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Modes of vaccine administration at a glance

Applikationsarten für Impfstoffe im Vergleich

Birgit Makoschey

Summary

A number of different vaccination techniques are applied in farm animals. The intramuscular, subcutaneous and intradermal injection of vaccines are parenteral application methods that are currently used for different attenuated and inactivated vaccines. The injection may be performed by needle or pressure. Depending on the method of application, the mucosal immunization can be performed intraocular, intranasal and/or oral. In general, the vaccine follows the natural route of infection of the respective pathogen. Attenuated vaccines usually replicate in the primary target organs.
Mucosal application of attenuated vaccines via drinking water or spray are routinely applied in poultry. Both techniques offer advantages for mass application.
The administration route and the method of vaccination have a great influence on the efficacy and safety of a vaccine. The instructions of the manufacturers must therefore be strictly respected.
Unfortunately, there is no ideal administration method applicable for any vaccine in all species.

Keywords: farm animals, vaccine safety, vaccine efficacy, application route

Zusammenfassung

In der Nutztiermedizin wird eine Vielzahl von verschiedenen Impftechniken angewendet. Die intramuskuläre, subkutane und intradermale Impfstoffinjektion sind parenterale Applikationsarten, die für verschiedene attenuierte und inaktivierte Impfstoffe angewendet werden. Die Vakzine wird dabei mittels Nadel oder durch Druck entsprechend tief in das Gewebe eingebracht.
Je nach Applikationsmethode kann eine mukosale Immunisierung intraokulär, intranasal und/oder oral verabreicht werden. Damit folgt die Impfung im Allgemeinen der natürlichen Infektionsroute des entsprechenden Erregers. Attenuierte Vakzinen replizieren dann im Allgemeinen in den primären Zielorganen. In der Geflügelhaltung wird die mukosale Immunisierung über das Trinkwasser oder mittels Spray zur Impfung großer Tierzahlen eingesetzt.
Die Applikationsart und die Impfmethode haben einen großen Einfluss auf die Wirksamkeit und Unschädlichkeit eines Impfstoffes. Die diesbezüglichen Angaben der Hersteller sollten daher unbedingt berücksichtigt werden. Leider gibt es keine ideale Applikationsmethode die für jeden Impfstoff und alle Tierarten geeignet ist.

Schlüsselwörter: Nutztiere, Unschädlichkeit, Wirksamkeit, Applikationsart

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Categorization of the different modes of administration accordingto the site of administration

The modes of administration and administraton techniques that are commonly used for the active immunization of farm animals are discussed here. According to the site of administration routes of application categorized into mucosal, also referred to as local, and parenteral administration routes (Fig. 1).

For mucosal administration, the vaccine is deposited on mucosal surfaces. While basically all mucosal surfaces have been investigated under experimental conditions, only the mucosae of the head of the animal, is used under field conditions, i. e. by oral, intransal or intraoccular vaccination.

Parenteral vaccination is the injection of the immunological product into the animal using a needle or pressure. Common routes in farm animals are the intramuscular, subcutaneous, and intradermal route (Fig. 2). The latter is technically challenging as the vaccine may not be deposited too deep or too superficial. Therefore, special devices have been developed, for example for the intradermal vaccination of pigs.

In ovo administration of poultry vaccines takes a special position. The vaccine is deposited into the amniotic sac, or directly into the embryo. Nowadays, most commercial broiler hatcheries in the US routinely apply in ovo vaccination by automated injection systems for the control of Marek's disease. Thanks to the advantages of convenience, the technology is also applied or under investigation for other viral vaccines including Newcastle, bronchitis and bursal disease, and bacterial and parasitic vaccines.

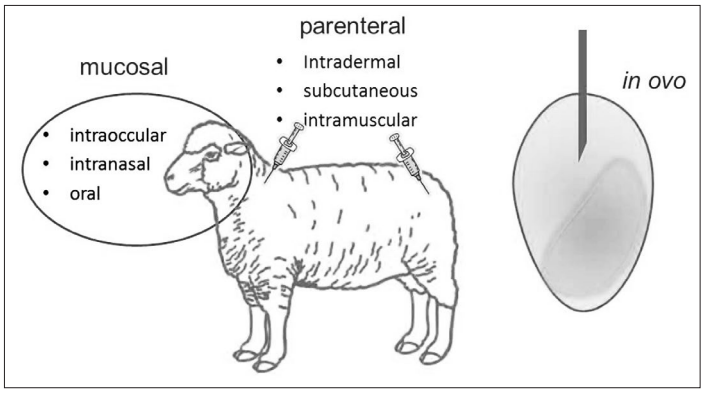

FIGURE 1: *Categorization of routes of administration according to the site of administration.*

