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Tomorrow's vector vaccines for small ruminants

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ABSTRACT

Inactivated and attenuated vaccines have contributed to the control or even the eradication of significant animal pathogens. However, these traditional vaccine technologies have limitations and disadvantages. Inactivated vaccines lack efficacy against certain pathogens, while attenuated vaccines are not always as safe. New technology vaccines, namely DNA and recombinant viral vector vaccines, are being developed and tested against pathogens of small ruminants. These vaccines induce both humoral and cellular immune responses, are safe to manufacture and use and can be utilized in strategies for differentiation of infected from vaccinated animals. Although there are more strict regulatory requirements for the safety standards of these vaccines, once a vaccine platform is evaluated and established, effective vaccines can be rapidly produced and deployed in the field to prevent spread of emerging pathogens. The present article offers an introduction to these next generation technologies and examples of vaccines that have been tested against important diseases of sheep and goats.

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1. Introduction

Since the time of Eduard Jenner and Louis Pasteur, vaccines have contributed to prevention, control and even eradication of human and animal diseases more than any other tool available to human or veterinary medicine (Riedel, 2005; Lombard et al., 2007). Classical vaccine technologies, including inactivated and attenuated vaccines, have been used for decades with significant success against a number of viral and bacterial diseases of livestock (Meeusen et al., 2007; Food and Agriculture Organization (FAO), 2011). However, these technologies have their limitation and disadvantages.

Inactivated ('killed') vaccines, while safe and relatively inexpensive to produce, if the relevant pathogen would grow well, are not effective against all diseases, as they mainly induce humoral immune responses. Thus, they do not protect against viruses or bacteria that require a strong cell-mediated immune response for elimination. Overall, inactivated vaccines are considered as poor immunogens and they do not always offer long-lasting immunity to the individual animal or the vaccinated population (Melnick, 1978). For this reason, often, they require addition of an adjuvant to boost their immunogenicity, especially when administered to immunologically naive animals.

Attenuated ('live') vaccines replicate in the cells of the immunized individual and induce strong antibody and cell-mediated immune responses, thus they are more effective compared to attenuated vaccines. On the other hand, they are less safe for the animals and occasionally, for humans. There are a number of rare incidents, in which attenuated viruses or bacteria have regained their pathogenicity following vaccine administration and have spread causing disease (Nielsen et al., 2001; Murti et al., 2013). The Rev 1 vaccine against *Brucella melitensis* is notorious for causing brucellosis to veterinarians vaccinating sheep or goats in eradication campaigns (Blasco and Diaz, 1993). Attenuation of highly virulent pathogens or newly-emerged viruses or bacteria poses a risk for animal and human health and requires high biosafety level facilities to manufacture; this process is also time-consuming, and may result in a too-late introduction to the field of a necessary control tool in the case of a novel disease outbreak. Finally, attenuated vaccines are also more difficult to preserve and transport, especially in tropical and subtropical climates, as they are not stable in high temperatures (Chen and Kristensen, 2009).

Furthermore, some viruses or bacteria do not grow well or at all *in vitro*, which means that neither attenuation nor inactivation can be employed for vaccine production (Small and Ertl, 2011).

Vaccines most frequently used in small ruminant health management include, among others, preparations against: *Chamydophila abortus*, *Clostridium perfringes*, *Clostridium chauvoei* and *Clostridium* tetani, *Fusobacterium necrophorum* and *Dichelobacter nodosus*, *Leptospira* spp., *Mycobacterium avium* subsp. *paratuberculosis*, *Mycoplasma agalactiae* and *Orf Virus*. These vaccines, when properly administered in a vaccination schedule adjusted to the

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needs of the flock/herd, are considered to be highly effective and can significantly improve the population's health (Responsible Use of Medicines in Agriculture Alliance, 2006; Menzies, 2012; Videnova and Mackay, 2012). Nevertheless, there are pathogens, e.g., *Foot-and-Mouth Disease Virus*, *Bluetongue Virus*, *Rift Valley Fever Virus*, *Peste des Petit Ruminants Virus*, Small ruminant Lentiviruses, *Coxiella burnetii*, *B. melitensis* and *Brucella* abortus, for which classical vaccine technologies have partly or completely failed to control or eradicate. This may not always be the result of vaccine inefficacy. Nevertheless, better and/or safer vaccines against these pathogens may contribute to their control.

