

Vaccination guidelines: a bridge between official requirements and the daily use of vaccines

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The present Editorial focuses on vaccination guidelines for companion animal practice, as they are presently developed at the national level (e.g. by the German Bundesverband der praktizierenden Tierärzte), internationally (e.g. for the feline species by the Advisory Board on Cat Diseases, see <http://www.vetscite.org/> and <http://www.abcd-vets.org/index.asp> and worldwide by the Vaccination Guidelines Group, a new Standardization Group of the World Small Animal Veterinary Association (WSAVA).

This article is reprinted with permission from the Office International des Epizooties (OIE), where it will appear in the series of Scientific and Technical Reviews (http://www.oie.int/eng/publicat/en_tarifs.htm?e1d11). Since it is intended to illuminate the interface between objective research data and collective expert opinion, the paper should be of interest for the veterinary scientist.

Introduction

Vaccination guidelines are non-compulsory recommendations which assist the veterinary practitioner to use vaccines efficiently. They complement the official information contained in the summary of product characteristics (SPC) that can be found in the package insert, (an SPC is part of the documentation required for an authorised medicinal product) [21]. However, although the vaccination schedule that appears in the package insert has been reviewed and approved by the licensing authorities, the practical use of the vaccine in the field can deviate from this official schedule. Furthermore, new scientific data can modify the vaccination approach, but the respective changes in the regulations can take several years before coming into force. In such cases, guidelines can serve as a bridge between official and unofficial recommendations for vaccine use.

The aim of this article is to clarify the role of guidelines and the ways in which they can ensure that vaccines are used effectively in practical conditions. The situation in the European Union (EU) will be taken as an example. The focus on pet animal vaccination is appropriate because it is less regulated by official policy and sanitary measures and more influenced by the behaviour of veterinarians and pet owners. The authors also undertake a comparison of several guidelines independently issued on the same subject. The role of vaccine producers and national and international authorities in the development and production of vaccines has been already described and discussed by Jones et al. in this issue [15]. Therefore, this paper intends to explain the increasing role of expert committees in publishing vaccination guidelines in order to help the veterinarian in his/her daily practice.

Why are guidelines useful?

It is important to produce guidelines because the time between the initial development of a vaccine and its use in the field can be very long: several different players become involved and scientific knowledge develops, so the initial recommendations for use may no longer be the most appropriate. In addition, a vaccine is usually used as part of a complex vaccination programme and also in very diverse field situations, not all of which can be documented in the package insert of the product. There are two main sets of factors which can affect the use of vaccines; the first concerns the process of developing and marketing a vaccine and the second concerns the variety of different bodies that make recommendations about their production and use. The first is as follows:

- a) academic research provides scientific data about the identification of infectious agents, their incidence and the fulfilment of Koch's postulates. Pathogenesis and immunity are also studied and all this scientific information is used to stimulate applied research on the development of vaccines [6];
- b) the pharmaceutical company designs a vaccine and carries out experimental and field studies in order to meet the requirements of the regulatory authorities for quality, safety and efficacy of the vaccine in a given species, a given age and for a given vaccination schedule [6];

- c) the pharmaceutical company submits a dossier to obtain a marketing authorisation in the EU, which must comply with several regulations: Directives of the European Commission, monographs of the European Pharmacopoeia and other international and national rules [8] [9] [26];
- d) the veterinary immunological product will follow a centralised or a decentralised procedure for granting a marketing authorisation in the EU [3];
- e) when the marketing authorisation is granted, the SPC of the vaccine is available in the product information. It gives the main properties of the compound and the approved vaccination schedule as it will appear in the package insert. It is based on the results of experiments performed in experimental stations and field trials carried out by the company [21];
- f) the product is released on the market and the company informs veterinary practitioners through its marketing communication; this communication may deviate from the officially approved recommendations for vaccine use [21];
- g) veterinary practitioners may use the vaccination in ways that are noticeably different from the recommendations of the package insert, particularly if it is incorporated in a larger scheme involving other vaccines.