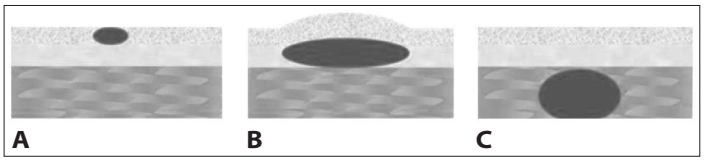

FIGURE 2: *Schematic representation of the location of vaccine deposition for the different routes for parenteral injection (A: intradermal, B: subcutaneous, C: intramuscular).*

Relevance for vaccine development

The safety and efficacy profile of a vaccine is not only determined by the composition but also by the mode of administration. Therefore, the intended mode(s) of administration need(s) to be defined already during the early research process for a new vaccine. The preferences often depend on animal species and practical aspects. Based on experiences from existing vaccines, it is possible to make a pre-selection of potential modes of administration, however this has to be confirmed by experimental data once the final composition of the vaccine is fixed. Manufacturers may directly compare different modes of administration in order to select the best one(s). Preferably, the easiest route of application can be used for a new development to simplify administration, reduce impact on animal welfare but keep the efficacy. Experiences from such comparative trials are reported here.

For each route of administration and each method of administration to be recommended, the safety and immunogenicity of a vaccine have to be demonstrated according to the European Legislation on vaccines for veterinary use (The European Directorate for the Quality of Medicines & Health Care, 2015).

Safety aspects

For live bacterial vaccines that cause tissue damage at the parenteral injection site, mucosal administration might be the safer adminstration route. On the other hand, we have investigated the shedding of a live marker vaccine against Infectious Bovine Rhinotracheitis (IBR) after intranasal and intramuscular vaccination (Makoschey and Beer, 2007). The vaccine virus could be detected in nasal discharge during several days following intranasal vaccination, while all swab samples taken from calves vaccinated intramuscularly were found negative for the vaccine virus. This observation is in line with a report from Mizuno and colleagues (Mizuno et al., 2008) who isolated a *Salmonella* Dublin vaccine strain for up to eight days from the faeces of orally vaccinated calves, but not intramuscularly vaccinated calves. By contrast, Kramer and colleagues (Kramer et al., 1987) measured transient fecal shedding of a *Salmonella* Dublin vaccine strain from pigs vaccinated IM, but not in two groups of pigs vaccinated intraoccularly.

It should be pointed out though, that a vaccine might also be shed regardless of the route of administration.

When comparing different parenteral routes in general, adverse reactions are typically milder after intradermal administration. In fact, the site effects after vaccination of calves with a *Brucella* vaccine according to the traditional route lead R. Walton in 1944 to investigate the possibility of intradermal vaccination. The results were satisfactory (Walton, 1944).

In the meantime, several vaccines for farm animals are routinely applied by the intradermal route (Fig. 3). This technique has a number of advantages with regards to safety aspects: It has been shown to be less invasive and painless (Ferrari et al., 2011). For those vaccines for which the intradermal route has been licensed, the tissue tolerance is very good. However, not all vaccines and especially not all adjuvants are suitable for intradermal application.

Immunological aspects

The immunological mechanisms following administration of a vaccine on mucosal surfaces are very much different compared to parenteral injection. After mucosal vaccination, especially intranasal or oral, attenuated vaccines might replicate to a larger or smaller extent in the primary target organs and mimic a natural infection. They bind to their specific receptors and enter the target cells, where they replicate. Replication can be associated with cell damage which provoques an immune response as well. Parentally administered inactivated vaccines must be taken up and processed by specific immune

