine SARs: number of animals = 1305

*Dogs: vaccine SARs: number of animals = 1022; non-vaccine SARs: number of animals = 1462

For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

- 2.4.7. Comparison of the breed distribution in cats for vaccine and non-vaccine SARs showed that there was a significantly higher proportion of pedigree cats in the vaccine SARs compared to the non-vaccine SARs, and proportionately fewer non-pedigree animals ($p < 0.001$), with some breeds (in particular Burmese and Semi-longhair) being over-represented ($p < 0.001$) (Table 6) (Appendix 1e).

Table 6. Percentage of cats with vaccine and non-vaccine SARs reported by breed* (1985–1999)

Breed	Percentage of Reports	
	Vaccine SARs (number of animals = 1060)	Non-vaccine SARs (number of animals = 1094)
Foreign	5.0	2.0
Burmese	9.6	3.0
Siamese	8.8	4.5
Semi-longhair	7.3	2.3
Non Pedigree	57.3	78.2
Other Pedigree & Pedigree Crosses	12.0	10.0

*Those cats with breed recorded as 'others' and 'unknown' were omitted from the analysis (30.9% and 31.4% of cats with vaccine and those with non-vaccine SARs respectively).

For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

This higher than expected incidence of vaccine SARs in pedigree cats may be explained in a number of ways. First, it may be a real effect whereby some breeds are more predisposed to reactions following vaccination: such a finding requires in-depth, systematic examination for possible causality. However, it may also be a reflection of possibly greater usage of vaccines in pedigree animals, and owners of such cats may be more inclined to report any reactions seen. Further analyses to examine the possible effects of confounding (for example, by age) were not undertaken.

In dogs, comparison of the number of animals involved in vaccine and non-vaccine SARs indicated evidence of significant difference ($p < 0.001$) amongst breed groups (Table 7) (Appendix 1e). In particular, there was a higher proportion of the Toy, and to a lesser extent, the Utility breed groups in the vaccine SARs compared to the non-vaccine SARs. In contrast, there was a lower proportion of the Gun breed group in the vaccine SARs. The reason for this is unknown but comparison of the distribution of VeDDRA SOCs 1995–1999 for the Toy breed group compared to all other breeds showed no marked difference in the distribution of clinical signs for vaccine SARs. Comparison of the distribution of individual breeds within the Toy breed group showed no marked difference in distribution for vaccine SARs compared to non-vaccine SARs. In both vaccine and non-vaccine SARs, the most commonly occurring Toy breeds were Yorkshire Terriers (29% and 44% respectively) and Cavalier King Charles Spaniels (CKCS) (21% and 27% respectively): the limitations of using the non-vaccine SARs as a comparator population for clinical signs are noted in section 2.3.8. Although CKCS appear to be susceptible to some cardiovascular and haemopoietic disorders^{208, 209, 210} which might predispose them to certain types of vaccine SARs, the distribution of VeDDRA SOC codes of CKCS for vaccine SARs compared to all other breeds showed no marked difference in the incidence of cardiac and associated signs. In fact there was a lower proportion of cardiac signs (0% CKCS cf. 6.9% all other breeds) and proportionately more application site (21.7% cf. 8%), behaviour (21.7 cf. 9.6%) and respiratory disorders (17.4% cf. 9.7%).

Further analysis of some individual breeds considered at possible risk was also undertaken (see sections 2.4.11.).

Table 7. Percentage of dogs with vaccine and non-vaccine SARs reported by breed* (1985–1999)

Breed	Percentage of Reports	
	Vaccine SARs (number of animals = 1081)	Non-vaccine SARs (number of animals = 1636)
Toy	15.9	7.1
Utility	10.0	6.4
Gun	17.9	27.8
Pastoral	16.0	14.2
Terriers	14.2	14.6
Hound	7.4	7.9
Working	8.9	9.7
Crossbreed and Others	9.7	12.3

*Those dogs classified as others (5.3% of those with vaccine SARs and 6.2% of those with non-vaccine SARs) were included with crossbreed but the analysis excluded unknowns (14.9% of dogs with vaccine SARs and 11.4% of those with non-vaccine SARs).

For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

- 2.4.8. Comparison of the age distribution in both cats and dogs showed that the percentages in each of the age classes observed for vaccine and non-vaccine SARs are clearly different, with a significantly higher proportion of 0–6 month old animals in the vaccine SARs group compared to non-vaccine SARs and proportionately fewer animals over the age of one year ($p < 0.001$ for both cats and dogs) (Table 8) (Appendix 1f). This effect is also clearly different to the small percentage of 0–6 month old animals as estimated for the age distribution of the GfK population (Table 8) (Appendix 1h). The possible effects of confounding were not examined.

Table 8. Percentage of animals in each age class for cat and dog vaccine SARs and two control groups (1985–1999)

	Control Populations		
	vaccine SARs	non-vaccine SARs	GfK data (1999 only)
Number of cats	1335	1361	Unknown
0–6 months	44.8%	18.8%	4.6%
6 months–1 year	2.8%	5.8%	4.4%
>1 year	52.4%	75.4%	91.0%
Number of dogs	1137	1468	Unknown
0–6 months	47.2%	16.9%	4.2%
6 months–1 year	4.5%	4.8%	4.8%
>1 year	48.3%	78.3%	91.0%

For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

The higher than expected reaction rate to vaccines in young kittens and puppies may relate to proportionately greater vaccine usage in this age group, or a higher reporting rate by owners. However there is evidence that it may indeed be a real effect (see section 2.4.9 below). Animals less than six months of age will be undergoing a primary course and they may therefore be more susceptible to some types of adverse reactions. However, some of these apparent reactions may be due to the coincidental onset of age-related diseases, or coincidental infection with field viruses: kittens and puppies are generally vaccinated at a stage when maternally derived antibody has just waned, leaving them susceptible to field virus infections.

- 2.4.9. The proportion of vaccines used in a primary course, as opposed to boosters, for vaccine SARs for cats and dogs was difficult to determine. However, information for the vet-visiting population was obtained by the Working Group from a small practice survey*. Of 14 veterinary practices questioned for the year 1999 six (42.8%) responded but one of these practices was unable to provide information. For cats the overall figure for primary vaccinations was 13.5% (range 9–20%) with boosters comprising 86.5%. For dogs, the overall figure for primary vaccination was 17.5% (range 10–22%) and 82.5% for boosters. Although not all primary vaccination courses will be given to young animals, this data nevertheless strongly supports the observation that young animals are over-represented with respect to vaccine SARs, since 44.8% and 47.2% of cat and dog vaccine SARs respectively were in animals less than six months of age (see section 2.4.8 above). An analysis of the distribution of VeDDRA SOC codes within the vaccine SARs shows no marked difference between each of the age groups, except for possibly greater suspected lack of efficacy in younger dogs and possibly more application site, behaviour, immunological, respiratory and skin disorders in older cats.

* The Working Group acknowledges with gratitude the contribution made by all the participating practices.

2.4.10. A breakdown of clinical signs according to VeDDRA SOC codes 1985–1999 for cat and dog vaccine and non-vaccine SARs is shown in Appendix 1i. It was recognised that non-vaccine SARs were not ideal for the purposes of comparison particularly with respect to clinical signs: the difficulty of obtaining data from a matched control population and other limitations of the control population are discussed in section 2.3.8.

For cats, the distribution of clinical signs appeared to be different between vaccine and non-vaccine SARs for some clinical signs (Appendix 1i). The most common clinical signs for vaccine SARs in cats were systemic, general, neurological and behavioural signs; in the non-vaccine SARs group the most common codes were systemic, neurological, digestive and skin disorders (Appendix 1i). In quantitative terms between 1995–1999, there appeared to be proportionately more vaccine SARs than non-vaccine SARs with general (29.5% cf. 9.7%), behavioural (24.9% cf. 14.3%) and immunological signs (8% cf. 2.5%) (all $p < 0.001$) in the vaccine SARs group compared to the non-vaccine SARs. Similarly, there were proportionately fewer cats with skin (4.6% cf. 28.5%), digestive (15.4% cf. 20.7%) and neurological signs (24.9% cf. 29.7%) ($p = < 0.001$, 0.007, and 0.03 respectively) in the vaccine SARs group compared to non-vaccine SARs.

For dogs, the distribution of clinical signs again appeared to be slightly different between vaccine and non-vaccine SARs for some clinical signs (Appendix 1i). The most common clinical signs for vaccine SARs in dogs were systemic, digestive, immunological and neurological signs; in the non-vaccine SARs group the most common codes were systemic, digestive, neurological, and skin disorders. Between 1995–1999 there were proportionately more dogs with suspected lack of efficacy (7.4% cf. 2.9%), general signs (22.8% cf. 10.6%), and immune disorders (26.3% cf. 10.5%) in the vaccine SARs group compared to the non-vaccine SARs ($p < 0.001$). Similarly there were proportionately fewer dogs with skin disorders in the vaccine SARs compared to the non-vaccine SARs (7.7% cf. 18.8%) ($p < 0.001$).

2.4.11. Further analysis was undertaken of specific clinical signs or conditions identified in the literature review (Section 1) as being of possible importance. The case definition for such signs was based on the VeDDRA system where the Higher Level Term (HLT) e.g. application site/injection site injection reaction incorporates a range of signs in the lower level terms. However, in some instances, both higher and lower level terms represented a predetermined diagnosis (e.g. anaphylaxis). The number of vaccine SARs for cats and dogs for specific disease signs for the period 1985–1999, 1995–1999, and for the year 2000 are shown in Tables 9 and 10. The number of non-vaccine SARs for particular disease signs is also given for comparison for the period 1995–1999 and for the year 2000. For the period 1995–1999 (where more accurate sales figures are available) the incidence per 10,000 doses sold of particular vaccine SARs was also calculated. Sales figures for the year 2000, and therefore incidence figures, were not available at the time of writing this report.

2.4.11.1. Over the period 1995–1999 the number of cases of anaphylaxis was 34 in cats and 63 in dogs giving incidences per 10,000 doses sold of 0.026 and 0.018 respectively, which is much lower than the estimated incidence of 1:15,000 vaccinated animals cited by Paul and Wolf³⁰ (section 1.3.3.1.) (Tables 9 and 10). Over the same period there were 28 and 88 cases of hypersensitivity in cats and dogs, with incidences of 0.022 and 0.028 per 10,000 doses respectively. In dogs there were also 21 cases of urticaria over this period, with no significant difference in the proportion of Dachshunds with anaphylaxis or urticaria compared to all other breeds²⁷. Comparison by vaccine therapeutic group (i.e. live vaccines (LV), inactivated

Table 9. Summary table: number and incidence of selected clinical signs for vaccine and non-vaccine SARs in the cat

Disease Signs	Number of vaccine SARs 1985–1999, n = 1190* (% of total)	Number of vaccine SARs 1995–1999, n = 835* (% of total)	Incidence of vaccine SARs per 10,000 doses sold 1995–1999 (number of SARs included [†])	Number of non-vaccine SARs 1995–1999, n = 1323* (% of total)	Number of vaccine SARs for 2000, n = 262* (% of total)	Number of non-vaccine SARs for 2000, n = 329 (% of total) ⁺	Comments
Anaphylaxis	51 (4.3)	34 (4.1)	0.026 (33 SARs)	10 (0.8)	13 (5.0)	4 (1.2)	Of the 34 vaccine SARs from 1995–1999, 22 of them involved domestic shorthair cats
Hypersensitivity	48 (4.0)	28 (4.4)	0.022 (28 SARs)	17 (1.3)	13 (5.0)	11 (3.3)	
Local, injection site reactions#	157 (13.2)	133 (15.9)	0.099 (127 SARs)	93 (7.0)	62 (23.7)	17 (5.2)	Of the 133 vaccine SARs from 1995–1999, 76 involved non-pedigree cats
Sarcoma	26 (2.2)	26 (3.1)	0.021 (26 SARs)	3 (0.2)	24 (9.2). Four of these do not state injection site	1 (0.3)	Of the 26 vaccine SARs from 1995–1999, 18 involved non pedigree cats
Immune mediated haemolytic anaemia	0 (0)	0 (0)	0 (0 SARs)	0 (0)	0 (0)	0 (0)	There were no cat SARs involving immune mediated haemolytic anaemia
Immune mediated thrombocytopenia	0 (0)	1 (0.1)	0.001 (1 SAR)	0 (0)	1 (0.4)	1 (0.3)	
Polyarthritis/polyarthropathies/polyarthrosis	64 (5.4)	59 (7.1)	0.044 (57 SARs)	6 (0.4)	14 (5.3)	2 (0.6)	Of the 59 vaccine SARs from 1995–1999, 31 involved non pedigree cats.
URT [^] +/- oral ulceration	40 (3.4)	38 (4.6)	0.028 (36 SARs)	0 (0)	0 (0)	0 (0)	Of the 38 vaccine SARs from 1995–1999, 27 involved live vaccines
URT [^] +/- oral ulceration, + lameness	8 (0.7)	8 (1.0)	0.006 (8 SARs)	0 (0)	0 (0)	0 (0)	Of the 8 vaccine SARs from 1995–1999, 6 involved live vaccines
Lameness with lethargy, pyrexia or anorexia	102 (8.6)	92 (11.0)	0.071 (91 SARs)	5 (0.4)	21 (8.0)	0 (0)	Of the 92 vaccine SARs from 1995–1999, 41 involved live and 39 involved vaccines grouped therapeutically as mixed
Suspected lack of efficacy	80 (6.0)	52 (6.2)	0.027 (35 SARs)	10 (0.8)	15 (5.7)	11 (3.3)	

*This figure is based on SARs received where there was an incident date recorded

[†] Sales data pre – 1995 incomplete so incidence figures are not available. Where no sales figures are available the SARs for the product for the years concerned are not included⁺ Sales data for 2000 not available at time of writing report, so incidences per 10,000 doses are not available

including alopecia

[^] URT = Upper respiratory tract disease

Table 10. Summary table: number and incidence of selected clinical signs for vaccine and non-vaccine SARs in the dog

Disease Signs	Number of vaccine SARs 1985–1999, n = 1133* (% of total)	Number of vaccine SARs 1995–1999, n = 639* (% of total)	Incidence of vaccine SARs per 10,000 doses sold 1995–1999 (number of SARs included [†])	Number of non-vaccine SARs 1995–1999, n = 1498* (% of total)	Number of vaccine SARs for 2000, n = 226* (% of total)	Number of non-vaccine SARs for 2000, n = 362 (% of total) ⁺	Comments
Anaphylaxis	101 (8.9)	63 (9.9)	0.018 (53 SARs)	25 (1.7)	30 (13.3)	8 (2.2)	
Hypersensitivity	235 (20.7)	88 (13.8)	0.028 (81 SARs)	109 (7.2)	46 (20.6)	24 (6.6)	Of the 88 vaccine SARs between 1995–1999, 20 involved breeds from the Gun breed group (15 labradors / retrievers)
Urticaria	37 (3.3)	21 (3.3)	0.007 (19 SARs)	65 (4.3)	14 (6.2)	12 (3.3)	
Local, injection site reactions #	48 (4.2)	40 (4.8)	0.012 (37 SARs)	50 (3.3)	19 (8.4)	16 (4.4)	Of the 40 vaccine SARs between 1995–1999, 8 involved breeds from the Toy breed group
Immune mediated haemolytic anaemia	5 (0.4)	4 (0.6)	0.001 (4 SARs)	0 (0)	2 (0.9)	2 (0.6)	All 5 vaccine SARs from 1985–1999 involved breeds from the Gun breed group. None of the dogs were related.
Immune mediated thrombocytopenia	5 (0.4)	5 (0.8)	0.002 (5 SARs)	7 (0.62)	3 (1.3)	1 (0.3)	
Pemphigus	0 (0)	0 (0)	0 (0 SARs)	0 (0)	0 (0)	2 (0.6)	No cases of pemphigus in dogs between 1985–1999
Myaesthesia gravis	0 (0)	0 (0)	0 (0 SARs)	0 (0)	0 (0)	0 (0)	No cases of myaesthesia gravis in dogs between 1985–1999
"Blue eye" / Eye corneal oedema	16 (1.4)	6 (0.9)	0.002 (6 SARs)	2 (0.1)	1 (0.4)	0 (0)	Of the 16 vaccine SARs, 15 were associated with the use of CAV2 vaccines. Five of the breeds were from the Gun, 3 from the Pastoral, 2 from the Working, 2 from the Hound (no Afghans) and 4 from the unknown, Crossbreeds or Other, breed groups.

