

# **Risk assessment related to veterinary biologicals: side-effects in target animals**

S. MARTINOD \*

*Summary:* Despite established control measures, the large-scale use of veterinary biologicals may involve side-effects. The most common side-effects observed include the following:

- injection site reactions
- systemic reactions
- allergic reactions
- effects on the immune system
- residual pathogenicity
- inadequate inactivation
- genetic recombination
- contamination.

*New technologies, new harmonised regulations, and commitment to quality will ensure a continuous supply of safe and innovative products.*

KEYWORDS: Safety – Side-effects – Vaccines.

## **INTRODUCTION**

Since the first use of rabies vaccines by Louis Pasteur a century ago, vaccines and other biologicals have been highly beneficial in eliminating or controlling human and animal diseases. The benefits derived from the use of vaccines far outweigh the risks. However, side-effects in target animals are observed from time to time. The major safety problems reported are as follows:

- injection site reactions
- systemic reactions
- allergic reactions
- effects on the immune system
- residual pathogenicity
- inadequate inactivation
- genetic recombination
- contamination.

This paper reviews the possible causes and consequences of these problems, and potential methods of prevention.

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\* Pfizer Inc. Central Research, 601 W. Cornhusker Highway, Lincoln, Nebraska 68501-0809, United States of America.

## INJECTION SITE REACTIONS

Oedema at the site of injection is commonly observed after the use of inactivated adjuvanted products. Oedema is caused by allergic mechanisms, however, and disappears quickly.

Inflammatory reactions can be acute or chronic. Bacterial vaccines are responsible for a significant proportion of side-effects, e.g. vaccines against infections with *Pasteurella haemolytica* (27), *Actinobacillus pleuropneumoniae* (39, 41) and clostridia (3, 38), and against atrophic rhinitis. Oil adjuvants are frequently cited as causing reactions. The reaction can become manifest in various ways, including granulomas, pyogranulomas, abscesses, lymphoplasmocytic inflammation, necrosis, mineralization, fibrosis or fibrosarcomas. Possible consequences include pain, blemishes at the injection site (responsible for significant loss to the meat industry) (14), abscesses or even life-threatening fibrosarcomas (21, 22, 24). The use of appropriate vaccination techniques and equipment, and new technological developments (adjuvants, downstream processing) are keys to the prevention of side-effects. During the development of new products, intensive laboratory studies and field trials should allow the vaccine manufacturers and regulators to identify potential problems and select safe products. The problem of fibrosarcomas in cats (21, 22, 24), however, is an exception to the rule: incidence is low and the tumor takes several years to develop, and therefore only vaccino-vigilance can detect the problem.