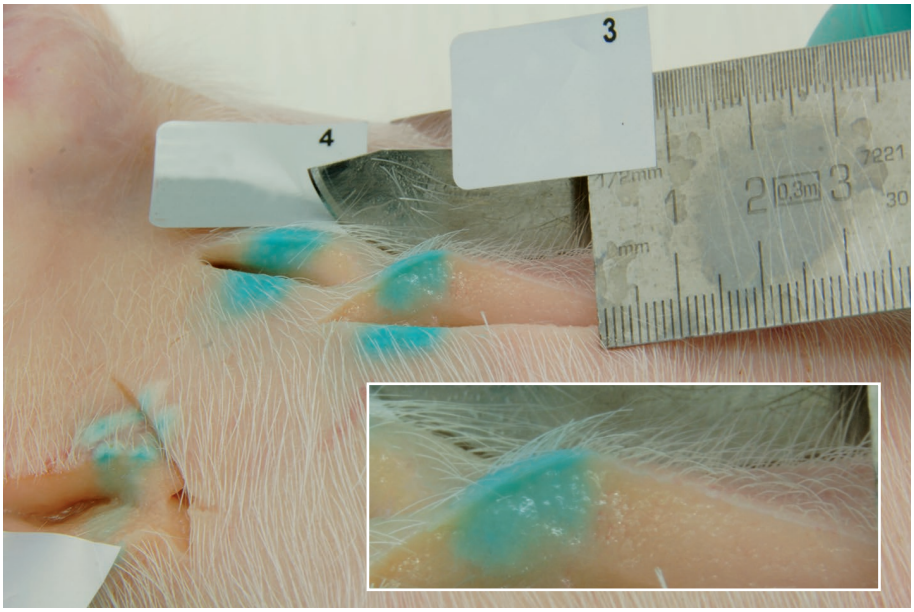

FIGURE 3: *Localization of a dye applied with an intradermal vaccination device.*

cells in order to induce a specific immune response. The immunological response to parentally applied live vaccines depends on the replication competence and dissemination of the vaccine strain in the vaccinees. If the vaccine reaches the target organs, the immune response might be similar to the response after mucosal vaccination. Vaccines that replicate poorly and remain located at the injection site behave similar to inactivated vaccines in this respect.

The mucosal surfaces are in direct contact with the outside environment. The immune system has evolved a range of specific mechanisms to set up a first line of defence (Holt et al., 2008). The nasopharynx-associated lymphoid tissue (NALT) and the Peyer's patches have an important role in the induction of mucosal immune responses (Kiyono and Fukuyama, 2004). Intranasal immunization can lead to the induction of antigen-specific protective immunity in both the mucosal and systemic immune compartments (Kiyono and Fukuyama, 2004).

Several studies with viral and bacterial vaccines have demonstrated that some vaccines can confer protection after mucosal or parenteral administration, though apparently different immunological pathways were activated as the measured immune parameters, for example antibody levels, varied between the different groups that were protected (Kimman et al., 1989; Hammond et al., 2003; Patel et al., 2004; Buddle et al., 2005; Ellis et al., 2007; Blodorn et al., 2014). In general, the local immune response including cytokines was more pronounced after mucosal administration and clinical protection might develop without notable systemic IgG or IgA responses at the time of challenge.

Some authors propose successive intranasal and intramuscular administration for better stimulation of the immune response (Labarque et al., 1999).

Mucosal administration of a vaccine does not only induce a specific immune response, but activates also the innate immune system (Ellis et al., 2007). A live IBR marker vaccine administered intranasally established partial protection against challenge with virulent field virus (Makoschey and Keil, 2000) prior to the development of an active immune response. On the other hand, intramuscular administration was superior to oral administration in case of an experimental *Salmonella* vaccine as better early onset protection in young calves following challenge was provided (Mizuno et al., 2008).

In general, vaccines, and especially attenuated vaccines might be hampered by maternal immunity when applied parenterally because the circulating antibodies can neutralize the vaccine. This does not or to a much lesser extent happen when they are applied mucosally (Kimman et al., 1987; van Oirschot, 1987). However, for some vaccines efficacy has been demonstrated also after parenteral application in face of maternally derived antibodies (Mawhinney and Burrows, 2005; Haake et al., 2014).

With regards to the different parenteral routes, only very limited information is available for the comparison between intramuscular and subcutaneous route. The choice between these two routes is often driven by practical aspects, such as available application devices rather than on immunological grounds. In a recent comparative study with an attenuated sheep vaccine better efficacy was demonstrated after intramuscular application as compared to subcutaneous application (Wichgers Schreur et al., 2015).