* This figure is based on SARs received where there was an incident date recorded.

† Sales data pre – 1995 incomplete so incidence figures are not available. Where no sales figures are available the SARs for the product for the years concerned are not included.

+ Sales data for 2000 not available at time of writing report, so incidences per 10,000 doses are not available

including alopecia.

continued opposite

Table 10. Summary table: number and incidence of selected clinical signs for vaccine and non-vaccine SARs in the dog - continued

Disease Signs	Number of vaccine SARs 1985–1999, n = 1133* (% of total)	Number of vaccine SARs 1995–1999, n = 639* (% of total)	Incidence of vaccine SARs per 10,000 doses sold 1995–1999 (number of SARs included†)	Number of non-vaccine SARs 1995–1999, n = 1498* (% of total)	Number of vaccine SARs for 2000, n = 226* (% of total)	Number of non-vaccine SARs for 2000, n = 362 (% of total)†	Comments
Cutaneous vasculopathy/vasculitis/skin vascular disorders	0 (0)	0 (0)	0 (0 SARs)	1 (0.1)	2 (0.9)	1 (0.3)	
Hypertrophic osteodystrophy	0 (0)	0 (0)	0 (0 SARs)	0 (0)	0 (0)	0 (0)	No cases of hypertrophic osteodystrophy in dogs between 1985–1999
Cellulitis	2 (0.2)	2 (0.3)	0.001 (2 SARs)	0 (0)	0 (0)	0 (0)	
Polyarthritis/polyarthropathies/polyarthrosis	20 (1.8)	17 (2.7)	0.006 (17 SARs)	26 (1.1)	6 (2.7)	8 (2.2)	
Polymeuritis	0 (0)	0 (0)	0 (0 SARs)	0 (0)	0 (0)	0 (0)	
Suspected lack of efficacy	170 (15.0)	47 (7.4)	0.016 (46 SARs)	37 (2.5)	11 (4.9)	10 (2.8)	Of the 47 SARs between 1995 – 1999 11 involved breeds from the Working breed group. Of these, nine involved Rottweilers. Forty out of the 47 suspected lack of efficacy SARs involved parvovirus vaccine.

* This figure is based on SARs received where there was an incident date recorded.

† Sales data pre-1995 incomplete so incidence figures are not available. Where no sales figures are available the SARs for the product for the years concerned are not included.

+ Sales data for 2000 not available at time of writing report, so incidences per 10,000 doses are not available

vaccines with aluminium-based adjuvants (IVAA), inactivated vaccines with other adjuvants (IVOA), or mixed vaccines (MV)) showed that in cats, a higher proportion of cases of anaphylaxis were in the IVOA and LV group compared to the other two groups ($p < 0.001$) (Table 11). There was a higher proportion of cases of hypersensitivity in cats in the LV group and a lower proportion in the IVAA group compared to the MV group ($p = 0.002$): numbers in the IVOA group were small for reliable comparisons. In dogs there was a higher proportion of anaphylaxis in the MV group compared to the LV group ($p < 0.001$) (Table 12), but no significant difference between the groups for hypersensitivity.

2.4.11.2. Local (injection site) reactions were more common in cats than dogs, with 133 cases reported from 1995–1999 (an incidence of 0.099 per 10,000) in cats compared to 40 cases in dogs (0.012 per 10,000 doses) (Tables 9 and 10). In cats, there was a lower proportion of injection site reactions in the LV group compared to the other three therapeutic groups ($p < 0.001$) (Table 11). In contrast, in dogs, there was no significant difference between the two therapeutic groups (Table 12). Interestingly, there are a number of cat vaccines which are inactivated or mixed and contain various adjuvants, whereas the only inactivated components of dog vaccines are leptospiral antigens, which are not adjuvanted. (Rabies vaccines, which are used in specific circumstances in the UK, do contain aluminium-based adjuvants but were excluded from the analysis for dogs).

Table 11: Results of chi-squared tests carried out on specific clinical signs for vaccine SARs in the cat (1995–1999)

Disease sign	Possible association tested	Chi-squared probability	Comments
Anaphylaxis	Therapeutic group* ^T	<0.001	Higher proportion of anaphylaxis in the IVOA and LV group compared to the other two therapeutic groups
Hypersensitivity	Therapeutic group* ^T	0.002	Higher proportion of hypersensitivity in the LV group and lower in the IVAA compared to the MV group [‡]
Local, injection site reaction	Therapeutic group*	<0.001	Lower proportion of injection site reactions in the LV group compared to the other three therapeutic groups
Sarcoma	FelV vaccines versus all others	0.085 (Yates corrected)	No significant difference although there is a slightly higher percentage of sarcomas in the FeLV group compared to all other vaccines
Sarcoma	Therapeutic group* ^T	<0.001	Higher proportion of sarcomas in the IVAA group compared to the live and mixed therapeutic groups [‡]
Sarcoma	Age	<0.001	Higher proportion of sarcomas in cats aged 5–10 years old and over compared to younger cats
Sarcoma	Pedigree compared to non pedigree	0.027 (Yates corrected)	Lower proportion of sarcomas in the pedigree compared to the non pedigree group
Upper respiratory tract disease +/- oral ulceration	Therapeutic group* ^T	0.009	Higher proportion of SARs with upper respiratory tract disease +/- oral ulceration in the LV group compared to the IVAA and MV therapeutic groups [‡]
Upper respiratory tract disease +/- oral ulceration, and lameness	Therapeutic group* ^T	0.14	No significant difference in the proportion of SARs with upper respiratory tract disease +/- oral ulceration, + lameness between the different therapeutic groups
Lameness with lethargy, pyrexia or anorexia	Therapeutic group*	0.03	Higher proportion of SARs with lameness with lethargy, pyrexia or anorexia in the MV group compared to the other three therapeutic groups
Suspected lack of efficacy	Semi-longhair compared to other pedigree + non pedigree cats ^T	<0.001	Higher proportion of suspected lack of efficacy in the Semi-longhair group compared to all others (6 of the 8 Semi-long hair cats came from the same breeding cattery)

* Live vaccine (LV), Inactivated vaccine with aluminium adjuvant (IVAA), Inactivated vaccine with other adjuvant (IVOA), Mixed vaccine – inactivated adjuvanted / live vaccine (MV)

^T Small sample sizes required pairwise 2x2 tables for comparisons of groups and the use of Yates' continuity correction.

[‡] In some cases the number of SARs associated with the IVOA group were small for reliable comparisons

Table 12: Results of chi-squared tests carried out on specific clinical signs for vaccine SARs in the dog (1995–1999)

Disease sign	Possible association tested	Chi-squared probability	Comments
Anaphylaxis	Therapeutic group*	0.001 (Yates corrected)	Lower proportion of anaphylaxis in the LV group compared to the MV group
Anaphylaxis	Dachshunds compared to all other breeds	0.18 (Yates corrected)	No significant difference in the proportion of anaphylaxis in Dachshunds compared to all other breeds
Hypersensitivity	Therapeutic group*	1.00 (Yates corrected)	No significant difference in the proportion of hypersensitivity reactions when comparing the two therapeutic groups.
Injection site reaction	Therapeutic group*	0.31 (Yates corrected)	No significant difference in the proportion of injection site reactions when comparing the two therapeutic groups
Urticaria	Therapeutic group*	0.17 (Yates corrected)	No significant difference in the proportion of urticaria reactions when comparing the two therapeutic groups
Urticaria	Dachshunds compared to all other breeds	0.52	No significant difference in the proportion of urticaria in Dachshunds compared to all other breeds (of the 25 Miniature Dachshunds involved in vaccine SARs only one had urticaria).
Suspected lack of efficacy	Working breed group compared to all other breed groups	0.0001 (Yates corrected)	Higher proportion of suspected lack of efficacy in the Working breed group compared to all other breed groups. Nine of the 11 dogs in the Working breed group were Rottweilers
Suspected lack of efficacy involving parvovirus	Rottweilers compared to all other breeds	0.22 (Yates corrected)	No significant difference in the proportion of parvovirus suspected lack of efficacy when comparing Rottweilers to all other breeds

* Live vaccines (LV) compared to mixed inactivated/live vaccines (MV)

Feline vaccine associated sarcomas are discussed below (see section 2.4.11.7).

2.4.11.3. There were five cases each of IMHA and IMTP in dogs between 1985 and 1999, and two and three cases respectively in the year 2000 (Table 10). All five cases of IMHA between 1985 and 1999 were in the Gun breed group (which were unrelated). The incidence of IMHA and IMTP between 1995 and 1999 was 0.001 and 0.002 respectively per 10,000 doses, which is lower than the incidence of 0.0001% (i.e. 0.01 per 10,000) estimated by Duval and Giger (1996)³⁴ (section 1.3.3.2.).

2.4.11.4. Sixteen cases of corneal oedema ('blue eye') occurred between 1985 and 1999, and 6 between 1995 and 1999 (Table 10). The incidence between 1995–1999 was 0.002 per 10,000 doses. Interestingly, 15 of the 16 cases involved modified live CAV-2 vaccines (one case involved neither), but, unlike live CAV-1 vaccines, CAV-2 vaccines are not thought likely to induce this syndrome (see section 1.3.3.3.). It is probable that some of these dogs were exposed to wildtype CAV-1, but the situation with respect to CAV-2 vaccines may also need further evaluation. There was no evidence of a breed disposition in these cases, although a breed disposition for this condition has been reported previously (see section 1.3.3.3.).

2.4.11.5. Fifty nine cases of polyarthropathies/ arthritis/ arthrosis were reported in cats and 17 in dogs between 1995–1999, giving incidences per 10,000 doses of 0.044 and 0.006 respectively, indicating the condition appears to be more common in cats than dogs (Tables 9 and 10). Lameness with lethargy, pyrexia or anorexia (LLPA) in cats following vaccination

appears to be relatively common: 92 cases were reported between 1995–1999 (incidence of 0.071 per 10,000 doses) and a further 21 cases were reported in 2000. This syndrome may be related to the use of adjuvants, but may also be difficult to distinguish from the febrile lameness syndrome, with or without respiratory/oral signs, that has also been reported in association with the use of live feline calicivirus vaccines⁵⁶ (section 1.3.3.5.). Interestingly, of the 92 cases of LLPA reported between 1995–1999, 41 involved the LV group, and 39 involved the MV group. On chi-squared analysis, there were proportionately more cases of LLPA amongst vaccine SARs in the MV group compared to the other three therapeutic groups ($p=0.03$) (Table 11). Thirty-eight cases of upper respiratory tract disease in cats with or without oral ulceration occurred between 1995–1999 (incidence of 0.028 per 10,000 doses) (Table 9). In this case, there was a significantly higher proportion of such cases in the LV group compared to the IVAA and MV groups ($p=0.009$) (Table 11): numbers in the IVOA group were small for reliable comparisons. Sequence analysis has shown that in some cases such vaccines reactions may be due to feline calicivirus vaccine although in other cases, it is due to coincidental field virus infection^{60, 61} (section 1.3.3.5).

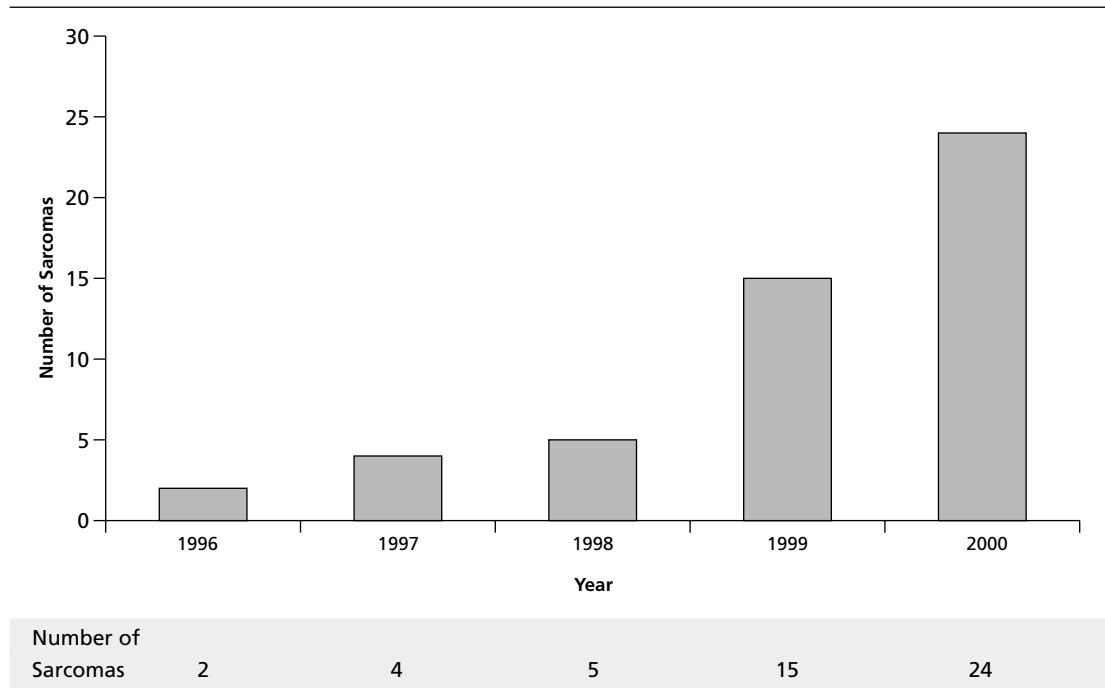
2.4.11.6. Fifty-two cases of suspected lack of efficacy were reported in cats and 47 in dogs between 1995–1999, giving incidences of 0.027 and 0.016 per 10,000 doses respectively (Tables 9 and 10). For cats and dogs, 15 (15.2%) occurred within three weeks of vaccination, 57 (57.6%) after three weeks, and for 27 (27.3%) the onset time was unknown. Of the 47 cases in dogs, 40 were suspected canine parvovirus vaccine lack of efficacy. There was a higher proportion of the Working breed group with suspected lack of efficacy compared to all other breed groups ($p<0.001$): nine of the 11 working breed group cases were Rottweilers (Table 12). However, when Rottweilers were compared to all other breeds for suspected parvovirus lack of efficacy, no significant difference was shown, possibly because of small numbers. (See section 1.3.5).

In cats with suspected lack of efficacy, there appeared to be a higher proportion of Semi-longhairs compared to all other pedigree and non-pedigree breeds ($p < 0.001$) (Table 11): however the Semi-longhairs all came from the same breeding cattery and the significance of this is therefore unclear.

2.4.11.7. Twenty six vaccine-associated sarcomas were reported in cats between 1995–1999 (0.021 incidence per 10,000 doses): the incidence appears to be rising over this period, with a further 24 cases reported in the year 2000 (Table 9, Figure 4). This suggests either increased occurrence, recognition, or reporting rate is occurring. In four of the 24 cases seen in the year 2000 an association with injection site was not stated, and four cases of sarcoma were also reported in cats in the non-vaccine SARs between 1995–2000. The incidence of sarcomas in FeLV vaccines in the UK for 1995–1999 was 0.045 per 10,000 FeLV vaccine doses sold, which compares to 0.009 per 10,000 non-FeLV vaccine doses, and 0.021 per 10,000 doses overall. This compares with estimates of 1-10 per 10,000, for FeLV or rabies vaccines administered in the USA (section 1.4.3.): in the UK, relatively few rabies vaccines (which all have aluminium based adjuvants) are used and also FeLV vaccine usage appears to be relatively low (see section 2.4.1). Although there was a higher percentage of sarcomas amongst vaccine SARs with FeLV vaccines compared with non-FeLV vaccines, this was not significant at the five percent level ($p=0.085$) (Table 11). A breakdown of the 1995–1999 UK figures per vaccine therapeutic group found incidences of 0.011, 0.053, 0.011 and 0.024 per 10,000 doses in therapeutic groups LV, IVAA, IVOA, and MV respectively, the highest figure being in the inactivated, aluminium adjuvanted group. Similarly, chi-squared analysis showed a significantly higher proportion of sarcomas in the IVAA therapeutic group compared to the LV and MV groups ($p<0.001$) (Table 11): numbers in the IVOA group were small for reliable

comparisons. It should be noted that the therapeutic group classification used in this study was based on the last vaccine used.