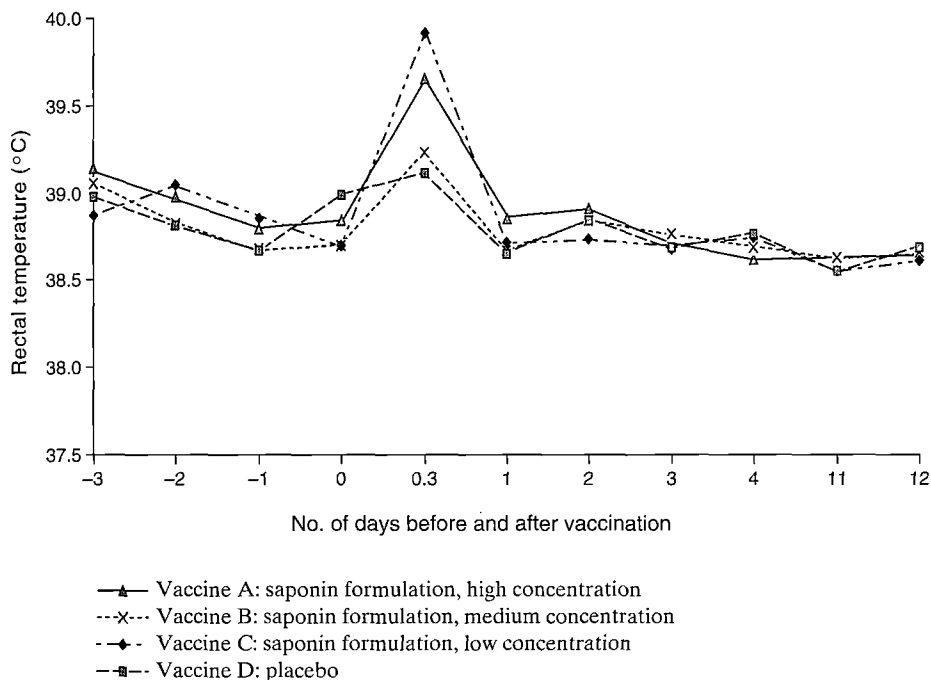
## SYSTEMIC REACTIONS

Short-term hyperthermia is very often observed after vaccination (Fig. 1). Anorexia, reduction in milk yield, reduced laying, vomiting, neurological problems, changes in blood parameters, and abortion have been described in the literature (12, 33). Residual endotoxin, and pyrogenic effect of the antigen and adjuvants (oil, saponin) are responsible for these reactions. Improved manufacturing processes (e.g. purification and clarification) and a new generation of adjuvants offer a measure of hope to alleviate this problem. During the development phase, the intensive safety trials (administration of one dose and one overdose) and large-scale field trials are designed to detect the problem products. It is of critical importance that a large number of animals be used. For example 4,916 cats were inoculated with a feline leukemia vaccine (43), and the reaction rate was 1.16%.

## ALLERGIC REACTIONS

Some allergic reactions must be expected with the use of biologicals. For example, with one of the most widely-used vaccines, foot and mouth disease vaccine, the reported reaction rates have ranged from 0.27% in Russia (11) to less than 0.1% in Germany (29), although far higher reaction rates have occurred in some regions (17). Allergic reactions have also been reported with canine adenovirus 1, influenza, leptospira and bordetella vaccines. The following factors are responsible for sensitization:

- cells (e.g. baby hamster kidney 21 cells for foot and mouth disease vaccine)
- residual animal serum content of vaccines (15)



**FIG. 1**

**Effect of various adjuvants on body temperature of cattle**

- ovalbumin (31)
- the antigens themselves
- other product components (e.g. preservatives).

Anaphylaxis (or type I hypersensitivity) occurs within minutes or hours of administration of vaccines, resulting in weakness, dyspnea, vomiting, trembling, mucous membrane pallor, ptialism, pulmonary oedema, abortion, collapse and sometimes death. Delayed reactions (type III hypersensitivity) occur eight to twenty-one days post injection. The problems can be localized cutaneously (papular, oozing eczemas) or subcutaneously (oedema, pruritis, adenomegaly). Dogs can develop an immune complex disease called 'blue eye' after administration of canine adenovirus 1 vaccine; this results from a corneal oedema, due to the deposition of antigen-antibody complex (33). Distemper vaccine in dogs may also potentiate the formation of immunoglobulin (Ig)E antibodies to pollens (18).

The risk of allergic reaction increases after the third or fourth injection of vaccine. During the development of a new vaccine, repeated administration (five times) of a normal dose under laboratory conditions should detect any potential sensitizing effect. The use of sensitizing agents (e.g. bovine serum or other animal albumins) should be reduced to the strict minimum and the products purified. A guinea-pig sensitization test - which consists of injecting a dose of vaccine after the intravenous injection of calf serum - has been shown to be reliable in checking the finished products (15).

## EFFECTS ON THE IMMUNE SYSTEM

Due to the difficulty in properly evaluating the effect on the immune system, this subject has been somewhat controversial in the past. Alteration of leukocyte trafficking has been confused with true immunosuppression.