The second set of factors relates to the official and non-official bodies that provide information and/or make recommendations about the production and use of vaccines. It can be described as follows:

- a) faculties and schools of veterinary medicine as well as other scientific institutes provide scientific knowledge;
- b) pharmaceutical companies develop vaccines using their own scientific and technological data and provide their own technical information about the product;
- c) regulatory authorities publish rules and guidelines and are associated in the writing of regulations regarding the production of vaccines in order to guarantee the quality of the new veterinary immunological medicinal products [21]. Examples of the main regulations that must be taken into account when preparing and using a new vaccine are the European Pharmacopoeia, European Commission Directives on medicinal products, and, in the United States of America, the Code of Federal Regulations [18]. Given the time that it takes to develop legislation, these regulations are sometimes not based on the most recent scientific knowledge;
- d) various kinds of veterinary associations produce guidelines for the proper use of vaccines in field conditions [12];
- e) animal owners and breeder associations can also influence the use of vaccines by veterinary practitioners [12].

The different sources of information regarding the use of vaccines explains why a discrepancy can be observed between the recommendations of the vaccine package insert and its use in the real conditions of veterinary practice. It is of primary importance that the vaccination schedules followed by the veterinary practitioners are the most efficacious ones even if this means that they do not strictly follow the recommendations of the package inserts.

How are guidelines developed?

The identified discrepancy between the official requirements for vaccine use and the practical use of vaccines in the field has been well recognised and whether this is acceptable or not should no longer be a matter of discussion. Therefore, there is a need to make a link between the authorised characteristics of the vaccine as described in the SPC and the package insert, the scientific knowledge available in published literature, and the requirements of veterinary practice. To this end, several committees have been created on the initiative of professional associations or experts in the field. These committees can be sponsored by pharmaceutical companies but, if they are, they must maintain full scientific independence from the sponsors. Their objective is to produce guidelines for the proper use of vaccines in the field and therefore to propose a coherent vaccination scheme which does not depend on the individual characteristics of licensed products. The authority of these committees is based on the experience of their members, who must be recognised experts in the field of infectious diseases, vaccination and internal medicine. Several committees are already at work, for example: the Feline Vaccine Advisory Panel of the American Association of Feline Practitioners [20]; the European Advisory Board on Cat Diseases [7] and the German Federal Association of Veterinary Practitioners [2].

Guidelines are issued after a long reviewing procedure which takes into consideration information from multiple sources such as:

- scientific literature, including scientific articles, conference proceedings and clinical reports providing results of controlled trials with a strong statistical significance
- vaccine package inserts, based on the marketing authorisation dossier and controlled experiments carried out by the company to fulfil the official requirements; the results of these trials are strictly limited to the product under testing
- information on the current vaccination practices of veterinarians (in order to take into account the experience gained in field conditions)
- information from evidence-based veterinary medicine, which combines the above-mentioned sources of different levels of evidence with a pragmatic approach to reach a decision [16].

These committees write general and specific recommendations for good vaccination practices and remain independent of any brand or any particular commercial product. They can skip the slow process of the development of regulations and can therefore make recommendations on adapting vaccination programmes on a yearly basis according to the latest scientific knowledge. Scientific literature may provide new data on already licensed vaccines or very similar products, and these new data may differ from those contained in the marketing authorisation dossier. These committees can modify the vaccination approach and make new recommendations which are not strictly supported by either the vaccine marketing authorisation dossier or the official regulations. For example, they can provide advice on the vaccine valences to be included in a vaccination programme (the so called 'core' vaccines are recommended for all companion animals; 'non-core' vaccines should be administered in specific risk conditions [20] [23], and make recommendations on which infectious agents should be vaccinated against depending on the age, the condition and the environment of the animal [24].

These committees can influence practitioners' use of vaccines because they are very close to their needs. Therefore, they are expected to become more and more important in the future. They could recommend alternative methods of using the vaccine that are not described in the SPC. This point should be taken into consideration by the official drug agencies and, in general, by all regulation-setting institutions. Regulations evolve quite slowly compared to the rapidly expanding needs of veterinary medicine and the evolution of scientific knowledge. It is likely that these committees could not only influence the vaccination habits of veterinary practitioners but also the official institutions like national and international drug agencies.

What issues do guidelines address?