Figure 4. Number of feline vaccine-associated sarcomas reported to the SAR Surveillance Scheme between 1996 and 2000

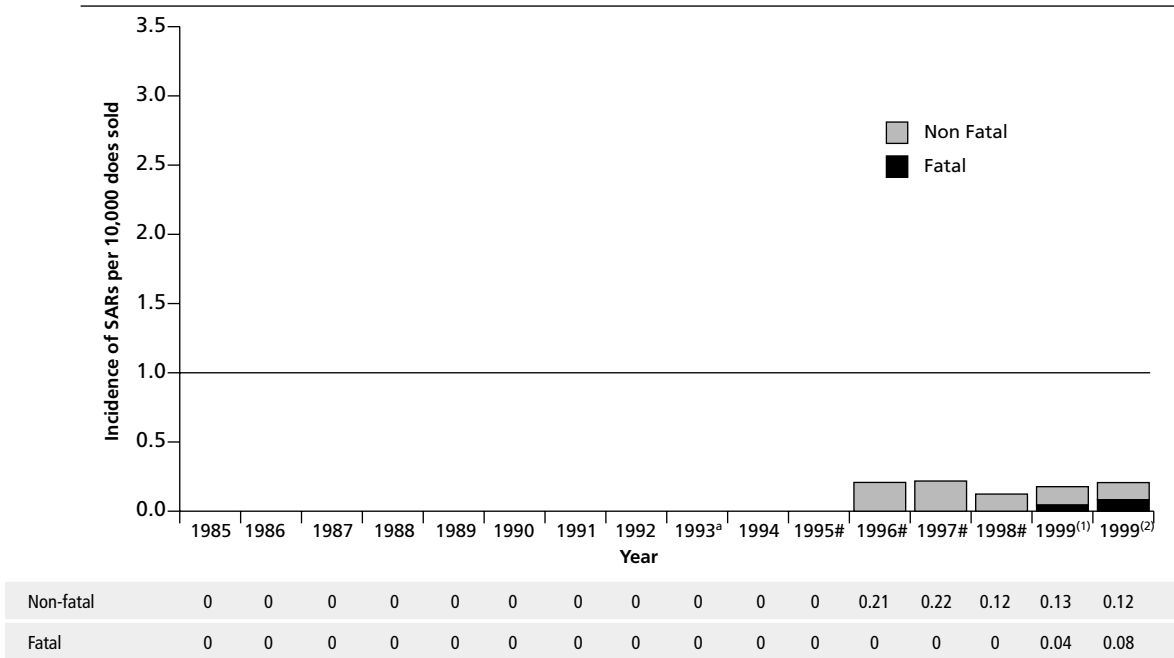


The age analysis showed that amongst cats with vaccine SARs, a significantly higher proportion of cats aged five to ten years or more were in the sarcoma group than in the non-sarcoma group (85% compared to 29%, and proportionately fewer cats aged 0–2 years (0% compared to 50%) ($p < 0.001$) (Table 11). The mean age of vaccine-associated sarcomas for the SAR Surveillance Scheme data between 1995–1999 was found to be 7.91 years ± 2.5 s.d. which compares with a mean age for vaccine sarcomas of 8.1 years ± 2.9 s.d. and that of non-vaccine sarcomas 10.5 years ± 4.1 s.d. found by Hendrick et al⁸⁹. Breed analysis showed that there was a significantly lower proportion of pedigree cats in the sarcoma group compared to the non-pedigree cats ($p = 0.027$) (Table 11).

2.5. Product-related control charts

- 2.5.1. Although pre-licensing laboratory and clinical trials should detect most adverse events associated with product use, not necessarily all of these will be identified, particularly those with a low incidence. Thus national schemes for post-marketing surveillance such as the VMD SAR Surveillance Scheme, although a passive reporting system, are important to detect accumulated problems or those that occur a long time after vaccination or are too rare to be detected in pre-licensing trials. Such schemes identify temporal (but not necessarily causal) relationships between vaccinations and adverse events.
- 2.5.2. The Working Group has produced a system for identifying temporal changes in the incidence of SARs per 10,000 doses sold for each of the vaccines. Plotting SARs incidence rates on a yearly, and more recently, (since 1999) half-yearly period, provides a very powerful way of detecting changes in incidence rates, both within products, and across products. This is an approach widely used in quality control systems^{211, 212}. When used in conjunction with product characteristics information, it offers the possibility of identifying a likely cause. Related approaches are discussed by Siev²¹³.
- 2.5.3. The approaches developed for cat and dog vaccine SARs are likely to have a bearing on non-vaccine products and the Working Group recommends that at a future date the VMD should give consideration to extending the methods and establish similar data sets for monitoring all SARs.
- 2.5.4. Control charts were devised and implemented for each vaccine for cats and dogs for the period 1985–1999 showing the incidence of SARs per 10,000 doses sold: the SARs were grouped into three ABON categories as in section 2.3.6. (i.e. A, B, Bm*; Total Os; and all ABONs). Twenty-three cat vaccines and 35 dog vaccines were represented at various times during this period. Figures 5a, b and c illustrate typical examples of the control charts produced for cat and dog vaccines showing the individual trend of adverse reactions for each vaccine over the fifteen year period. Similar control charts for all vaccines were produced by year, enabling comparison between products for an individual year: typical examples are shown in Figures 5d, e and f. Actual product related control charts were presented as part of this report to the VPC.
- 2.5.5. The control limit or “warning line” for incidence figures which signals that further investigation may be required has been set at 1 or more per 10,000 sold. It is recommended that action will be taken if:
- (i) two out of three consecutive years have incidences of 1 or more per 10,000 for a particular vaccine;
 - (ii) an exceptional incidence of 3 or more per 10,000 occurs on any one occasion;
 - (iii) a consistent rising trend is seen over 5 years, irrespective of whether or not each incidence figure is above the warning line.

Figure 5a. An example of a control chart for the number of vaccine SARs (A, B, Bm*) to a specific product per 10,000 doses sold from 1985–1999**



Number of SARs (A, B, Bm*) reported to a vaccine by year

Year	1985	1986	1987	1988	1989	1990	1991	1992	1993 ^a	1994	1995 [#]	1996 [#]	1997 [#]	1998 [#]	1999 ⁽¹⁾	1999 ⁽²⁾
Non-fatal	0	0	0	0	0	0	0	0	0	0	0	4	9	6	3	3
Fatal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2

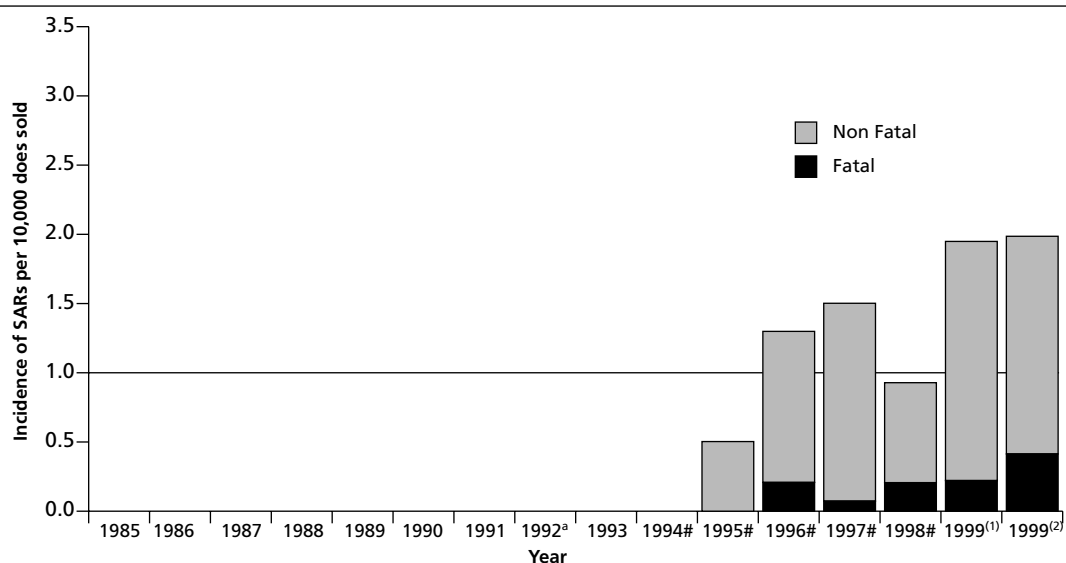
Key

- A, B, Bm*-
- A Reaction probably related to use of the product
- B Reaction possibly related to use of the product
- Bm* Multiple vaccines used concurrently prior to the reaction which is possibly related to use of one or more of the products
- Total O-
- Bm Multiple products (vaccines and pharmaceuticals) used concurrently prior to reaction occurring which is possibly related to one or more of the products used (excluding Bm*)
- B-Opru A concurrent product is thought to possibly be related to the reaction rather than the product reported
- B-factor Multifactorial aetiology but still a possibility that the product is involved in the reaction
- O Insufficient data to assess whether the reaction due to use of the product
- All ABONs-
- A, B, Bm*, Total O and N (reaction not due to use of the product)

- a For figures 5a-c, this represents the first year the product was authorised.
- @ SARs reported during the year but there are no sales figures available
- # Sales figures averaged from periodic safety update reports
- (1) First half of the year (01/01/99 – 30/06/99)
- (2) Second half of the year (01/07/99 – 31/12/99)

** Some details have been changed to preserve confidentiality

Figure 5b. An example of a control chart for the number of vaccine SARs (total O) to a specific product per 10,000 doses sold from 1985–1999**



Non-fatal	0	0	0	0	0	0	0	0	0	0	0.50	1.09	1.43	0.72	1.73	1.57
Fatal	0	0	0	0	0	0	0	0	0	0	0	0.21	0.07	0.21	0.22	0.41

Number of SARs (Total O) reported to a vaccine by year

Year	1985	1986	1987	1988	1989	1990	1991	1992 ^a	1993	1994 [#]	1995 [#]	1996 [#]	1997 [#]	1998 [#]	1999 ⁽¹⁾	1999 ⁽²⁾
Non-fatal	0	0	0	0	0	0	0	0	0	0	4	21	59	35	39	38
Fatal	0	0	0	0	0	0	0	0	0	0	0	4	3	10	5	10

Key

A, B, Bm*-

- A Reaction probably related to use of the product
- B Reaction possibly related to use of the product
- Bm* Multiple vaccines used concurrently prior to the reaction which is possibly related to use of one or more of the products

Total O-

- Bm Multiple products (vaccines and pharmaceuticals) used concurrently prior to reaction occurring which is possibly related to one or more of the products used (excluding Bm*)
- B-Opru A concurrent product is thought to possibly be related to the reaction rather than the product reported
- B-factor Multifactorial aetiology but still a possibility that the product is involved in the reaction
- O Insufficient data to assess whether the reaction due to use of the product

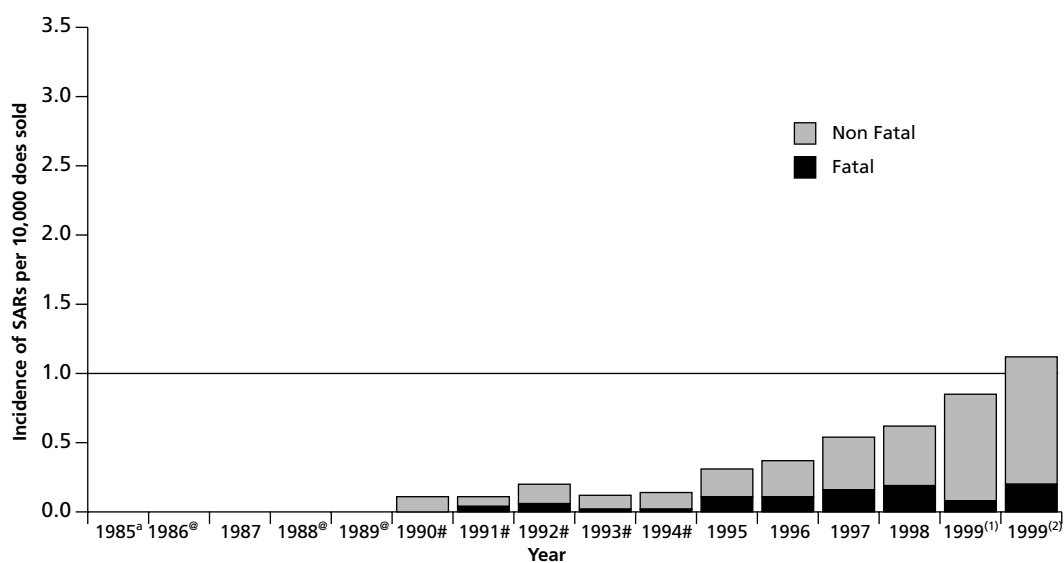
All ABONs-

A, B, Bm*, Total O and N (reaction not due to use of the product)

- a For figures 5a-c, this represents the first year the product was authorised.
- @ SARs reported during the year but there are no sales figures available
- # Sales figures averaged from periodic safety update reports
- (1) First half of the year (01/01/99 – 30/06/99)
- (2) Second half of the year (01/07/99 – 31/12/99)

** Some details have been changed to preserve confidentiality

Figure 5c. An example of a control chart for the number of vaccine SARs (all ABONs) to a specific product per 10,000 doses sold from 1985–1999**



Non-fatal	0	0		0.11	0.08	0.14	0.08	0.1	0.2	0.26	0.36	0.43	0.77	0.92	
Fatal	0	0	0	0	0	0.04	0.06	0.02	0.02	0.11	0.11	0.16	0.19	0.08	0.2

Number of SARs (All ABONs) reported to a vaccine by year

Year	1985 ^a	1986 [@]	1987	1988 [@]	1989 [@]	1990 [#]	1991 [#]	1992 [#]	1993 [#]	1994 [#]	1995	1996	1997	1998	1999 ⁽¹⁾	1999 ⁽²⁾
Non-fatal	0	3	0	1	2	3	2	5	4	5	7	12	18	21	19	23
Fatal	0	0	0	0	0	0	1	2	1	1	4	5	8	9	2	5

Key

A, B, Bm*-

A Reaction probably related to use of the product

B Reaction possibly related to use of the product

Bm* Multiple vaccines used concurrently prior to the reaction which is possibly related to use of one or more of the products

Total O-

Bm Multiple products (vaccines and pharmaceuticals) used concurrently prior to reaction occurring which is possibly related to one or more of the products used (excluding Bm*)

B-Opru A concurrent product is thought to possibly be related to the reaction rather than the product reported

B-factor Multifactorial aetiology but still a possibility that the product is involved in the reaction

O Insufficient data to assess whether the reaction due to use of the product

All ABONs-

A, B, Bm*, Total O and N (reaction not due to use of the product)

a For figures 5a-c, this represents the first year the product was authorised.