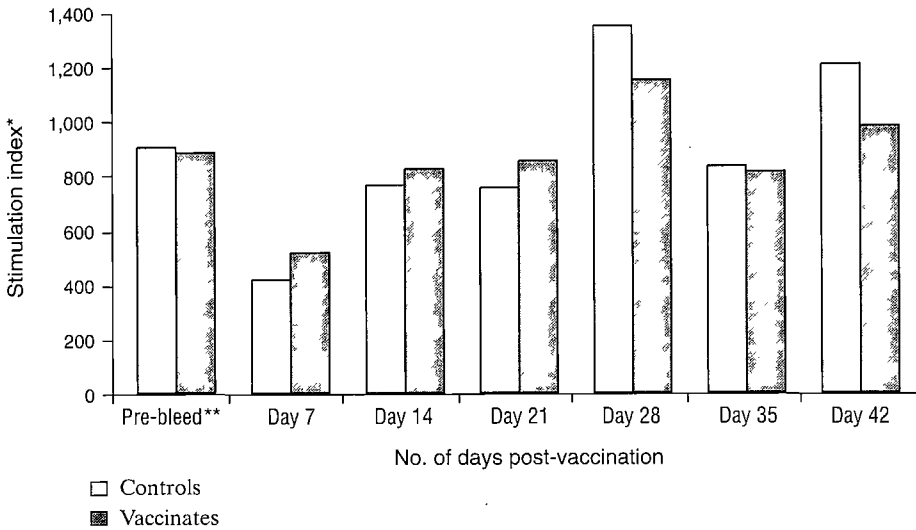
Some modified live viruses can cause immunosuppression in the vaccinated animals. Bovine herpesvirus 1 (BHV-1), bovine virus diarrhoea virus, canine distemper virus combined with canine adenovirus (3), and the SG33 strain of myxomatosis virus have been shown to induce immunodepression. BHV-1 vaccine can alter the immune response to *Pasteurella haemolytica* vaccine if both products are administered at the same time (20). A product containing canine distemper virus and canine adenovirus caused a significant decrease in lymphocyte responsiveness, as measured by an *in vitro* immune function assay, the lymphocyte blastogenesis test (32). In buildings where concurrent pathologies exist, vaccination with the SG33 strain of myxomatosis virus can induce the appearance of various diseases in rabbits (9). As immunosuppression is transitory, persisting for a maximum of seven to ten days, vaccination alone is unlikely to cause detectable adverse reactions in animals, apart from those mentioned above.

The potential immunosuppressive effect can be detected by co-administration of two vaccines (in a single animal at the same time) and evaluation of the immune response or efficacy of both products. The lymphocyte transformation assay is the most convenient test to measure cell-mediated immunity. Figure 2 shows an example of the use of this assay to test the potential suppressive effect of a new vaccine. Differential cell counts (13), measurement of leukocyte trafficking and the CD4/CD8 ratio could also be used. Field trials to assess the safety of a new vaccine should include some farms or locations infected with pathogens other than those included in the vaccine.

## RESIDUAL PATHOGENICITY

Attenuation of viruses or bacteria has traditionally been achieved by passage in culture until the selected strains have lost pathogenicity. In some instances, low levels of pathogenicity may persist and become apparent during widespread use under certain conditions. Fatal, generalized BHV-1 infection has been associated with the administration to neonatal calves of a modified live virus vaccine against infectious bovine rhinotracheitis/parainfluenza 3 (10). Necrotic oophoritis in heifers has been described after intravenous administration of a BHV-1 vaccine during oestrus, together with the possibility of a reduced fertility rate (36). BHV-1 modified live vaccine enhanced infectious bovine keratoconjunctivitis caused by *Moraxella bovis* (19). Severe generalized skin reactions were observed in vaccinated dairy cattle after administration of a capripox vaccine, and resulted in a decrease in milk production (47). Certain strains of avian infectious laryngotracheitis virus vaccine can cause severe respiratory signs if administered as a spray rather than by the recommended ocular route (34).