The immune response induced by intradermal vaccination of pigs in comparison with the intramuscular route was studied with an attenuated vaccine against Aujeszky's disease (Ferrari et al., 2011) and an inactivated vaccine against Food and Mouth disease (Eble et al., 2009). After intradermal application, the vaccine is taken up by dendritic cells. These cells process the antigens and transport them to the local draining lymphnode. This results in an optimal stimulation of the immune system. For several vaccines it has been demonstrated that a lower dose is required for intradermal application as compared to intramuscular application to obtain the same level of efficacy. This may reduce the production costs per dose of vaccine markedly. However, this is not always the case as we experienced in a recent trial with a live attenuated Rift Valley Fever vaccine for sheep (unpublished data).

Technologies for vaccination of large numbers of animals

Needle-less devices have been developed to facilitate the parenteral vaccination of large numbers of animals. The available devices have an internal piston that is driven back by gas or electric power. At the time of injection, the dose is delivered by the piston. The initial fluid jet pierces the skin, allowing the dose to be delivered into the dermis, subcutaneous tissues and, depending on the device, orifice size and pressure setting, into the muscle. This technology has multiple advantages from the animal health point of view. The dosing is more accurate because contact with the animal is required to trigger vaccine delivery. Secondly, pathogens cannot be transmitted between animals via the injection device. In addition, there are also advantages for the personnel performing the vaccination in terms of less repetitive motion injuries and no needle stick accidents. Last but not least also the risk of broken needles in carcasses that account for large volumes of condemned meet is eliminated.

Currently, needle-free devices are mainly applied to vaccinate pigs due to the larger herd sizes as compared to cattle because the implementation is more costly than conventional needle and syringe.

Distinct techniques have been developed to vaccinate the large numbers of animals in poultry farms. The in ovo vaccination has been mentioned before. Fully automated devices can inject more than 100 000 eggs per hour.

Mucosal application of attenuated vaccines via drinking water or spray are routinely applied in poultry. Both techniques offer the advantages of mass application: requiring less time, labor and minimizing bird stress while inducing good mucosal and systemic immunity.

Even though these techniques involve application to thousands of birds at one time, the goal is the same as for individual bird vaccination: deliver a minimum of one dose of vaccine to the target organ of each bird. Not only does the dose of vaccine have to be adequate, but it must be alive when it reaches the birds in order to replicate and induce an immune response. Under practical conditions the aim is to vaccinate the highest possible proportion of birds in a flock in order to minimize the effects of a particular disease.

Both, for spray vaccination and for vaccination by drinking water, it is of utmost importance that the technique is performed correctly. In the case of spray vaccination, the droplet size affects which part of the respiratory tract the spray reaches. Larger droplets are precipitated in the upper range, smaller droplets reach the deeper regions of the lungs and air sacs. Thus, the droplet size has a decisive influence on the effectiveness of the spray vaccination. The distribution of the droplet size also depends on the nebulizer used.

When vaccinating by drinking water, the specificities of the watering system must be respected to secure the effectiveness of the vaccine.

Future perspectives

As herd sizes continue to increase, technologies that allow vaccination of large numbers of animals will gain in importance, also for pigs and cattle.

In wild animals there are good experiences with oral immunization in the control of rabies (Muller et al., 2012) and classical swine fever (Dietze et al., 2013). Moreover, the oral route has been studied experimentally also for bacteria (Buddle et al., 2005). This could offer new opportunities in the future for the vaccination of livestock.

Despite the good experiences with intranasal vaccination, results with an aerosolized attenuated vaccine in cattle were not very promising (Jericho and Langford, 1982; Mann et al., 1983).

Currently mass application methods are limited to attenuated vaccines. Peters and colleagues (Peeters et al., 2014) provided a proof-of-concept that pulmonary vaccination using a powder formulation of an inactivated vaccine is able to protect chickens from lethal challenge. Yet, the efficacy needs to be improved before the technology can be applied in the field.

Conclusion

The examples show that the route of administration and the method of vaccination have a great influence on the efficacy and safety of a vaccine. The instructions of the manufacturers must therefore be strictly followed.

There is no ideal administration method applicable for any vaccine in all species.

Conflict of interest

The author is employee of MSD Animal Health, a company that markets animal health products. The author does not have any financial, professional or other personal interests in a product that might have influenced the content of the manuscript presented above.

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