@ SARs reported during the year but there are no sales figures available

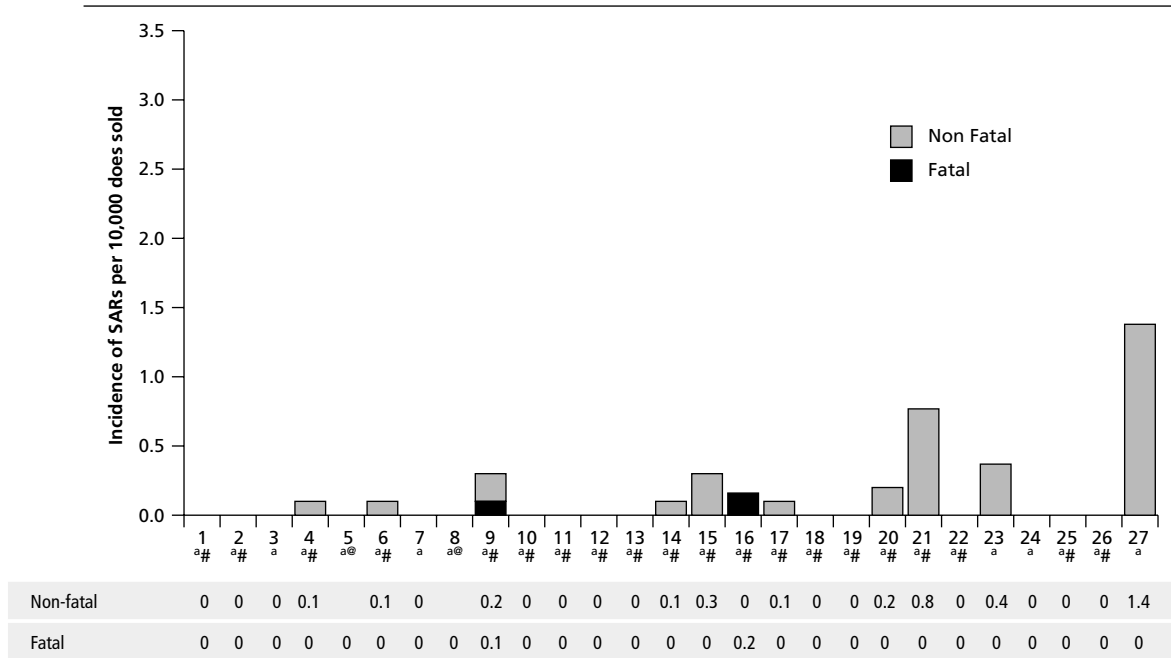
Sales figures averaged from periodic safety update reports

(1) First half of the year (01/01/99 – 30/06/99)

(2) Second half of the year (01/07/99 – 31/12/99)

** Some details have been changed to preserve confidentiality

Figure 5d. An example of a control chart for the number of SARs (A, B, Bm*) per 10,000 doses sold for the individual vaccines for the year 1998



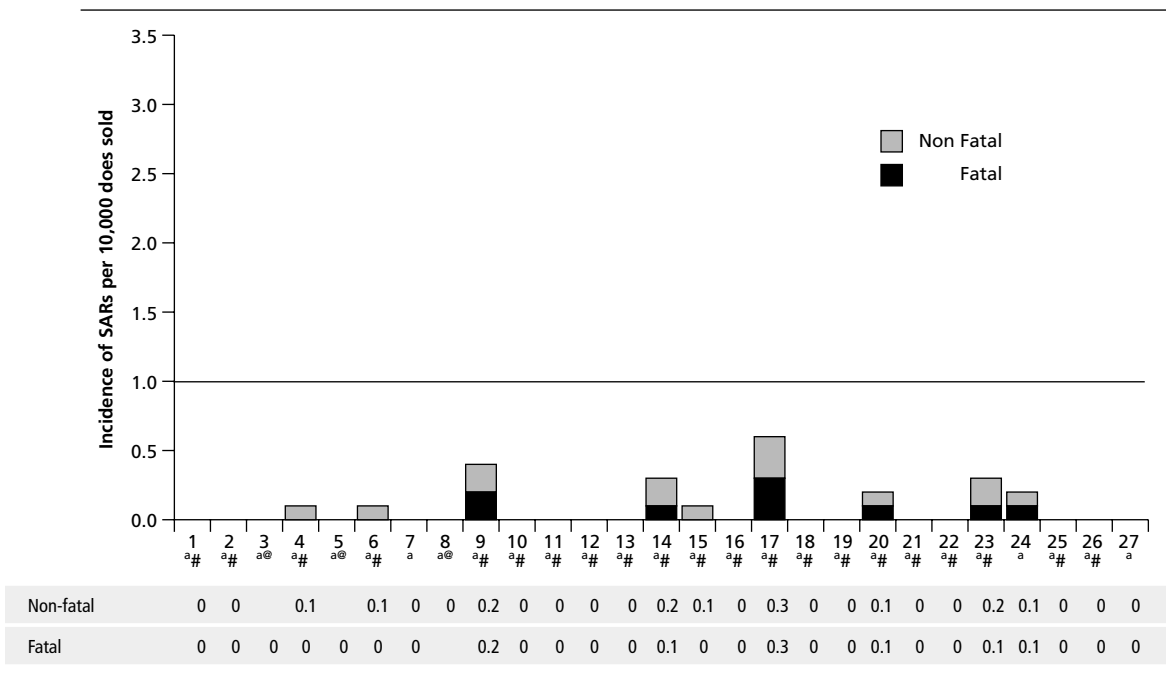
Year 1998, A, B, Bm* Number of SARs reported to the Individual Vaccines																											
Vaccine Code	1a [#]	2a [#]	3a	4a [#]	5a [@]	6a [#]	7a	8a [@]	9a [#]	10a [#]	11a [#]	12a [#]	13a [#]	14a [#]	15a [#]	16a [#]	17a [#]	18a [#]	19a [#]	20a [#]	21a [#]	22a [#]	23a	24a	25a [#]	26a [#]	27a
Non-fatal	0	0	0	2	1	1	0	1	10	0	0	0	0	10	2	0	4	0	0	6	2	0	21	0	0	0	1
Fatal	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0

Key

- A, B, Bm*-
- A Reaction probably related to use of the product
- B Reaction possibly related to use of the product
- Bm* Multiple vaccines used concurrently prior to the reaction which is possibly related to use of one or more of the products
- Total O-
- Bm Multiple products (vaccines and pharmaceuticals) used concurrently prior to reaction occurring which is possibly related to one or more of the products used (excluding Bm*)
- B-Opru A concurrent product is thought to possibly be related to the reaction rather than the product reported
- B-factor Multifactorial aetiology but still a possibility that the product is involved in the reaction
- O Insufficient data to assess whether the reaction due to use of the product
- All ABONS-
- A, B, Bm*, Total O and N (reaction not due to use of the product)

- a For figures 5d-f, this represents whether the authorisation was current for that year.
- @ SARs reported during the year but there are no sales figures available
- # Sales figures averaged from periodic safety update reports

Figure 5e. An example of a control chart for the number of SARs (total O) per 10,000 doses sold for the individual vaccines for the year 1998



Year 1998, Total O, Number of SARs reported to the Individual Vaccines

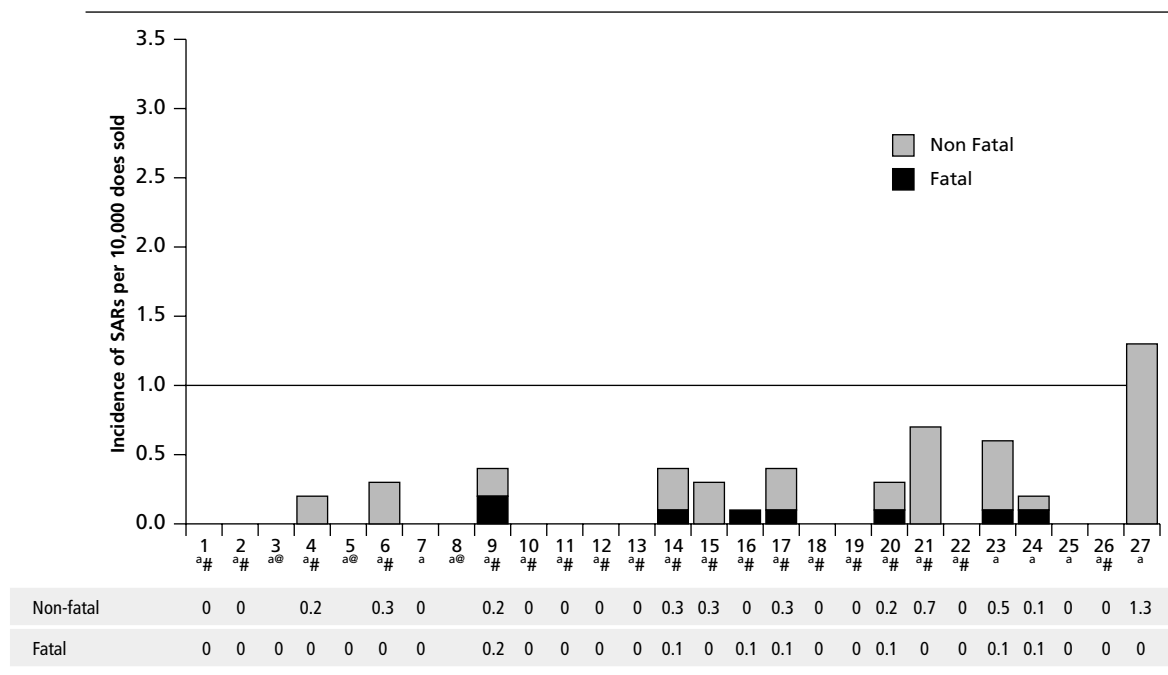
Vaccine Code	1a [#]	2a [#]	3a [@]	4a [#]	5a [@]	6a [#]	7a	8a [@]	9a [#]	10a [#]	11a [#]	12a [#]	13a [#]	14a [#]	15a [#]	16a [#]	17a [#]	18a [#]	19a [#]	20a [#]	21a [#]	22a [#]	23a [#]	24a ^a	25a [#]	26a [#]	27a ^a
Non-fatal	0	0	1	2	4	2	0	0	16	0	0	0	0	15	3	0	1	0	0	5	0	0	9	1	0	0	0
Fatal	0	0	0	0	0	0	0	2	16	0	0	0	0	7	0	0	1	0	0	4	0	0	6	1	0	0	0

Key

- A, B, Bm*-
- A Reaction probably related to use of the product
- B Reaction possibly related to use of the product
- Bm* Multiple vaccines used concurrently prior to the reaction which is possibly related to use of one or more of the products
- Total O-
- Bm Multiple products (vaccines and pharmaceuticals) used concurrently prior to reaction occurring which is possibly related to one or more of the products used (excluding Bm*)
- B-Opru A concurrent product is thought to possibly be related to the reaction rather than the product reported
- B-factor Multifactorial aetiology but still a possibility that the product is involved in the reaction
- O Insufficient data to assess whether the reaction due to use of the product
- All ABONs-
- A, B, Bm*, Total O and N (reaction not due to use of the product)

- a For figures 5d-f, this represents whether the authorisation was current for that year.
- @ SARs reported during the year but there are no sales figures available
- # Sales figures averaged from periodic safety update reports

Figure 5f. An example of a control chart for the number of SARs (all ABONs) per 10,000 doses sold for the individual vaccines for the year 1998



Year 1998, All ABONs, Number of SARs reported to the Individual Vaccines																											
Vaccine Code	1a [#]	2a [#]	3a [@]	4a [#]	5a [@]	6a [#]	7a	8a [@]	9a [#]	10a [#]	11a [#]	12a [#]	13a [#]	14a [#]	15a [#]	16a [#]	17a [#]	18a [#]	19a [#]	20a [#]	21a [#]	22a [#]	23a ^a	24a ^a	25a ^a	26a [#]	27a ^a
Non-Fatal	0	0	1	4	2	3	0	1	21	0	0	0	0	25	5	0	5	0	0	12	2	0	30	1	0	0	1
Fatal	0	0	0	0	0	0	0	2	17	0	0	0	0	8	0	1	2	0	0	5	0	0	6	1	0	0	0

Key

- A, B, Bm*-
- A Reaction probably related to use of the product
- B Reaction possibly related to use of the product
- Bm* Multiple vaccines used concurrently prior to the reaction which is possibly related to use of one or more of the products
- Total O-
- Bm Multiple products (vaccines and pharmaceuticals) used concurrently prior to reaction occurring which is possibly related to one or more of the products used (excluding Bm*)
- B-Opru A concurrent product is thought to possibly be related to the reaction rather than the product reported
- B-factor Multifactorial aetiology but still a possibility that the product is involved in the reaction
- O Insufficient data to assess whether the reaction due to use of the product
- All ABONs-
- A, B, Bm*, Total O and N (reaction not due to use of the product)

- a For figures 5d-f, this represents whether the authorisation was current for that year.
- @ SARs reported during the year but there are no sales figures available
- # Sales figures averaged from periodic safety update reports

- 2.5.6. Amongst the cat vaccines, no vaccine fulfilled the criteria for action in the A, B, Bm* causality code. Four vaccines fulfilled criterion (i) (section 2.5.5) in the “total Os” and “all ABON” groups in the last five years, although all were at less than 3 per 10,000. One vaccine also fulfilled criterion (iii) in the “all ABON” causality code over the past five years, although all annual incidences for this product for the five years were very low (less than one per 10,000). A rising trend in “total Os” or “all ABON”, but not in A, B, Bm*s may reflect a rise in non-specific reporting, or it may reflect a rise in real but possibly unrecognised vaccine reactions which may need further investigation.
- 2.5.7. For dog vaccines, no vaccine fulfilled the criteria for action except one vaccine in “total Os” which fulfilled criterion (iii). However, all the annual incidences for this vaccine over the period in question (1995–1999) were very low (less than 0.5 per 10,000).
- 2.5.8. The average annual incidence per 10,000 doses sold for each product, per number of years authorised, for “all ABON” group is shown in Table 13. Out of 23 cat vaccines where sales figures were available, five had zero average annual incidence, the remainder ranging from 0.07–1.67. Similarly, of 27 dog vaccines where sales figures were available, three had zero average annual incidence, and the rest ranged from 0.03 – 0.79.
- 2.5.9. The validity of the incidence data depends on the integrity of the denominator (sales figures) data, which until 1999, were in some cases averaged, cumulative data (see section 2.2.1.), or unobtainable, and this was an area of concern for the Working Group. From 1999 onwards, six-monthly sales figures have been used and thus the validity of the control charts should increase in strength with each six-monthly period. Nevertheless, some inconsistencies and anomalies were noted with both recent and historic sales data, and companies were given the opportunity to confirm their figures. It was also noted that PSURs are not usage figures but sales figures and that products could be held at wholesalers prior to use by veterinary surgeons/owners of animals. As accurate sales data are fundamental to the validity of the control charts, the Working Group strongly recommends that audited sales figures should be provided by the companies.
- 2.5.10. The Working Group discussed the concept of using a formal risk assessment procedure for evaluating SARs (as in the Report of the CIOMS Working Group IV, 1998¹⁹) and of determining the relative risk for each product with a view to releasing such information into the public domain. However it was felt that at the present time, notwithstanding the current climate of freedom of information, it was inappropriate to do so, given the variable quality of, and many factors influencing the reporting rates and denominator data. It was also noted that in human medicine, although product information is given out, only medically substantiated SAR reports are used in the MCA report (see section 2.2.1) making the data released more reliable.
- 2.5.11. At the present time therefore, the Working Group recommends that if deviations from the normal trend occur for a particular vaccine in the control charts, the company should be approached first for a possible explanation. Subsequent analysis of the database as in section 2.4. would then be carried out if appropriate. If it was decided that the risk/benefit of the product had altered significantly, then the licensing authority, usually in conjunction with the VPC, would consider what action needed to be taken in terms of the product itself, and the need to inform the veterinary profession and the end-user.