The appropriate attenuation technique should be used to prepare the master seed of a new vaccine. During the development phase of a new product, it is important to conduct safety studies using the most susceptible animals, the route of administration most likely to lead to reversion of virulence, and material from a passage level which is least attenuated between the master seed and the final product. The reverse passage studies evaluating the potential reversion to virulence of attenuated vaccines should be



$$* \text{ stimulation index} = \frac{\text{CPM of vaccinated animals}}{\text{CPM of media control}}$$

CPM: counts per minute  
Con A: concanavalin A

\*\* blood sample taken before vaccination

**FIG. 2**

**Comparison of peripheral blood lymphocyte responses to Con A at a dilution of 2 µg/ml, as shown by the stimulation index (mean CPM + Con A) (mean CPM + mean alone) for the 'pre-bleed' sample and at various times post-vaccination, in control calves (which received a placebo) and in calves vaccinated with a four-way vaccine against bovine respiratory disease (infectious bovine rhinotracheitis, bovine virus diarrhoea, bovine respiratory syncytial virus disease, parainfluenza 3)**

completed for all modified live products, and at least five passages *in vivo* should be undertaken. The shedding pattern of the vaccine strain should also be determined, to evaluate the risk of transmission from vaccinated animals to more susceptible animals (e.g. neonates) or non-target species. Obviously, the use of inactivated vaccines is an efficient way to avoid this problem.

## **INADEQUATE INACTIVATION**

Inactivation of pathogens or toxins using acetylenimine, binary ethylenimine or formaldehyde is a common approach in vaccine production. Inadequate inactivation can have dramatic consequences. Some outbreaks of foot and mouth disease in Western Europe have been caused by improperly inactivated vaccines (4, 7, 8, 37). Likewise, formaldehyde-inactivated Venezuelan equine encephalomyelitis vaccines were the probable cause of the outbreaks of this disease in Central America in 1969-1972. Some viruses (e.g. porcine parvovirus) are difficult to inactivate.

Only properly-validated inactivation techniques should be used for the manufacture of biologicals. Before using the product on a large scale, at least three inactivation curves at production scale should be completed. The use of formaldehyde should be avoided whenever possible. Testing individual lots of the final product for innocuity can be important in some cases, although the number of samples which can be handled is often too small for the results to be statistically significant.

## GENETIC RECOMBINATION

Recombination between live vaccinal strains and virulent strains is possible under specific conditions, and may result in reversion to virulence of recombinant DNA (rDNA) vaccines (25, 30) or conventional vaccines (26). Furthermore, vaccines marked by the deletion of a gene can regain the deleted gene, with dramatic consequences for eradication programmes.

The appropriate rDNA methods should be used in preparing new vaccine strains. If doubts exist, co-administration of the vaccine and wild strain should be undertaken in the target or other species. It is also wise to avoid mixing different strains of viruses with a high frequency of recombination (e.g. coronaviruses) in the same vaccine bottle.

## CONTAMINATION

Contamination with extraneous pathogens is probably the worst nightmare of any manufacturer of biologicals. Fungi, bacteria, mycoplasma and viruses can be responsible for contamination. Fungi and bacteria are usually detected easily by the quality control department, as they change the visual appearance of the product. Contamination with mycoplasma is also fairly common (5, 40). Mycoplasma can be of human origin (due to defective conditions of manipulation of the vaccine) or from animal origin (present in the material of biological origin, e.g. cells, sera or eggs). Tests to detect mycoplasma are described in European Pharmacopoeia monographs (16) and the United States Code of Federal Regulations (2).

The most dramatic consequences are observed with viruses. The contamination reported in the literature is summarized in Table I.

Pestiviruses are the most common contaminants. The potential consequences of such contamination include severe disease in the vaccinated animals, and seroconversion (which could cause major problems in non-endemic areas or during eradication/elimination campaigns).

The control of materials of biological origin for adventitious agents should be mandatory: cell-lines, animal sera, trypsin of porcine origin, eggs, and viral and bacterial seeds should be tested extensively prior to manufacture. Whenever possible, the use of primary cell-lines should be avoided. The appropriate production procedures should be employed. Sera should be inactivated. All procedures should be conducted under sterile conditions, and should be validated in accordance with 'good manufacturing practice' and using 'state-of-the-art' technologies. Final products should be tested for sterility, safety and extraneous agents, either *in vitro* (using the most sensitive test systems) or *in vivo* (using seroconversion). Field trials should also form part of the prevention programmes, with intensive monitoring of animals before a licence is issued and vaccino-vigilance after marketing authorization is obtained.