Onset of immunity

Primary vaccination schedule

The SPC gives a minimum age for vaccination, which can, in practice, vary depending on several factors: the age at which the puppy or the kitten is shown to the practitioner for the first time; the behaviour and the environment of the animal; and the infectious agents that the vaccination is intended to combat. For instance, vaccination against canine parvovirus (CPV) can start early, at five to six weeks of age. The efficacy of the vaccination at this very young age is influenced by the level of maternally derived antibodies (MDA). Furthermore, the interval between injections cannot always be strictly applied due to practical constraints, and especially if the pet animal is not shown to the practitioner at the appropriate age. Certain combinations of vaccines will also mean that some deviation from the recommendations of the vaccine SPC are necessary. Guidelines are needed, therefore, to advise the veterinarian about the best decision to take in all the various circumstances encountered in practice.

Interference with maternally derived antibodies

At a very young age, MDA can significantly interfere with the efficacy of vaccination. This is a general statement since no individual testing is performed on a regular basis. In the future, diagnostic kits to measure the level of MDA interference will become available for some vaccines and are already in use, for canine distemper virus (CDV) and CPV [25]. At a later age, duration of MDA depends on the level of immunity of the bitch or the queen, on the amount of colostrum uptake by the puppies or the kittens (differences between offspring of the same litter) and on the infectious agent. For example, vaccine package inserts propose a double vaccination schedule in cats at 9 and 12 weeks of age for both feline herpesvirus 1 (FeHV-1) and feline calicivirus (FCV). Knowing that MDA have a prolonged

duration, especially for FCV, guidelines can recommend that a third round of vaccination be performed at 16 weeks of age [7] [20].

Duration of immunity

In European vaccine SPCs, intervals between vaccinations are strictly regulated by analysing the results of protection experiments at the end of the claimed duration of immunity [8] [9].

First booster vaccination

The recommendation for the time of the first booster vaccination is based on the results of the duration of immunity experimental studies. It is most often one year after the primary vaccination. However, experts can suggest that cats and dogs be vaccinated earlier, six months after the primary vaccination [7]. This statement is based on the fact that several animals are not properly vaccinated with the primary vaccination because of interference by MDA. This intermediate vaccination is designed to prevent dogs remaining unprotected over a one-year period. However, such modification remains compatible with the vaccine SPC because revaccination is carried out within the demonstrated duration of immunity.

Intervals between vaccinations

The current trend is to increase the interval between booster vaccinations. It is supported by several scientific publications [4] [5], but drug companies are required to carry out their own experiments and publish their own results before any modification can be made to the SPC, and as this is expensive and not in their interest they do not provide the necessary data and SPCs remain unchanged. Performing the first booster vaccination after one year is highly recommended [14]. Taking CDV and canine adenovirus 2 (CAV-2) as examples, the protection conferred by attenuated vaccines is long-lasting and most likely longer than the duration of the immunity officially reported in the vaccine package inserts [14]. One challenge study supports claims that there is a three-year duration of immunity after vaccination at 7 and 11 weeks of age [11]. CDV and CAV-2 antibodies persist at least four years after vaccination [17]. Other studies suggest that there may be an even longer duration of immunity against these viruses [23]. This development is now apparent in the most recent versions of vaccine guidelines, where three-year intervals between rounds of vaccination are usually proposed for core vaccines [20].

Combination of vaccines

Vaccine SPCs do not give any recommendation about the simultaneous or the sequential use of vaccines sold by different companies. The compatibility between vaccines is therefore a safety concern which is usually not addressed by the package inserts of the products and which needs specific guidelines. Both safety and efficacy must be considered since some vaccine valences may have interfering effects that decrease the efficacy of other vaccine components. In addition, it is the role of guidelines to provide the practitioner with coherent vaccination programmes (including the all important valences) and to propose modifications to the vaccine schedule to take account of various different factors such as specific epidemiological conditions or the type of animal being vaccinated, e.g. immunodepressed animals, animals in shelters, animals in breeding colonies, etc. [7] [24]. Therefore, guidelines aim to provide comprehensive advice on vaccination programmes for both 'core' and 'non-core' vaccines, justifying their use under specific conditions.