Table 13: Ranking table of the average annual incidence of vaccine SARs for each cat and dog vaccine per 10,000 doses sold between 1985–1999 or over the period when sales figures were available

Cat																											
Vaccine code	1	13	8	19	7	12	15	10	16	6	18	3	5	11	2	20	9	21	4	14	17*	22	23				
Overall Incidence	1.67	1.65	1.46	0.94	0.89	0.61	0.55	0.49	0.41	0.39	0.34	0.32	0.31	0.29	0.27	0.26	0.13	0.07	0.00	0.00	0.00	0.00	0.00				
Dog																											
Vaccine code	19	21	4	20	23	9	3	22	24	10	12	27	14	16	17	18	11	6	25	26	5	15	1	2	8*	7	13
Overall Incidence	0.79	0.62	0.52	0.43	0.41	0.39	0.38	0.36	0.32	0.31	0.30	0.29	0.26	0.21	0.20	0.19	0.10	0.10	0.06	0.05	0.04	0.03	0.03	0.03	0.00	0.00	0.00

* SARs do exist to this product however no sales figures are available

2.6. Resource implications

2.6.1. The collation and interpretation of data is central to the work of the SAR Surveillance Scheme. Most of this activity revolves around the records of reported SARs and the scrutiny of information on vaccine product ingredients combined with the interpretative experience and expertise of the surveillance team in identifying trends. The recent developments associated with the TIGRESS database for recording the details associated with each vaccine adverse reaction has proved invaluable and this investment in information technology (IT) now represents an important resource.

During the course of the review it was recognised that the function and efficiency of the SAR Surveillance Scheme team could be enormously enhanced by making greater use of new analytical methods and IT. Consequently the Working Group, in association with the surveillance team, explored (a) the use of control charts for monitoring trends associated with each vaccine over time and (b) the development of the multivariate component data set using spreadsheet information systems. Both of these approaches have now been successfully piloted. This has required extensive use of manual data extractions from a variety of information sources, and full scale use of the approaches will require IT expertise. It is therefore recognised that specialist IT support should be incorporated within the SAR Surveillance Scheme function.

The Working Group concludes that:

- IT support should be provided for routine maintenance and periodic reviews of the TIGRESS database;
- an early detection system for adverse reactions associated with each vaccine should be implemented using controls charts; and
- that these approaches should be extended from vaccines to all veterinary products.

The Working Group advises that the SAR Surveillance Scheme team should further evaluate the use and analysis approaches to the multivariate component data set.

2.6.2. In the longer term, the Working Group recommends that a way should be found to allow the data held by the VMD SAR Surveillance Scheme to be analysed in partnership with the wider research community. The Working Group recognises that there are issues of confidentiality and reliability of data that need to be addressed before this can take place. Nevertheless, the Working Group considers that this represents a means whereby there can be expert, independent and ongoing scrutiny of SAR Surveillance Scheme data to identify significant associations and newly emerging trends.

Section 3:

The Feasibility and Value of Conducting a Survey of Feline and Canine Post Vaccination Reactions

- 3.1. There is clear evidence that the SAR Surveillance Scheme has and will continue to play an increasingly important role in the identification and cause of adverse reactions. Recent improvements in the design of the collection and analysis of the data will lead to a process which will further enhance the value of the SARs data and its potential for early identification of health risks that could be associated with cat and dog vaccinations
- 3.2. It is recognised that the SAR Surveillance Scheme principally addresses the early detection and cause of adverse reactions occurring at point of treatment. However, broader issues of the occurrence of long-term, low incidence, or unrecognised adverse effects will have to be addressed by epidemiological studies. Although several studies have recently been reported or initiated, there are major constraints to identifying such adverse reactions.
- 3.3. In the first instance, such adverse events have low rates of occurrence in vaccinated populations. To detect changes in the incidence of rare events requires large representative samples of both vaccinated and unvaccinated control animals to be compared in order to have sufficient statistical power to substantiate any effect that could arise due to vaccination. Secondly, accessing information on unvaccinated animals is particularly difficult in view of the large proportion of companion animals that currently receive some form of vaccination during their life span.
- 3.4. Several epidemiological approaches could be adopted. A cross-sectional case-control study could be applied at a single point in time. Animals could be classified into groups: those with a particular adverse reaction (cases) and those without (controls). Vaccination history, sex, breed, nutrition etc. could then be examined as risk factors. Case-control studies are often preferable because they are fast, less expensive and suitable for rare diseases. However, they have the disadvantage of requiring recalled information that is often inaccurate and unreliable. This is likely to be the case for cat and dog populations. Moreover, it would not be possible to estimate rates of disease from such a study because of the absence of denominator data and data not being collected over time.
- 3.5. Alternatively, a prospective cohort study could follow a large number of vaccinated and unvaccinated animals to monitor the rate at which adverse reactions such as sarcomas occur in animals. Comparisons could be made for animals of age one year, two years, three years and so on up until ten years. The study would reveal whether vaccination produced a higher proportion of animals with a particular long term adverse effect, it would indicate age of onset of the adverse reaction, the time of the adverse effect following primary and booster vaccinations etc. Moreover, a 'dose response' effect could be tested by comparing the incidence of the adverse effect in animals vaccinated one, twice, three times etc. Health records of each animal would have to be maintained, in particular all events pertaining to vaccination.

- 3.6. The Working Group conclude that although a cohort study would have the disadvantage of taking time and also being expensive, it would have the advantage of providing better quality information, providing estimates of relative risk and disease incidence rates. Moreover, such a long-term surveillance scheme would provide information on a large number of treatment related problems and it could pioneer the establishment of a national database for small-animal populations that could be used for monitoring the effects of veterinary medicines other than vaccines. This is an approach which has been adopted in some human studies, and in particular in the ongoing Avon Longitudinal Study of Parents and Children (2001) (formerly the Avon Longitudinal Study of Pregnancy and Childhood) (2000) (ALSPAC) study,¹⁸ although it is recognised that there may be some logistical problems associated with this approach.
- 3.7. Irrespective of what type of study is implemented, statistical power calculations indicate that a very large sample of animals would have to be studied if there were to be any reasonable prospect of detecting long term increased risk associated with vaccination in view of many of the adverse events being very rare. Small-scale short term studies are not likely to be sufficiently discerning. Such an investigation would require commitment and need to be carried out under a national management programme using veterinary practices, University veterinary hospitals, research centres, diagnostic laboratories etc. Central to the study would be the establishment of a centralised database to deal with the collection and analysis of data. Funding and co-ordination would be a major challenge. However, considering the number of stake holders i.e. industry, government, charities, universities, research councils, welfare groups etc. it could become cost effective and also generate information beyond the immediate goals of the study.

Section 4:

Current Vaccination Programmes and Current Advice on Repeat Immunisation

- 4.1. For the majority of current cat and dog vaccines authorised in the UK, re-vaccination intervals of one year are recommended by the manufacturers based on controlled experimental challenge data and field studies carried out for each component of each individual product. Because of expense, time, and animal welfare considerations, such studies tend to determine a minimum rather than a maximum duration of immunity. In addition, in multivalent vaccines the claim for duration of immunity has to reflect the component with the shortest duration demonstrated.
- 4.2. The Working Group concluded from the literature review (section 1.6.) that there is some reasonable evidence that duration of protection may be significantly longer than one year for some diseases such as canine distemper, canine parvovirus 2 infection, infectious canine hepatitis, and feline panleucopenia. For other diseases such as feline herpesvirus and feline calicivirus infection, whilst protection may last longer in some animals, it is likely to be incomplete. Such conclusions are generally based, however, on extrapolation from the natural disease, from serological studies, and from studies on different vaccines within a product category using various challenge systems which may not reflect the field situation.
- 4.3. The Working Group recognises that ideally, in the longer term, the true duration of immunity, rather than the minimum duration should be established for each disease and for each vaccine, under normal conditions of use. It is recognised that this may be difficult to achieve, but ways in which it may be facilitated include:
 - (i) undertaking long-term experimental challenge studies – but bearing in mind the limitations outlined in section 1.6.3;
 - (ii) developing standardised potency tests for each disease and their vaccines, where European Pharmacopoeia monographs are not available;
 - (iii) standardising serological assays between veterinary laboratories;
 - (iv) where appropriate, developing *in vitro* correlates of protection, and determining duration of immunity by monitoring vaccinated sentinel groups in the field;
 - (v) developing centralised surveillance schemes and carrying out epidemiological studies (including modelling studies) to determine disease incidence and risk factors for a disease;
 - (vi) obtaining audited vaccine sales figures and population estimates for cats and dogs such that the level of vaccine coverage in the population can be accurately determined and in the long-term increased.
- 4.4. At present, the Working Group concludes that there is currently insufficient information to propose re-vaccination intervals on product literature other than those proposed by the manufacturer, and approved by the regulatory process. However, the Working Group recommends that for both cat and dog vaccines a statement be added to the product literature indicating that the regime for booster vaccinations is based on a minimum duration of immunity rather than a maximum, and that a risk/benefit assessment should be

made for each individual animal by the veterinary surgeon in consultation with the owner so that, if required, an informed choice may be made by the owner with respect to the necessity for a particular vaccine and the frequency of its use. The assessment should include discussion on the likelihood of exposure, available data on duration of immunity, and the risks related to vaccination. The Working Group also recommends that more information should be provided for veterinary surgeons and owners by Marketing Authorisation Holders in order to facilitate such decision-making.

In view of the findings of the Working Group on vaccine-associated feline sarcomas, (see section 2.4.11.7) and the seriousness of the condition, the Working Group recommends that a generic warning should be placed on the product literature for all feline vaccines administered by injection. The proposed warning should state that current knowledge suggests that, very rarely, sarcomas may occur at the site of vaccination, and that although other vaccines may be involved, there is some evidence to suggest that this may be more associated with the use of aluminium adjuvanted vaccines. The situation with respect to the role of FeLV vaccines in general, or the use of other adjuvants, is unclear and should be kept under review. The Working Group further recommends that discussion of such risks should be part of the informed risk/ benefit assessment carried out, as above, by the veterinary surgeon in consultation with the owner.

It is also suggested that professional and educational bodies in the UK should recommend that good veterinary practice should include the use of standardised vaccination procedures, as recommended by VAFSTF, in terms of sites of vaccination, in order to help identify causes of such reactions and aid treatment. VAFSTF also note that any vaccine site masses that persist for greater than three months following vaccination; are greater than 2cm in diameter; or are increasing in size one month after vaccination, should be biopsied, and if malignant, be surgically excised. Advanced diagnostic imaging to identify the full extent of the tumour is suggested before extensive surgical excision is carried out^{99, 101}.

- 4.5. In the longer term, manufacturers and other organisations should be encouraged to obtain data on disease incidence and duration of immunity in the field. Epidemiological studies should help identify risk factors for a disease. Once such information is available it may be possible to alter recommended revaccination intervals, initially on an individual vaccine basis, and perhaps, in the longer term, overall. It is recognised that the current system maximises protection for the individual and that in some cases this may be helpful, since there may be biological variation in response. However, in the longer term, population immunity should be increased such that exposure to infection is reduced. It is also recommended that manufacturers are encouraged to market single component as well as multivalent products in order to retain flexibility in their use.
- 4.6. The Working Group also recommends that the EU Member States' regulatory authorities produce clear legislation and guidelines which encourage determination of as long a duration of immunity for each product as possible. It is important that the regulatory authorities distinguish between companion animals in their guidelines, and food-producing animals, in view of the longer life expectancy of companion animals and the likelihood of their receiving many repeated vaccinations over their lifetime.

Acknowledgements

The Working Group would like to thank all the many people, organisations and institutions who contributed to this report, but in particular, Pedigree Masterfoods for their contribution of GfK Home Audit 1999 data on sex and age distribution of cats and dogs in the UK; the veterinary practices who contributed to the survey on primary and booster vaccinations administered in their practice in 1999; Mr David Sutton, Chairman of the Companion Animal Veterinary Group, National Office of Animal Health Limited; Professor Michael Day, Department of Pathology and Microbiology, University of Bristol ; Professor Philip H. Kass, Associate Professor of Epidemiology, Department of Population Health and Reproduction, School of Veterinary Medicine, University of California; Dr Michael Herrtage, Queens Veterinary School Hospital, University of Cambridge; and Dr Martha Spagnuolo-Weaver, VMD Immunologicals Team.

Appendix 1a


Sources of Information

Information on issues which related to the objectives of the Working Group was obtained from a variety of sources:

- (i) the scientific literature
- (ii) lay articles and those related to consumer concerns.
- (iii) requests for information from veterinary schools in the USA and UK; to licensing authorities in the USA and EU; and to various other UK professional bodies including veterinary and trade associations and animal groups such as the Kennel Club and the Governing Council of the Cat Fancy. (In general, response rates were relatively low, but some useful information was obtained.)
- (iv) information obtained through the Internet, including useful client information prepared by various USA interest groups and USA veterinary schools, and information provided by the American Veterinary Medical Association (AVMA) Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) www.avma.org/vafstf¹
- (v) guidelines developed for USA practitioners, in particular, the Feline Vaccine Guidelines from the Advisory Panel on Feline Vaccines^{2,3}, and the AVMA Council for Biologics and Therapeutics (www.avma.org)⁴
- (vi) EU legislation; EU Directive 81/851 Article 42b⁵; Committee for Veterinary Medicinal Products guidelines (CVMP Note for Guidance (NfG): Pharmacovigilance of Veterinary Medicinal Products(CVMP/183/96)⁶); The International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs) VICH GL24 CVMP/547/00⁷ and Veterinary Medicines Directorate (VMD) Guidance Animal Medicines European Licensing Information and Advice (AMELIA) 12⁸; EU directive 81/852/EEC⁹; 'Requirements for immunological veterinary medicinal products' Title II, part 8 of the Annex to EC directive 92/18/EEC¹⁰; the European Pharmacopoeia 1997 Evaluation of Safety of Veterinary Vaccines section 5.2.6 and Evaluation of Efficacy of Veterinary Vaccines section 5.2.7¹¹; CVMP guideline III/5736/94 'Specific requirements for the production and control of live and inactivated viral and bacterial vaccines for cats and dogs'¹²; CVMP Note for Guidance: Duration Of Protection Achieved By Veterinary Vaccines CVMP/682/99¹³.
- (vii) relevant areas in the human field, in particular, literature searches of vaccine-associated safety issues including the possible association of autism with measles, mumps and rubella (MMR) vaccination in human infants^{14,15}; Medicines Control Agency¹⁶; Committee on Safety of Medicines (1999)¹⁷; the Avon Longitudinal Study of Parents and Children (2001) (formerly the Avon Longitudinal Study of Pregnancy and Childhood (2000)) (ALSPAC) (www.ich.bris.ac.uk/alspacext/Default.html)¹⁸; Report of Council for International Organisations for Medical Science (CIOMS) Working Group IV Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals (a US-discussion paper on periodic safety updates and risk benefit analysis)¹⁹; guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Safety Data Management: periodic safety update reports for marketed drugs (ICH Harmonised Tripartite Guideline CPMP/ICH/288/95 Adopted December 1996²⁰).

Appendix 1b

Yellow Forms (MLA252A)



Department for Environment, Food and Rural Affairs
Veterinary Medicines Directorate
 FREEPOST KT 4503, Woodham Lane, New Haw, Addlestone,
 Surrey KT15 3BN
 Tel. No 01932 338427 Fax + 01932 338816

IN CONFIDENCE

Suspected Adverse Reaction Surveillance Scheme (SARSS)
Animal suspected adverse reaction report

● This form should be completed in BLOCK LETTERS and sent to the FREEPOST address given above whenever a suspected adverse reaction is observed in animals including birds and fish, during or after the use of a veterinary medicine.