TABLE I

*Sources and consequences of vaccine contamination reported in the literature*

Contaminant (ref.)	Vaccines	Consequences
Bluetongue virus (1, 46)	Modified live combination (CPIV, CDV, CAV <sub>2</sub> , CPV)	Abortion, death
Border disease virus (28, 42)	Pseudorabies/orf vaccine	Reproductive failure in sows and goats Iatrogenic pathology in piglets: - locomotor disorders - arthritis - eyelid oedema
Bovine virus diarrhoea virus (44, 45)	Cell culture	Seroconversion Immunosuppression
Bovine leukosis virus (35)	Babesiosis/anaplasmosis	Seroconversion during eradication programmes
Hog cholera virus (6, 23)	Pseudorabies/cell-lines	Seroconversion
Reticuloendotheliosis virus (48)	Marek's disease	Immunosuppression
Pseudovirus (48)	Marek's disease	Anaemia

CPIV: canine parainfluenza virus

CDV: canine distemper virus

CAV: canine adenovirus type 2

CPV: canine parvovirus

## CONCLUSIONS

Many infectious diseases of animals have been controlled through the use of vaccines. Although vaccination is frequently believed to be an innocuous procedure, it is important to recognize that vaccines can cause adverse reactions. Vaccination is a serious medical act. However, only a few directly observable detrimental effects occur as a result of immunization; this observation is a testament to the overall quality of commercial vaccines and current regulations. Manufacturers are developing effective quality assurance programmes. Co-operation between manufacturers, the government authorities granting licences and monitoring adverse reactions, and the end-users is necessary to guarantee the safety of biological products. New technologies and new regulations can be expected to make the new products even safer. These advances, together with the harmonization of legislation, should enable free trade of biologicals between an increasing number of countries.

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**ÉVALUATION DES RISQUES LIÉS AUX PRODUITS BIOLOGIQUES À USAGE VÉTÉRINAIRE : EFFETS SECONDAIRES CHEZ LES ESPÈCES ANIMALES CIBLES. – S. Martinod.**

**Résumé :** *En dépit de procédures de contrôle bien établies, l'utilisation à grande échelle de produits biologiques à usage vétérinaire peut entraîner des effets secondaires dont les plus répandus sont les suivants :*

- réactions locales suite à l'injection ;
- réactions systémiques ;
- réactions allergiques ;
- effets sur le système immunitaire ;
- pathogénicité résiduelle ;
- inactivation inadéquate ;
- recombinaison génétique ;
- contamination.

*Pour disposer en permanence de produits nouveaux et sûrs, il faut non seulement recourir aux technologies nouvelles mais aussi harmoniser les réglementations et veiller au respect des normes de qualité.*

MOTS-CLÉS : Effets secondaires – Sécurité – Vaccins.

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**EVALUACIÓN DE RIESGOS APLICADA A PRODUCTOS BIOLÓGICOS DE USO VETERINARIO: EFECTOS SECUNDARIOS EN LOS ANIMALES TRATADOS. – S. Martinod.**

**Resumen:** *A pesar de las acostumbradas medidas de control, el empleo a gran escala de productos biológicos en la medicina veterinaria puede entrañar la aparición de efectos secundarios. Entre los observados con mayor frecuencia se encuentran los siguientes:*

- reacciones locales en el punto de inyección
- reacciones sistémicas
- reacciones alérgicas
- efectos en el sistema inmunitario
- patogenicidad residual
- inactivación inadecuada
- recombinación genética
- contaminación.

*Nuevas tecnologías, nuevas normativas legales armonizadas y un compromiso de calidad deben asegurar en el futuro un aporte continuo de productos innovadores y seguros.*

PALABRAS CLAVE: Efectos secundarios – Seguridad – Vacunas.