Vaccination and ageing

Ageing is known to increase susceptibility to infectious diseases and decrease the efficacy of vaccinations, mainly due to a partial loss of the antibody response and a reduction of T helper lymphocyte activity [10] [19]. A few data are available in domestic animals [10] [13]. However, even the average age when ageing could modify the immune response is not known for companion animals and can only be extrapolated from the measurement of some physiological modifications. For example, while many cats begin to show clinically significant changes between the ages of 7 and 10, most of them start to be affected at 12 years of age [1]. Several recommendations have already been made in the literature [22]. For example, old dogs have high anti-rabies antibody titres before revaccination, meaning that a good vaccination schedule applied in the young and adult period can efficiently protect aged animals [13]. More data should be made available by other studies in order to better substantiate the vaccination of aged animals. Indeed this matter is considered neither by regulations nor by pharmaceutical companies and is not properly included in vaccination guidelines due to this lack of knowledge [20].

Comparison of three guidelines

The three sets of guidelines compared here were all produced to guide the veterinary practitioner in the vaccination of cats. They were produced by the American Association of Feline Practitioners [20], the European Advisory Board on Cat Diseases [7] and the German Federal Association of Veterinary Practitioners [2], respectively. Only certain sections of these guidelines have been compared, namely, the sections that deal with vaccination programmes to protect cats against upper respiratory tract disease caused by FeHV-1 and FCV. The differences which can be observed between the three guidelines can be explained by at least two factors. First, the disease approach is different depending on the country or the region: the cultural aspects (e.g. with regard to the importance of animal welfare), the level of medical care of pet animals and the available vaccines. Secondly, there are so far no definite rules to control infectious diseases and the expert opinion, as reflected in the guidelines, is always based on a consensus between experts. This consensus opinion may differ depending on the composition of the expert panel.

Conclusions

Vaccination guidelines are essential tools to help veterinarians use vaccination effectively. They fill the gap that exists between the official recommendations issuing from the regulations and the licensing dossiers, and the daily use of vaccines. Vaccines are developed and produced with the aim of protecting animals against important, often lethal, infectious diseases. Therefore, good vaccination guidelines can improve the quality of the vaccine-induced protection in the field, provided they take into account both the latest scientific data and knowledge of the practice conditions.

Acknowledgements

We would like to offer our sincere thanks to our colleagues at the European Advisory Board on Cat Diseases, with whom we had many helpful discussions. We extend our thanks to Hervé Poulet and Jean-Christophe Thibault (Merial, Lyon), Angélique Zicola, Marie-Lys Van de Weerd and Dominique Quatpers (Virology, Faculty of Veterinary Medicine, University of Liège) for stimulating discussions.

References

1. American Association of Feline Practitioners (AAFP)., 2005. American Association of Feline Practitioners/Academy of feline medicine panel report on feline senior care. *J feline Med Surg* 7: 3-32.
2. Anon., 2006. Deutsche Impfempfehlungen für die Kleintierpraxis [German recommendations for vaccination in small animal practice]. Bundesverband praktizierender Tierärzte [German Federal Association of Veterinary Practitioners].
3. Brunko P., 1997. Procedures and technical requirements in the European Union. In: *Veterinary Vaccinology*, P.-P. Pastoret, J. Blancou, P. Vannier, C. Verschuere, eds. Amsterdam, Elsevier, 674-679.
4. Coyne M.J., Burr J.H.H., Yule T.D., Harding M.J., Tresnan D.B., McGavin D., 2001. [Duration of immunity in dogs after vaccination or naturally acquired infection](#). *Vet Rec.* 149: 509-515.
5. Coyne M.J., Burr J.H.H., Yule T.D., Harding M.J., Tresnan D.B., McGavin D., 2001. [Duration of immunity in cats after vaccination or naturally acquired infection](#). *Vet Rec.* 149: 545-548.
6. Desmettre P., Martinod S., 1997. Research and development. In: *Veterinary Vaccinology*. P.-P. Pastoret, J. Blancou, P. Vannier, C. Verschuere, eds., Amsterdam, Elsevier, 175-194.
7. European Advisory Board on Cat Diseases., 2007. Guidelines on feline infectious diseases. Available at: <http://www.abcd-vets.org/guidelines/> (accessed on 17 May 2007).
8. European Communities (EC)., 2001. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. *Off J Eur Communities*, L 311, 28/11/2001, 0001-0066.
9. European Communities (EC)., 2004. Directive 2004/28/EC of the European Parliament and of the Council of 31 March code relating to veterinary medicinal products. *Off J Eur Communities*, L 136, 30/04/2004, 0058-0084.
10. Fermaglich D.H., Horohov D.W., 2002. [The effect of aging on immune responses](#). *Vet Clin North Am Equine Pract.* 18: 621-630.
11. Gore T.C., Lakshmanan N., Duncan K.L., Coyne M.J., Lum M.A., Sterner F.J., 2005. [Three-year duration of immunity in dogs following vaccination against canine adenovirus type-1, canine parvovirus, and canine distemper virus](#). *Vet. Ther.* 6: 5-14.
12. Hill R.E., 1997. Role of the consumer in the use and regulation of veterinary biological products. In: *Veterinary Vaccinology*, P.-P. Pastoret, J. Blancou, P. Vannier, C. Verschuere, eds. Amsterdam, Elsevier, 744-762.
13. HogenEsch H., Thompson S., Dunham A., Ceddia M, Hayek M., 2004. [Effect of age on immune parameters](#)