All reporters MUST complete this section

Full name of product: _____

Company name (as label): _____ Supplier name: _____

Has the form to be copied to the Company (Matching Administration) in order to help that they investigate the reported suspected adverse reaction to their product? This may wish to contact you for the details. If you do, not want the name and address of the form to be revealed? YES NO

Has the Company already been informed? YES NO

Your reference No. (if any): _____

Full name and address of person submitting this form to VMD: _____

Full address to manufacturer if not occurring: _____

Full name and address of veterinarian involved: _____

Details of animal suspected adverse reaction(s)

Reason for using product: _____

No. of animals treated: _____ No. of animals reacting: _____ No. of deaths: _____ Actual amount of product administered: _____

Administered by: _____ Date of first administration: _____ Country of origin: _____

Site & nature of clinical signs: _____ Frequency of product administration: YES NO If YES, number of times: _____

Date	Species/Breed	Weight (kg)	Sex	Name of case (including time of onset and duration of symptoms)

Label name of product given concurrently (if any): _____

Immediate treatment given (if any): _____

Previous vaccination history or administration of product involved in suspected adverse reaction (product number) and batch number: _____

Post mortem and/or laboratory tests:
 Have any post mortem or laboratory tests been performed? YES NO

If YES please attach notes or forward to VMD in due course

*The product number is preceded by PL, VM or MA.

Comments: _____
 Extra forms: Tick this box if you wish to request more forms.

Receipt of this form will be acknowledged

MLA252A (Rev 8.01)

Appendix 1c

Governing Council of the Cat Fancy (GCCF) Recognised Breeds

Longhair (Persian)	Semi-longhair	British Shorthair	Foreign	Oriental	Burmese	Siamese
Bicolour	Birman	Bicolour	Abyssinian	Angora	Self	Self-pointed
Cameo	Mainecoon	Colour-pointed	Asian (incl. Bombay and Burmilla)	Oriental Selves (incl. Havana and Foreign White)	Tortie	Tabby – pointed (incl. Tortie Tabby)
Chinchilla	Norwegian Forest cat	Manx	Tiffanie (longhaired Asian)	Shaded		Tortie – pointed
Colourpoint	Ragdoll	Self	Bengal	Smoke		Balinese (Longhaired Siamese)
Exotic short haired (persian type)	Somali	Smoke	Cornish Rex	Tabby (Incl. Tortie Tabby)		
Golden	Turkish Van	Tabby (incl. Tortie Tabby)	Devon Rex	Tortie		
Pewter		Tipped	Korat			
Self		Tortie (incl. Tortie and White)	Ocicat			
Shaded			Russian			
Smoke			Singapura			
Tabby (incl. Tortie Tabby)			Tonkinese			
Tortie (Incl. Tortie and White)						

For the purposes of this report further categories were added to the above list to include the following

Pedigree Crosses

Non Pedigree – Domestic shorthair (DSH), Domestic longhair (DLH)

Other – This category included animals where the exact breed grouping was not stated and therefore they could not be classified into one of the above groups.

Web site – http://ourworld.compuserve.com/homepages/GCCF_CATS/breed.htm (accessed 11/05/01)

Appendix 1c – Continued

Kennel Club UK Recognised Breeds

Hound	Toy	Gun	Working	Utility	Terrier	Pastoral
Afghan Hound	Affenpinscher	Bracco Italiano	Alaskan Malamute	Boston Terrier	Airedale Terrier	Anatolian Shepherd Dog
Basenji	Australian Silky Terrier	Brittany	Beauceron	Bulldog	Australian Terrier	Australian Cattle Dog
Basset Blue de Gascogne	Bichon Frise	English Setter	Bernese Mountain Dog	Canaan Dog	Bedlington Terrier	Australian Kelpie
Basset Fauve De Bretagne	Bolognese	German Short-Haired Pointer	Bouvier de Flanders	Dalmatian	Border Terrier	Australian Shepherd Dog
Basset Griffon Vendeen (grand)	Cavalier King Charles Spaniel	German Wired-Haired Pointer	Boxer	French Bulldog	Bull Terrier (Miniature)	Bearded Collie
Basset Griffon Vendeen (petit)	Chihuahua (long coat)	Gordon Setter	Bullmastiff	German Spitz (Klein)	Bull Terrier (Standard)	Belgian Shepherd Dog – Groenendael
Basset Hound	Chihuahua (smooth coat)	Hungarian Wirehaired Vizsla	Dobermann	German Spitz (Mittel)	Cairn Terrier	Belgian Shepherd Dog – Laekenois
Beagle	Coton Tuléar	Irish Red and White Setter	Dogue de Bordeaux	Japanese Akita	Ceskey Terrier	Belgian Shepherd Dog – Malinois
Bloodhound	English Toy Terrier	Irish Setter	Eskimo Dog	Japanese Shibu Inu	Dandie Dinmont Terrier	Belgian Shepherd Dog – Tervueren
Borzoi	Griffon Bruxellois	Italian Spinone	Giant Schnauzer	Japanese Spitz	Fox Terrier (Smooth)	Bergamasco
Dachshund (Standard Long haired)	Havanese	Kooikerhondje	Great Dane	Keeshond	Fox Terrier (Wire)	Briard
Dachshund (Miniature Long haired)	Italian Greyhound	Large Munsterlander	Hovawart	Lhaso Apso	Glen of Imaal Terrier	Collie (Rough)
Dachshund (Standard Smooth haired)	Japanese Chin	Nove Scotia Duck Tolling retriever	Leonberger	Miniature Schnauzer	Irish Terrier	Collie (Smooth)
Dachshund (Miniature Smooth haired)	King Charles Spaniel	Pointer	Mastiff	Poodle (Miniature)	Kerry Blue Terrier	Estrela Mountain Dog

Appendix 1c – Continued

Hound	Toy	Gun	Working	Utility	Terrier	Pastoral
Dachshund (Standard Wire haired)	Lowchen	Retriever (Chesapeake bay)	Neopolitan Mastiff	Poodle (Standard)	Lakeland Terrier	Finnish Lapphund
Dachshund (Minature Wire haired)	Maltese	Retriever (Curly Coat)	Newfoundland	Poodle (Toy)	Manchester Terrier	German Shepherd Dog
Deerhound	Miniature Pinscher	Retriever (Flat Coat)	Pinsher	Schipperke	Norfolk Terrier	Hungarian Kuvaz
Elkhound	Papillon	Retriever (Golden)	Portugese Water Dog	Schnauzer (Standard)	Norwich Terrier	Hungarian Puli
Finnish Spitz	Pekingese	Retriever (Labrador)	Rottweiler	Shar Pei	Parson Russell Terrier	Komondor
Foxhound	Pomeranian	Spaniel (American Cocker)	St Bernard	Shih Tzu	Scottish Terrier	Lancashire Heeler
Grande Bleu De Gascoigne	Pug	Spaniel (Clumber)	Siberian Husky	Tibetan Spaniel	Sealyham Terrier	Maremma Sheepdog
Greyhound	Yorkshire Terrier	Spaniel (Cocker)	Tibetan Mastiff	Tibetan Terrier	Skye Terrier	Norwegian Buhund
Hamiltonstovare		Spaniel (English Springer)			Soft Coated Wheaten Terrier	Old English Sheep Dog
Ibizian Hound		Springer (Field)			Staffordshire Bull Terrier	Polish Lowland
Norwegian Lundehound		Spaniel (Irish Water)			Welsh Terrier	Pyrenean Sheepdog
Otterhound		Spaniel (Sussex)			West Highland White Terrier	Samoyed
Pharaoh Hound		Spaniel (Welsh Springer)				Shetland Sheepdog
Rhodesian Ridgeback		Spanish Water Dog				Swedish Lapphund
Saluki		Weimaraner				Swedish Vallhund
Segugio Italiano						Welsh Corgie – Cardigan
Sloughi						Welsh Corgie – Pembroke
Whippet						

For the purposes of this report further categories were added to the above list to include the following –

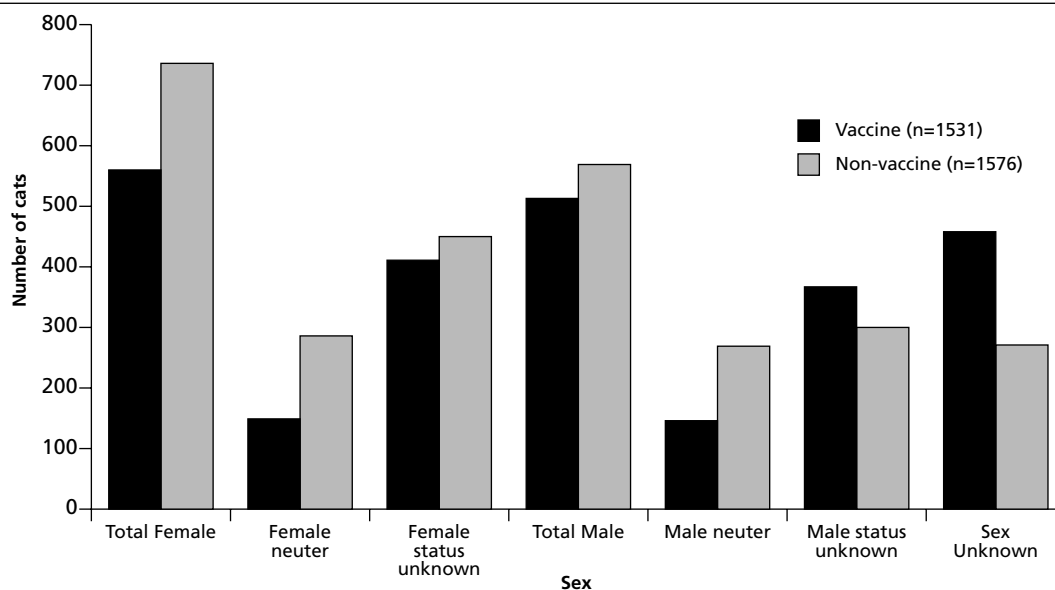
Crossbreed

Other – Breeds not recognised by the Kennel Club

Web Site – <http://web.ukonline.co.uk/ukdogs/> (accessed 11/05/01)

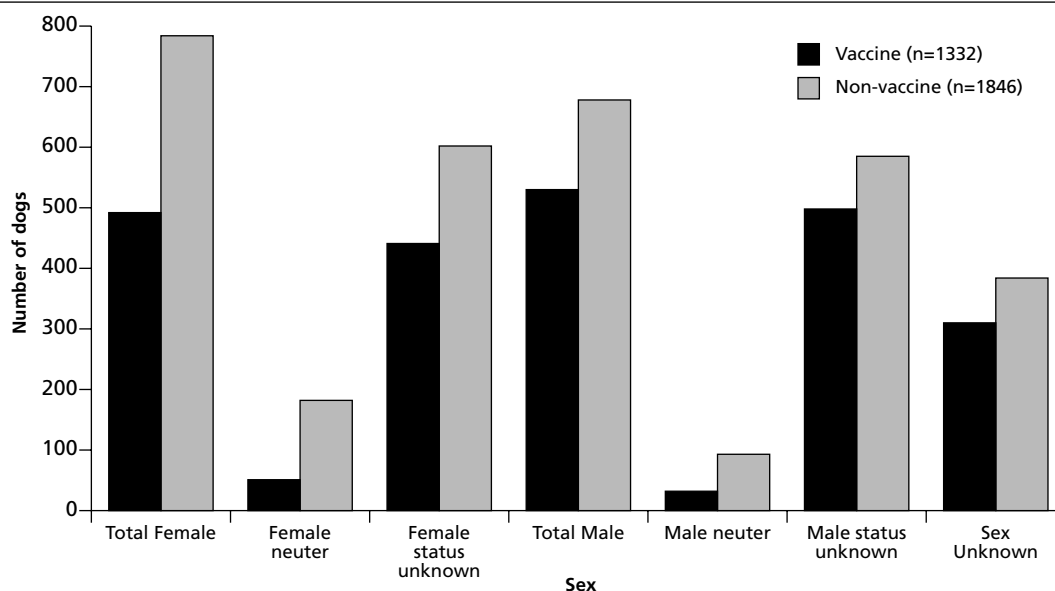
Appendix 1d

Appendix 1d(i). Vaccine and non-vaccine SARs (1985–1999): number of cats reported by sex*



Vaccine (n = 1531)	560	149	411	513	146	367	458
Non-vaccine (n = 1576)	736	286	450	569	269	300	271

Appendix 1d(ii). Vaccine and non-vaccine SARs (1985–1999): number of dogs reported by sex*

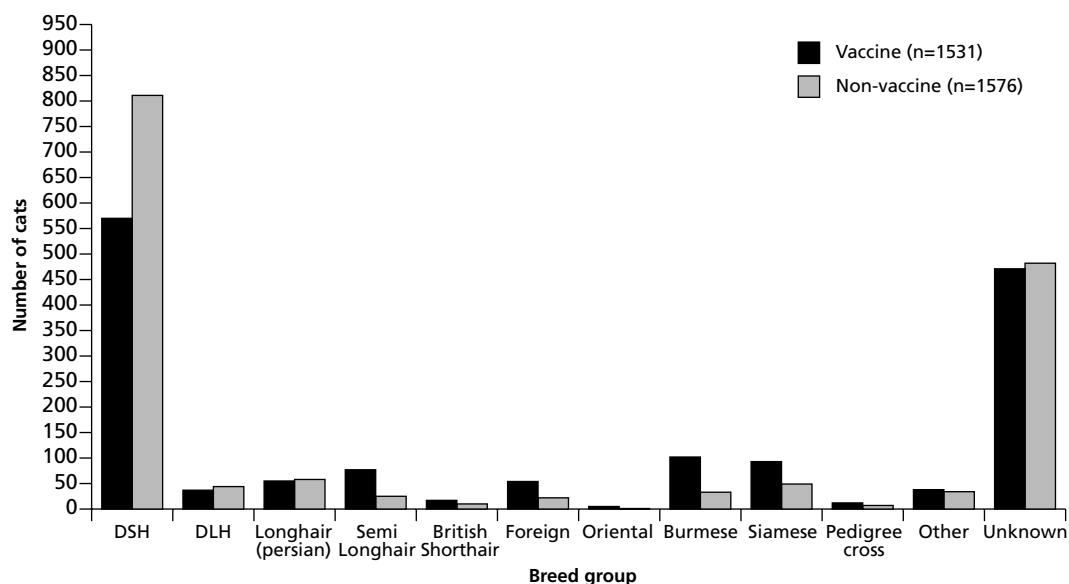


Vaccine (n = 1332)	492	51	441	530	32	498	310
Non-vaccine (n = 1846)	784	182	602	678	93	585	384

* For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

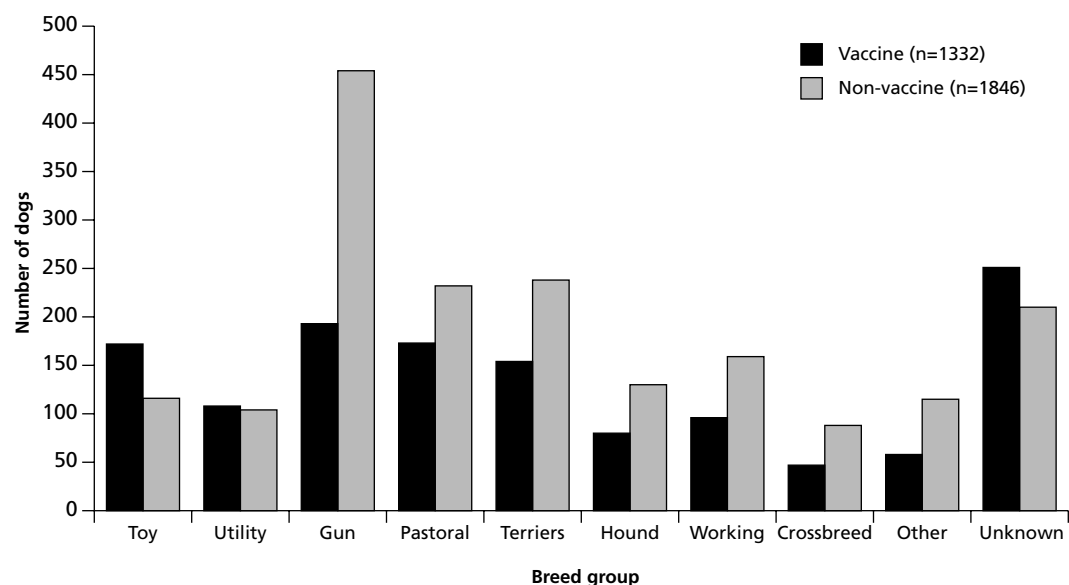
Appendix 1e

Appendix 1e(i). Vaccine and non-vaccine SARs (1985–1999): number of cats reported by breed*