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## REFERENCES

1. AKITA G., IANCONESCU M., MCLACHLAN N., OSBURN B. & GREENE R. (1994). – Bluetongue disease in dogs associated with contaminated vaccine. *Vet. Rec.*, **135**, 283-284.
2. ANON. (1994). – Title 9, Section 113.28. United States Code of Federal Regulations. United States Government Printing Office, Washington, D.C.
3. APLEY M., ARMSTRONG D. & WRAY M. (1994). – Subcutaneous injection site comparison of two multiple valent clostridial bacterin-toxoids in feedlot cattle. *Agri. Practice*, **15** (12), 9-12.
4. BARTELING S., WOORTMEYER R. & VISSER N. (1983). – Innocuity testing of foot and mouth disease vaccines. I. Formaldehyde inactivated alhydrogel vaccines. *J. biol. Standard.*, **11**, 297-304.
5. BENISHEVA T., SOVOVA V., IVANOV I. & OPALCHENOVA G. (1993). – Comparison of methods used for detection of mycoplasma contamination in cell culture and live virus vaccines. *Folia. biol.*, **39** (5), 270-276.
6. BOLIN S., BLACK J., FREY M., KATZ J., RIDPATH J. & ROBLIN R. (1994). – Detection of a cell line contaminated with hog cholera virus. *J. Am. vet. med. Assoc.*, **205** (5), 742-745.
7. BROWN F. (1991). – An overview of the inactivation of FMDV and the implications when residual virus is present in vaccines. *Dev. biol. Stand.*, **75**, 37-41.
8. BROWN F. (1993). – Review of accidents caused by incomplete inactivation of viruses. *Dev. biol. Stand.*, **81**, 103-107.
9. BRUN A., GODARD A. & MOREAU Y. (1981). – La vaccination contre la myxomatose – vaccins hétérologues et homologues. *Bull. Soc. Sci. vét. Méd. comp. Lyon*, **83** (5), 251-254.
10. BRYAN L., FENTON R., MISRA V. & HAINES D. (1994). – Fetal generalized bovine herpes virus type 1 infection associated with a modified live infectious bovine rhinotracheitis parainfluenza 3 vaccine administered to neonatal calves. *Can. vet. J.*, **35**, 223-228.
11. CHEPURKIN A., ONUFRIEV V., MURAVEV V., SHUL'GA A. & CHEKHORISKI G. (1975). – Anaphylactic reaction to foot and mouth disease vaccines in cattle. *Veterinariya, Moscow*, **5**, 64.
12. COETZEE L. & ROGERS E.J. (1983). – The detrimental side effects of *Haemophilus paragallinarum* oil emulsion vaccine on chickens of varying ages [in Spanish]. In Abstracts XXII World Veterinary Congress (C. Main, ed.). Perth, Australia, 21-26 August. World Veterinary Congress Organising Committee, Perth, Australia, 190.
13. DALGLEISH R. & LOVE S. (1993). – Possible basis of adverse reactions to vaccination against equine influenza. *Vet. Rec.*, **132**, 658-659.
14. DEXTER D., COWMAN G., MORGAN J., CLAYTON R., TATUM S., SOFOS J., SCHMIDT G., GLOCK R. & SMITH G. (1994). – Incidence of injection site blemishes in beef top sirloin butts. *J. Anim. Sci.*, **72**, 824-827.
15. ERDOS L., LANG C., JASZOVSZKY I. & NYERGES G. (1975). – The demonstrations of the sensitizing effect of the residual animal serum content of vaccines. *J. biol. Standard.*, **3**, 77-82.
16. EUROPEAN PHARMACOPOEIA (1991). – Monograph V. 2. 1. 3. 6. Maisonneuve, Paris.
17. FEDIDA M., DANNACHER G., BELLI P. & COUDERT M. (1986). – Accidents survenus après vaccination anti-aphteuse au cours de la campagne 1984-1985 : les causes possibles. *Rec. Méd. vét.*, **162**, 947-971.
18. FRICK O. & BROOKS D. (1981). – Immunoglobulin E antibodies to pollens augmented in dogs by virus vaccines. *Am. J. vet. Res.*, **44** (3), 440-445.