- [and the immune response of dogs to vaccines: a cross-sectional study](#). Vet Immunol Immunopathol. 97: 77-85.
14. Horzinek M.C., 2006. [Vaccine use and disease prevalence in dogs and cats](#). Vet Microbiol. 117: 2-8.
 15. Jones P.G.H., Cowan G., Gravendyck M., Nagata T., Robinson S., Waits M., 2007. Regulatory requirements for vaccine authorisation. In: Animal vaccination. Part 2: Scientific, economic, regulatory and socio-ethical issues, P.-P. Pastoret, M. Lombard & A.A. Schudel, eds. Rev. sci. tech. Off. int. Epiz., 26 (2), in press
 16. Kastelic J.P., 2006. [Critical evaluation of scientific articles and other sources of information: an introduction to evidence-based veterinary medicine](#). Theriogenology. 66: 534–542.
 17. Mouzin D.E., Lorenzen M.J., Haworth J.D., King V.L., 2004. [Duration of serologic response to five antigens in dogs](#). J Am vet med Assoc. 224: 55-60.
 18. Pastoret P.-P., Falize F., 1999. [Viral veterinary vaccines](#). Dev Biol Stand. 101: 73-78.
 19. Plowden J., Renshaw-Hoelscher M., Engleman C., Katz J., Sambhara S., 2004. [Innate immunity in aging: impact on macrophage function](#). Aging Cell 3: 161-167.
 20. Richards J.R., Elston T.H., Gaskell R.M., Hartmann K., Hurley K.F., Lappin M.R., Levy J.L., Rodan I., Scherk M., Schultz R.D., Sparkes A.W., 2006. [The 2006 American Association of Feline Practitioners Feline Vaccine Advisory Panel Report](#). J Am vet med Assoc. 229: 1405-1441.
 21. Roberts B., Sanders A., 1997. Registration and marketing. In: Veterinary Vaccinology, P.-P. Pastoret, J. Blancou, P. Vannier, C. Verschueren, eds. Amsterdam, Elsevier, 243-254.
 22. Schultz R.D., 1982. Theoretical and practical aspects of an immunization program for dogs and cats. J Am vet med Assoc. 181: 1142-1149.
 23. Schultz R.D., 2006. [Duration of immunity for canine and feline vaccines: a review](#). Vet Microbiol. 117: 75-79 .
 24. Thiry E., 2006. Clinical virology of the dog and cat. Paris, Editions du Point Vétérinaire.
 25. Twark L., Dodds W.J., 2000. [Clinical use of serum parvovirus and distemper virus antibody titers for determining revaccination strategies in healthy dogs](#). J Am vet med Assoc. 217: 1021-1024.
 26. World Organisation for Animal Health (OIE), 2004. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (mammals, birds and bees), 5th Ed. Paris, OIE.