Vaccine (n = 1531)	570	37	55	77	17	54	5	102	93	12	38	471
Non-vaccine (n = 1576)	811	44	58	25	10	22	1	33	49	7	34	482

Appendix 1e(ii). Vaccine and non-vaccine SARs (1985–1999): number of dogs reported by breed*

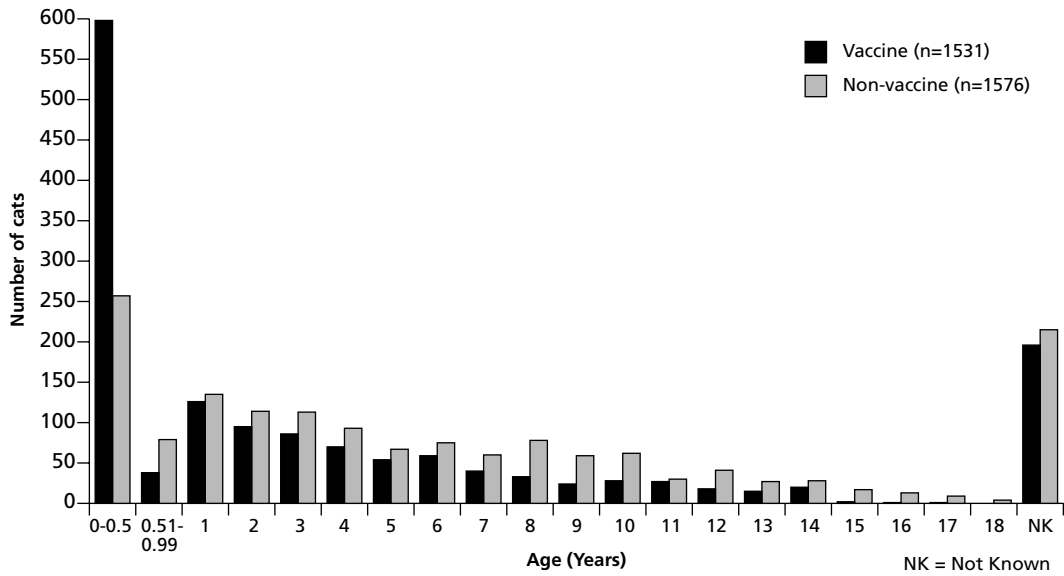


Vaccine (n = 1332)	172	108	193	173	154	80	96	47	58	251
Non-vaccine (n= 1846)	116	104	454	232	238	130	159	88	115	210

* For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

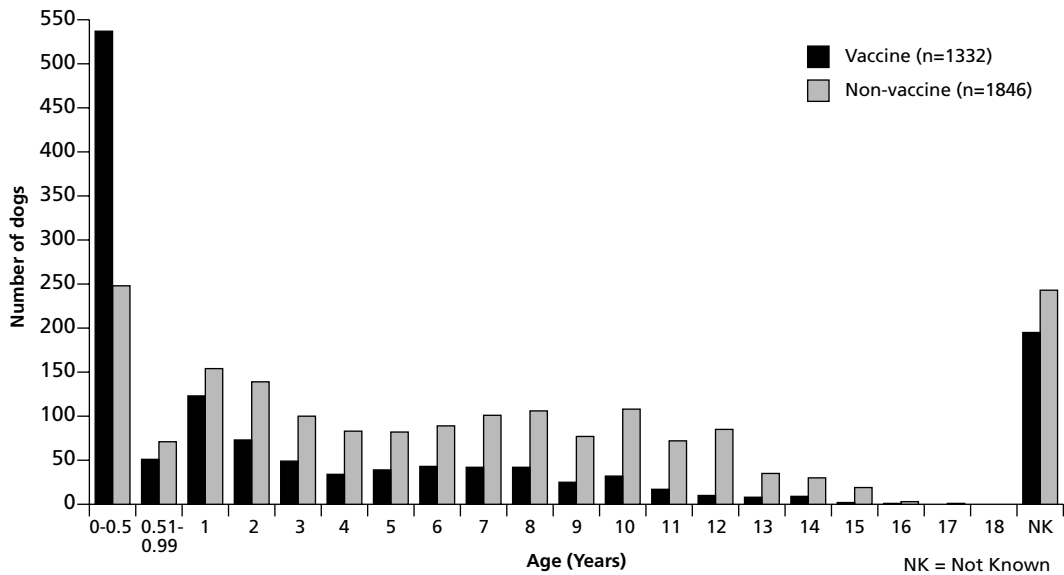
Appendix 1f

Appendix 1f(i). Vaccine and non-vaccine SARs (1985–1999): number of cats reported by age*



Vaccine (n = 1531)	598	38	126	95	86	70	54	59	40	33	24	28	27	18	15	20	2	1	1	0	196
Non-vaccine (n = 1576)	257	79	135	114	113	93	67	75	60	78	59	62	30	41	27	28	17	13	9	4	215

Appendix 1f(ii). Vaccine and non-vaccine SARs (1985–1999): number of dogs reported by age*

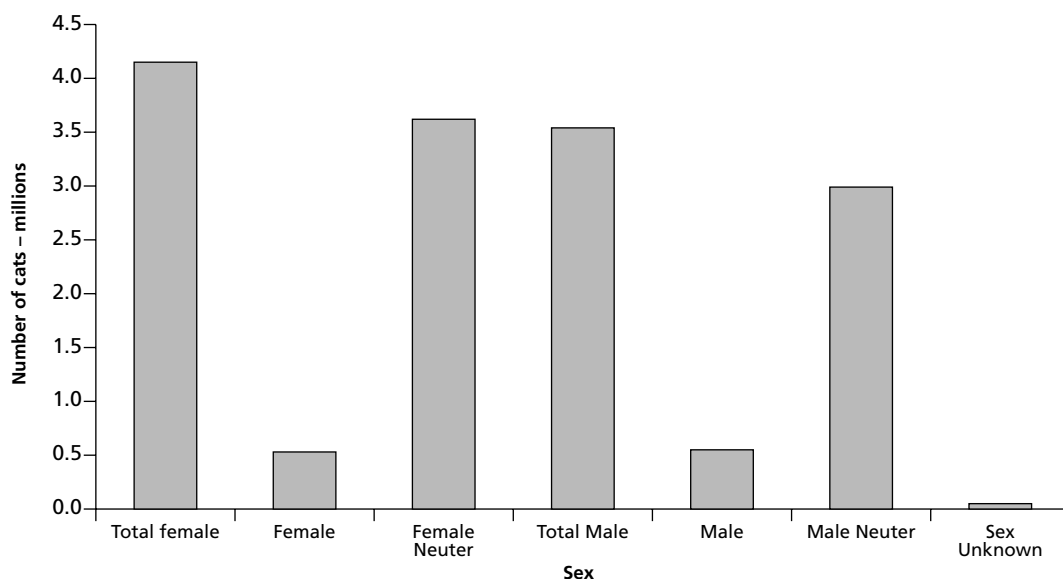


Vaccine (n = 1332)	537	51	123	73	49	34	39	43	42	42	25	32	17	10	8	9	2	1	0	0	195
Non Vaccine (n = 1846)	248	71	154	139	100	83	82	89	101	106	77	108	72	85	35	30	19	3	1	0	243

* For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

Appendix 1g

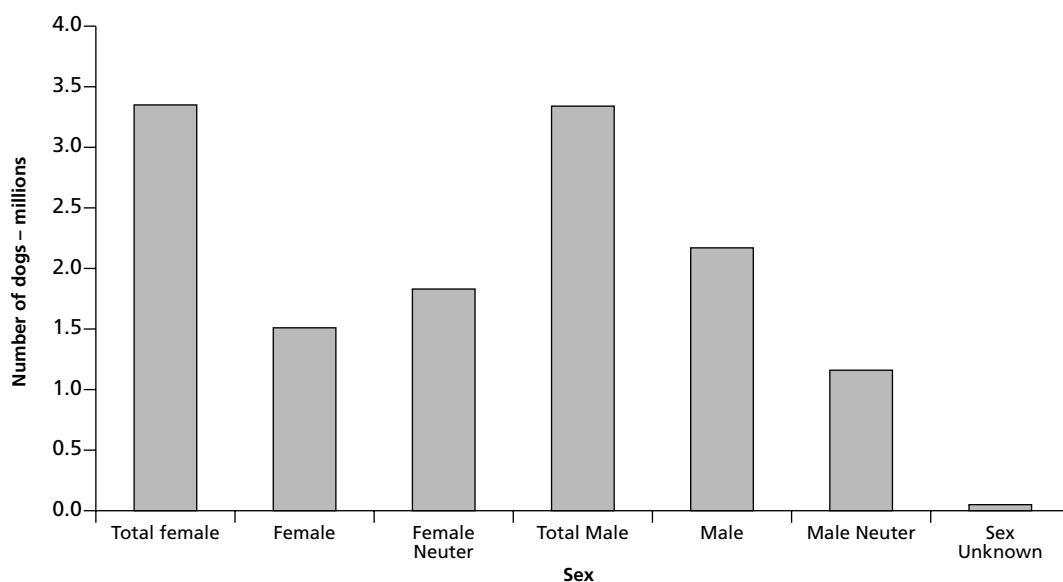
Appendix 1g(i) GfK Home Audit 1999: UK estimated cat sex distribution*



No. of cats (million)*	4.15	0.53	3.62	3.54	0.55	2.99	0.05
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*Total population estimated to be 7.74 million cats

Appendix 1g(ii) GfK Home Audit 1999: UK estimated dog sex distribution*

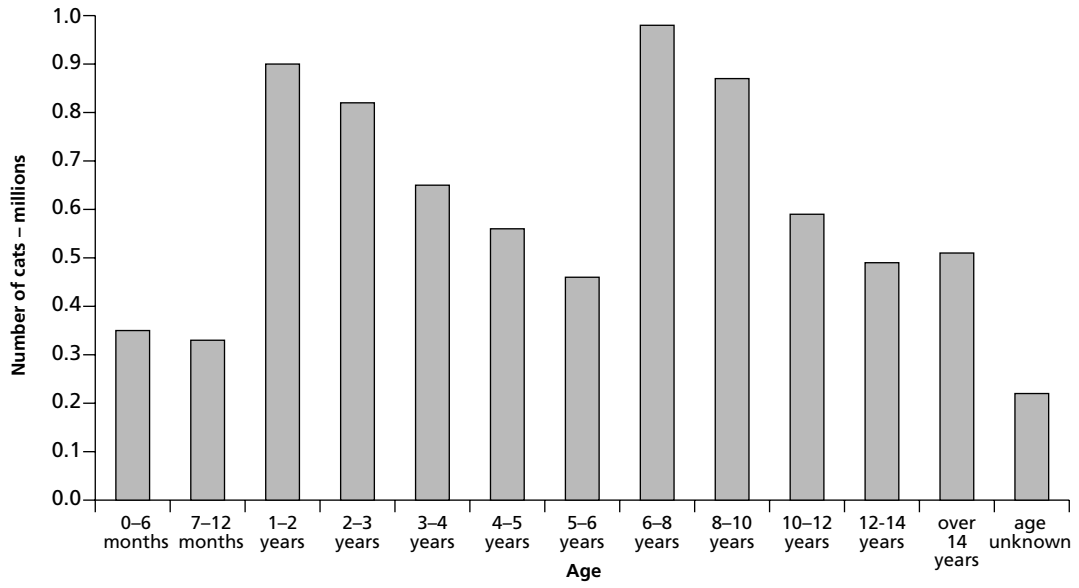


No. of dogs (million)*	3.35	1.51	1.83	3.34	2.17	1.16	0.05
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*Total population estimated to be 6.73 million dogs

Appendix 1h

Appendix 1h(i). GfK Home Audit 1999: UK estimated cat age distribution

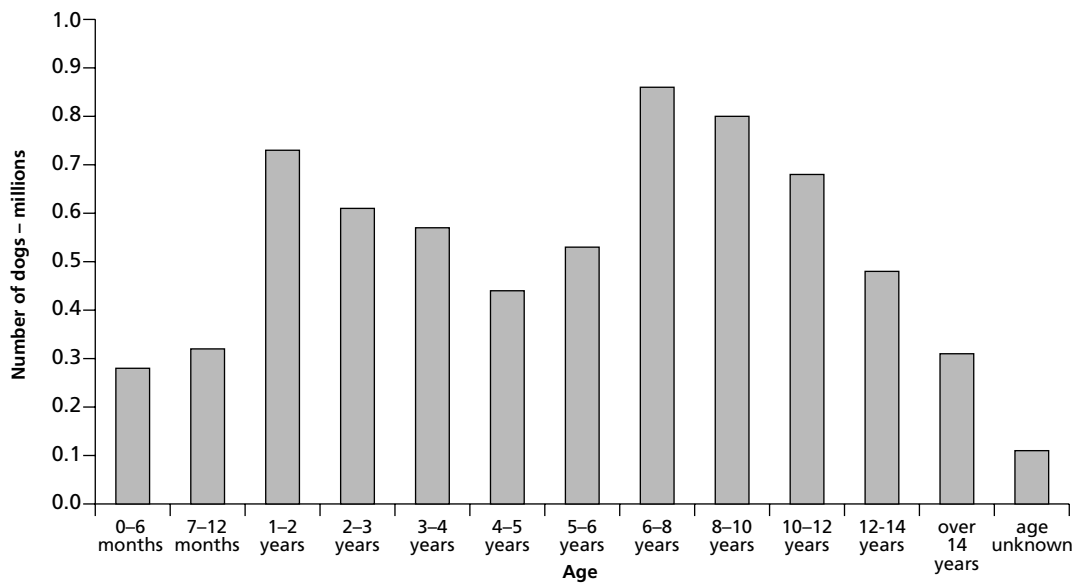


No. of cats (million)*	0.35	0.33	0.90	0.82	0.65	0.56	0.46	0.98	0.87	0.59	0.49	0.51	0.22
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The data for cats aged more than 6 years are in 2 year class intervals instead of 1 year and all cats aged more than 14 years are grouped together

*Total population estimated to be 7.74 million cats

Appendix 1h(ii). GfK Home Audit 1999: UK estimated dog age distribution



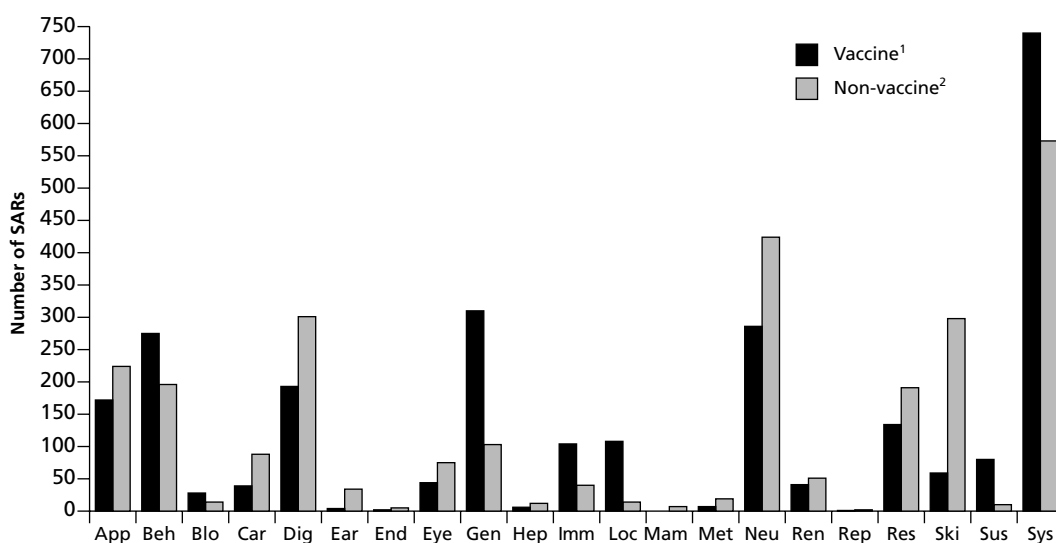
No. of dogs (million)*	0.28	0.32	0.73	0.61	0.57	0.44	0.53	0.86	0.80	0.68	0.48	0.31	0.11
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The data for dogs more than 6 years are in 2 year class intervals instead of 1 year and all dogs aged more than 14 years are grouped together