19. GEORGE L., ARDANS A., MIHALYI J. & REINA JUERRA M. (1988). – Enhancement of infectious bovine keratoconjunctivitis by modified live infectious bovine rhinotracheitis virus vaccine. *Am. J. vet. Res.*, **49** (11), 1800-1805.
20. HARLAND R., POTTER A.A., VAN DRUNEN LITTEL-VAN DEN HURK S., VAN DONKERSGOED J., PARKER M., ZAMB T. & JANZEN E. (1992). – The effect of subunit or modified live herpes virus 1 vaccines on the efficacy of a recombinant *Pasteurella haemolytica* vaccine for the prevention of respiratory disease in feedlot calves. *Can. vet. J.*, **33**, 734-741.
21. HENDRICK M., GOLDSCHMIDT M., SHOFER F., WANG Y. & SOMLYO A. (1992). – Postvaccinal sarcomas in the cat: epidemiology and electron probe microanalytical identification of aluminum. *Cancer Res.*, **52** (19), 5391-5394.
22. HENDRICK M., SHOFER F., GOLDSCHMIDT M., HAVILAND J., SCHELLING S., ENGLER S. & GLIATTO J. (1994). – Comparison of fibrosarcomas that developed at vaccination sites and at nonvaccination sites in cats: 239 cases (1991-1992). *J. Am. vet. med. Assoc.*, **205** (10), 1425-1429.
23. HOLMJENSEN M. (1981). – Hog cholera antibodies in pigs vaccinated with an Aujeszky vaccine based on antigen produced in IBR-S-2 cells. *Acta vet. scand.*, **22**, 517-523.
24. KASS P., BARNES W., SPANGLER W., CHOMEL B. & CULBERTSON M. (1993). – Epidemiologic evidence for a causal relation between vaccination and fibrosarcoma tumorigenesis in cats. *J. Am. vet. med. Assoc.*, **203**, 396-405.
25. KATZ J.B., HENDERSON L.M. & ERICKSON G.A. (1990). – Recombination *in vivo* of pseudorabies vaccine strains to produce new virus strains. *Vaccine*, **8**, 286-288.
26. KUSTERS J.G., JAGER E.J., NIESTERS H.G.M. & ZEIJL B.A.M. VAN DER (1990). – Sequence evidence for RNA recombination in field isolates of avian coronavirus infectious bronchitis virus. *Vaccine*, **8**, 605-608.
27. LITLEDIKE E. (1993). – Variation of abscess formation in cattle after vaccination with a modified live *Pasteurella haemolytica* vaccine. *Am. J. vet. Res.*, **54** (8), 1244-1248.
28. LOKEN T., KROGSRUD J. & BJERKA S. (1991). – Outbreaks of border disease in goats induced by a pestivirus-contaminated orf vaccine with virus transmission to sheep and cattle. *J. comp. Path.*, **104** (2), 195-209.
29. LORENZ R. & STRAUB O. (1971). – Statistische Erhebungen über Impfschaden nach der Maul- und Klauenseuche – Schutzimpfung im Jahr 1968-1969. *Zentbl. Bakt. I Orig.*, **216**, 448-465.
30. METTENLEITER T., KLUPP B., WEILAND F. & VISSER M. (1994). – Characterization of a quadruple glycoprotein-deleted pseudorabies virus mutant for use as a biologically safe live virus vaccine. *J. gen. Virol.*, **75** (7), 1723-1733.
31. NYEGES G., MASTON A., KOROSSY S. & VINEZE I. (1982). – Sensitizing activity to egg protein of an AIPO<sub>4</sub> adjuvanted full virus influenza vaccine. *Acta microbiol. Acad. Sci. hung.*, **23**, 245-253.
32. PHILLIPS T., JENSEN J., RUBINO M., YANG W. & SCHULTZ R. (1989). – Effects of vaccines on the canine immune system. *Can. J. vet. Res.*, **53**, 154-160.
33. PHILLIPS T. & SCHULTZ R. (1992). – Canine and feline vaccines. In *Current veterinary therapy*, XI (R. Kirk & J. Bonagura, eds). W.B. Saunders Co., Philadelphia, 202-206.
34. PICAULT J.P., GUITTET M. & BENNEJEAN G. (1982). – Innocuité et activité de différents vaccins de la laryngotrachéite infectieuse aviaire. *Avian Pathol.*, **11**, 39-48.
35. ROGERS R., DIMMOCK C., DE VOS A. & RODWELL B. (1988). – Bovine leukosis virus contamination of a vaccine produced *in vivo* against bovine babesiosis and anaplasmosis. *Aust. vet. J.*, **65** (8), 285-287.