*Total population estimated to be 6.73 million dogs

Appendix 1i

Appendix 1i(i). Vaccine and non-vaccine SARs (1985–1999): distribution of VeDDRA SOC codes for cats*



Vaccine ¹	172	275	28	39	193	4	2	44	310	6	104	108	0	7	286	41	1	134	59	80	740
Non-vaccine ²	224	196	14	88	301	34	5	75	103	12	40	14	7	19	424	51	2	191	298	10	573

1 Total number of feline vaccine SARs = 1531

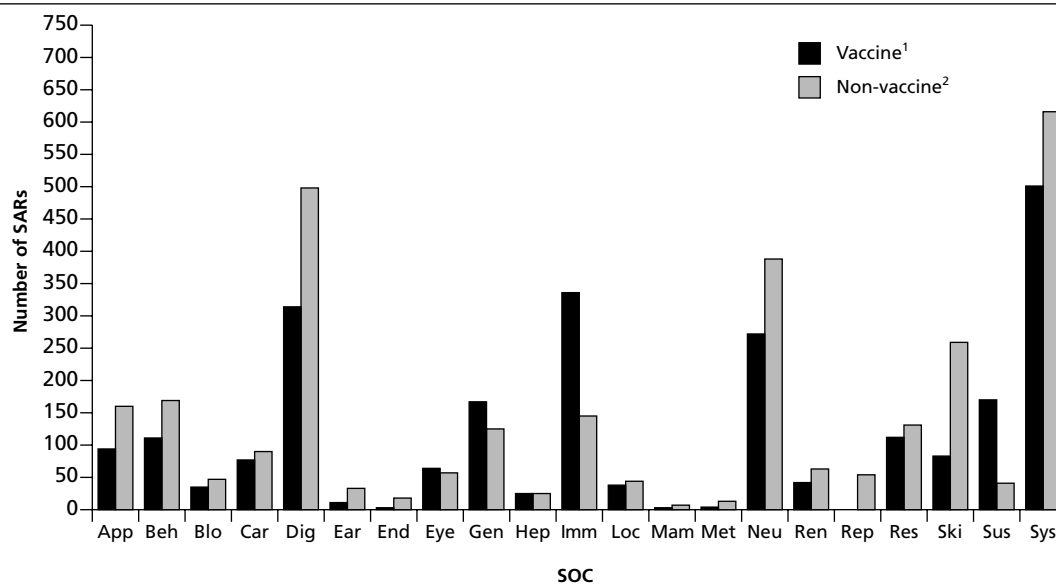
2 Total number of feline non-vaccine SARs = 1576

n.b. – There can be more than one VeDDRA SOC code per SAR

For key to clinical signs see over page.

*For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

Appendix 1i(ii). Vaccine and non-vaccine SARs (1985–1999): distribution of VeDDRA SOC codes for dogs*



Vaccine ¹	94	111	35	77	314	11	3	64	167	25	336	38	3	4	272	42	0	112	83	170	501
Non Vaccine ²	160	169	47	90	498	33	18	57	125	25	145	44	7	13	388	63	54	131	259	41	616

1 Total number of canine vaccine SARs = 1332

2 Total number of canine non-vaccine SARs = 1846

n.b. – There can be more than one VeDDRA SOC code per SAR

For key to clinical signs see over page.

*For details of sample populations and statistical analyses see sections 2.3.8 and 2.3.9.

Key –

App = Application site disorders
Beh = Behaviour disorders
Blo = Blood and lymphatic system
Car = Cardiovascular disorder
Dig = Digestive tract disorders
Ear = Ear and labyrinth
End = Endocrine System
Eye = Eye disorders
Gen = General disorders
Hep = Hepatobiliary disorders
Imm = Immune System

Loc = Locomoter Disorders
Mam = Mammary gland disorders
Met = Metabolism and Nutrition
Neu = Neurological disorders
Ren = Renal and urinary disorders
Rep = Reproductive system
Res = Respiratory disorders
Ski = Skin and integument disorders
Sys = Systemic disorders
Sus = Suspected lack of efficacy

Glossary

Active	The ingredient in a product which induces an immune response
Adjuvants	Substances used to enhance an immune response
Alphaherpesviruses	A particular group of herpes viruses
Anaphylaxis	An acute generalised allergic reaction
Anterior uveal tract	A group term for the iris, ciliary body and choroid of the eye
Antigen	A substance, typically a protein, which induces an immune response
Ataxia	Inco-ordination and difficulty standing or walking
Autoagglutination	A clump or grouping of red blood cells
Autoimmunity	A condition where the immune system works against the host's normal body tissues
Basophil	A type of white blood cell
<i>Bordetella bronchiseptica</i>	An organism involved in respiratory disease in cats, dogs and some other species
<i>Borrelia burgdorferi</i>	A cause of Lyme disease in animals and man transmitted by ticks
Canine adenovirus	A virus causing an infectious liver disease or respiratory signs in dogs
Canine coronavirus	A virus which causes enteric disease in dogs
Canine parainfluenza	A virus which causes tracheobronchitis or kennel cough in dogs
Canine parvovirus	A virus causing acute disease involving fever, diarrhoea, vomiting and death in dogs
Cell mediated immune response	Immunity involving sensitised white blood cells
(Juvenile) cellulitis	Painful skin condition with swelling and discharge usually of face and lips
Cerebellar hypoplasia	A congenital reduction in the size of the cerebellum of the brain resulting in poor movement control
Challenge (of a vaccine)	To expose animals to a substance or virus to test immunity
<i>Chlamydia psittaci</i> (<i>Chlamydophila felis</i>)	An organism which induces conjunctivitis and also in some cases respiratory signs in cats. Closely related organisms affect some other species.
Complement	A component of serum involved in the immune response
Cutaneous vasculopathy	Inflammation and degeneration of blood vessels in the skin
Degranulation	Discharge of the contents of cytoplasmic granules by basophils and mast cells
Dyspnoea	Breathing difficulties
Encephalitis	Inflammation of the brain
Encephalomyelitis	Inflammation of the brain and spinal cord
Epizootiology	The science of how a disease spreads in a population of animals
Erythema	A reddening of the skin

Feline calicivirus	A virus which causes moderate flu like signs and oral ulceration in cats
Feline herpesvirus	A virus which causes flu like signs in cats
Feline immunodeficiency virus	A chronic viral infection of cats which affects their immune system making them susceptible to secondary infections
Feline leukaemia virus	A virus which suppresses the immune system and causes tumours (lymphosarcomas) and in some cases anaemia in cats
Feline panleucopenia	A virus which causes a severe enteritis and a reduction in the number of white blood cells in cats
Fibrosarcomas	A tumour formed from fibrous connective tissue
Follicular epithelium	Lining cells of hair follicles in the skin
<i>Giardia lamblia</i>	An organism commonly causing chronic diarrhoea but which does not always cause clinical signs
Granuloma	A chronic localised inflammatory lesion
Humoral immune response	Immunity involving antibody responses
Hypersensitivity	An allergic reaction to a substance that the individual has been previously exposed to
Hypertrophic osteodystrophy	An inflammatory bone disease of unknown cause that leads to bone enlargement and lameness
Hypotensive shock	A sudden fall in blood pressure due to a stress or challenge to the body
Idiopathic	A disease or condition where the cause is unknown
(Antigen-specific) IgE	A type of antibody involved in allergic reactions which is specific for a particular antigen
IgG	A type of antibody mainly found in the circulatory system which also transfers immunity to offspring
Immune-mediated haemolytic anaemia (IMHA)	A reduction in the number and/or size of red blood cells as a result of damage or destruction of these cells by the individual's own immune system
Immune-mediated thrombocytopenia (IMTP)	A reduction in the number of platelets in the blood as a result of destruction of these cells by the individual's own immune system
Immunodeficiency	A deficient immune system
Immunogenicity	The ability of a substance to stimulate an immune response
Immunohistochemistry	A method of identifying an agent (e.g. a virus) within tissue by probing the tissue with antibodies specific for the agent
Intranasal	Into the nose
Intravascular haemolysis	A breakdown of the red blood cells within the circulation
Ischaemic vasculopathy	Degeneration or blockage of blood vessels resulting in death of the tissue supplied by those vessels
<i>Leptospira spp</i>	A group of organisms which cause damage to the liver and kidneys
Lymphocyte	A type of white blood cell involved in the immune response

Macrophage	A type of white blood cell which has migrated into tissues and is involved in the immune response
Malignant fibrous histiocytomas	A type of tumour derived from mesenchymal tissue
Mast cell	A type of white blood cell found in connective tissue, particularly in the skin and mucosae (e.g. gut, respiratory tract)
Maternally derived antibody	Antibody acquired without exposure to the antigen passed mainly in cats and dogs from mother to offspring via colostrum (early milk)
Mesenchymal	Derived from embryonic connective tissue
<i>Microsporium canis</i>	An organism causing dermatophytosis (ringworm) in cats, dogs and humans
Modified live	A live infectious agent which has been modified for inclusion in a vaccine in order to produce an immune response without causing disease
Morbilliviruses	A group of viruses which includes canine distemper and measles viruses
Multicentric fibrosarcomas	Multiple fibrosarcomas throughout the body
Multifocal ischaemic dermatopathy	Degeneration or blockage of multiple small blood vessels supplying areas of skin, resulting in death of those areas supplied by the vessels
Multivalent vaccine	A vaccine containing more than one active viral/bacterial component
Myaesthesia gravis	A condition which may be inherited or acquired, in which antibodies block the acetylcholine receptors at the neuromuscular junction causing episodic muscle weakness
Myofibroblastic sarcomas	A type of sarcoma, similar to fibrosarcomas
Neutralising antibody	Antibody which binds to antigen rendering it ineffective
Neutrophil	A type of white blood cell
Oedema	Swelling caused by the accumulation of fluid in tissues
Oro-nasal	Oral and nasal
Oro-pharynx	Oral and pharyngeal area
Pathogenesis	How a disease is caused and progresses
Pemphigus	An autoimmune disease where an individual's own antibodies disrupt the structure of skin epidermis causing blistering
Peripheral polyneuropathy	An inflammatory disease affecting peripheral nerves
Platelet	A cellular component of the blood involved in the formation of blood clots
Polyarthritis	Multiple, simultaneous joint inflammation
Polyneuritis (polyradiculoneuritis)	An inflammatory disease which affects nerve roots and peripheral nerves
Polyvalent vaccine	A vaccine containing more than one active viral/bacterial component
Prophylaxis	Prevention of a condition by treatment of a healthy individual, for example prevention of a specific disease by vaccination
Pruritis	Itching

Pulmonary oedema	Fluid in the tissue of the lungs
Pyrexia	Body temperature above normal (fever)
Pyrogens	A substance which can cause fever (pyrexia)
Recombinant vaccine	A vaccine in which genes have been transferred from one organism into another
Rheumatoid-like arthritis	Chronic immune mediated condition involving progressive damage to joints
Rhinitis	Inflammation of the mucous membranes of the nose
Sarcomas	A group of malignant tumours derived from mesenchymal tissues
Serological	Relating to antibody component of the serum
Serotypes	Different types of organisms identified by antibody responses in serum/blood
Serum neutralising antibody	Antibodies contained within serum which render viruses ineffective
Soft tissue sarcomas	A sarcoma of soft (connective) tissue
Systemic	Affecting the entire body
Thrombocytopenia	A reduction in the number of platelets in the blood
Titres	A measure of the amount of antibody in a serum sample
Urticaria	Wheals or lumps in the skin associated with an allergic reaction to a substance
Uveitis	Inflammation of the iris and associated parts of the eye
Vasoactive mediators	Substances which cause the dilation or constriction of blood vessels
Viraemia	The presence of viruses in the bloodstream

Definitions of Acronyms

Acronym	Definition
9CFR	Code of Federal Regulations Title 9
A	Reaction probably relating to use of product
AAFP	American Association of Feline Practitioners
AER	Adverse Event Reporting
ALSPAC	Avon Longitudinal Study of Parents and Children
AVMA	American Veterinary Medicines Association
B	Reaction possibly relating to use of the product
B-Factor	Multifactorial aetiology but still a possibility that the product is involved in the reaction
Bm	Multiple products (vaccines and pharmaceuticals) used concurrently prior to the reaction occurring which is possibly related to one or more of the products used (excluding Bm*)
Bm*	Multiple vaccines used concurrently prior to the reaction which is possibly related to one or more of the products
B-Opru	A concurrent product is thought to possibly be related to the reaction rather than the product reported
BPSU	British Paediatric Surveillance Unit
BSAVA	British Small Animal Veterinary Association
CAHI	Canadian Animal Health Institute
CAV	Canine adenovirus
CD	Canine distemper
CDSC	Communicable Disease Surveillance Scheme
CDV	Canine Distemper Virus
CFIA	Canadian Food Inspection Agency
CHC	Canine Health Concern
CIOMS	Council for International Organisations for Medical Science
CKCS	Cavalier King Charles spaniels
CPV	Canine parvovirus
CVMA	Canadian Veterinary Medicines Association
CVMP	Committee of Veterinary Medicinal Products
EMEA	European Medicines Evaluation Agency
EPA	Environmental Protection Agency
EU	European Union
FCV	Feline calicivirus
FDA CVM	Food and Drug Administration Center for Veterinary Medicines
FelV	Feline leukaemia virus

FHV	Feline herpes virus
FP	Feline panleucopenia
GfK	Organisation which carried out survey on behalf of Pedigree Masterfoods
GREFI	the Group d'Etude Francais des Fibrosarcoma
ICH	International Conference on Harmonisation
IMHA	Immune Mediated Haemolytic Anaemia
IMTP	Immune Mediated Thrombocytopenia
IT	Information technology
IVAA	Inactivated vaccines with aluminium-based adjuvants
IVOA	Inactivated vaccines with other adjuvants
LLPA	Lameness with lethargy, pyrexia or anorexia
LV	Live vaccines
MA	Marketing Authorisation
MAH	Marketing Authorisation Holders
MCA	Medicines Control Agency
MMR	Measles, mumps and rubella
MV	Mixed vaccines (i.e. live plus an inactivated vaccine)
N	Reaction not due to use of the product
NfG	Note for Guidance
NOAH	National Office of Animal Health
O	Insufficient data to assess whether reaction due to use of the product
PCR	Polymerase chain reaction
PETS	Pet Travel Scheme
PHLS	Public Health Laboratories Service
PSUR	Periodic Safety Update Report
S.D.	Standard deviation
SARs	Suspected Adverse Reactions
SOC	System Order Class
SPCs	Summary of Product Characteristics
TIGRESS	Totally integrated graphical relational electronic surveillance system
UK	United Kingdom
USA	United States of America
USDA	United States Department of Agriculture
USDA CVB	United States Department of Agriculture Center for Veterinary Biologics
USP	United States Pharmacopoeia
VAFSTF	Veterinary-Association Feline Sarcoma Task Force
VeDDRA	Veterinary Dictionary for Drug Regulatory Authorities
VICH	The International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VMD	Veterinary Medicines Directorate
VN	Virus neutralising
VPC	Veterinary Products Committee
VPR	Veterinary Practitioners Reporting
WHO	World Health Organization

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