36. SMITH P., NUSBAUM K., KWAPIEN R., STRINGFELLOW D. & DRIGGERS K. (1990). – Necrotic oophritis in heifers vaccinated intravenously with infectious bovine rhinotracheitis virus vaccine during estrus. *Am. J. vet. Res.*, **51** (7), 963-972.
  37. SOOS T. (1987). – Some problems of testing foot and mouth disease vaccine. 1. Innuocuity testing. *Acta vet. hung.*, **35** (3), 319-330.
  38. STOKKA G., EDWARDS A., SPIRE M., BRANDT R. & SMITH J. (1994). – Inflammatory response to clostridial vaccines in feedlot cattle. *J. Am. vet. med. Assoc.*, **204** (3), 415-419.
  39. STRAW B., SHIN S., CALLIHAN D. & PETERSEN M. (1990). – Antibody production and tissue irritation in swine vaccinated with *Actinobacillus* bacterins containing various adjuvants. *J. Am. vet. med. Assoc.*, **196** (4), 600-604.
  40. THORNTON D. (1986). – A survey of mycoplasma detection in veterinary vaccines. *Vaccine*, **4**, 237-240.
  41. VANNIER P. (1986). – Immunisation des porcs charcutiers contre la maladie d'Aujeszky avec deux vaccins à adjuvants huileux. Etude des réactions locales. *Rec. Méd. vét.*, **162** (1), 37-44.
  42. VANNIER P., LEFORBAN Y., CARNERO R. & CARIOLET R. (1988). – Contamination of a live virus vaccine against pseudorabies (Aujeszky's disease) by an ovine pestivirus pathogen for the pig. *Ann. Rech. vét.*, **19**, 283-290.
  43. WALSH J. & HINES D. (1993). – Clinical field safety trial for a feline leukemia virus vaccine. *Feline Practice*, **21** (1), 22-23.
  44. WELLERMANS G. & VAN OPDENBOSCH E. (1987). – Mise en évidence du virus BVD (*bovine viral diarrhoea virus*) dans plusieurs lignées cellulaires. *Ann. Rech. vét.*, **18**, 99-102.
  45. WENSVOORT G. & TERPSTRA C. (1988). – Bovine viral diarrhoea virus infections in piglets born to sows vaccinated against swine fever with contaminated vaccine. *Res. vet. Sci.*, **45**, 143-148.
  46. WILBUR L., EVERMANN J., LEVINGS R., STOLL I., STARLING D., SPILLERS C., GUSTAFSON G. & MCKEIRNAN A. (1994). – Abortion and death in pregnant bitches associated with a canine vaccine contaminated with bluetongue virus. *J. Am. vet. med. Assoc.*, **11**, 1762-1765.
  47. YERUHAM I., PERL S., NYSKA A., ABRAHAM A., DAVIDSON M., HAYMOVITCH M., ZAMIR O. & GRINSTEIN H. (1994). – Adverse reactions in cattle to a capripox vaccine. *Vet. Rec.*, **135**, 330-332.
  48. YUASA N., TANIGUCHI T. & YOSHIDA I. (1988). – Isolation and some characteristics of an agent inducing anemia in chickens. *Avian Dis.*, **23** (2), 366-385.
-