Climate change combined with unrestricted trade of animals and animal products over the last two decades have resulted in the emergence or re-emergence of novel or historic pathogens that rapidly spread within animal populations. Examples include the Foot-and-Mouth disease outbreak in the United Kingdom in 2001 (Anon, 2001), Bluetongue in Northern Europe in 2006 (Elbers et al., 2008; OIE, 2006) and the emergence of Schmallenberg virus in 2011 (Hoffmann et al., 2012). These events further demonstrate a need for development and application of new technologies that would allow production of effective, safe, rapid-to-manufacture and cost-effective vaccines. Whilst development of inactivated vaccines against most pathogens remains the most realistic approach, alternative technologies should also be considered.

Progress of molecular technologies, including PCR, next generation sequencing and, most importantly, genetic engineering with the exploitation and utilization of double-stranded DNA molecules (plasmids), have allowed us to manipulate DNA and viruses, in order to produce new technology vaccines that offer promising alternatives to inactivated and attenuated vaccines (Ferraro et al., 2011; Small and Ertl, 2011).

DNA and recombinant virus vector vaccines have been proven to elicit both humoral and cell-mediated immune responses (Shedlock and Weiner, 2000; Nayak and Herzog, 2010), they are safe to produce and use, as only the genes coding significant antigens of a pathogen are required for vaccine production and they can be rapidly manufactured, because ready-to-use platforms are being developed or are currently available (Verity et al., 2012; Vellinga et al., 2014).

Furthermore, it should be stressed out that these new technology vaccines maintain another significant advantage over most classical vaccines: they may be used in differentiation of infected and vaccinated animals (DIVA) strategies, which are critical for the eradication of animal diseases and control of new introductions of historical pathogens in disease-free regions (Capua and Cattoli, 2007; Noad and Roy, 2009).

Objective of this review is to present these new generation vaccine technologies, focusing on the most widely tested platforms that have generated vaccines against sheep and goat pathogens. Other new technology vaccines, such as subunit, virus-like particle and disabled infectious single cycle (DISC) vaccines will not be discussed.

2. DNA vaccines

Plasmids are double-stranded circular DNA molecules, originally found in bacteria as extra-chromosomic DNA, usually carrying antibiotic resistance genes (Thomas and Summers, 2008). Plasmids can be genetically engineered *in vitro*, where one or more genes expressing the desired key antigens (proteins) from viruses, bacteria or parasites may be added. Once delivered to the target species, plasmids transfect the host cells and the desired gene or genes are expressed in the cytoplasm or on the cell surface. Similarly to attenuated vaccines, plasmid DNA vaccines generate both $CD4^+$ and $CD8^+$ T-cell responses (Shedlock and Weiner, 2000; Ferraro et al., 2011). Several delivery methods have been proposed and tested, including needle-free approaches (e.g., particle bombardment using a gene gun). The degree of stimulation of different immune responses largely depends on the route of vaccination (Ferraro et al., 2011). Needle inoculation, whether intramuscular, intradermal or intraperitoneal injection, leads to an increased cell-mediated immune response, while gene gun and electrocorporation promote a stronger antibody production (Torres et al., 1997; Feltquate et al., 1997; Rosati et al., 2008).

Naked DNA was first used *in vivo* in the 1980s when insulin expression was observed following injection of plasmid DNA coding the protein in rats (Nicolau et al., 1983; Benvenisty and Reshef, 1986; Wolff et al., 1990 Wolff et al., 1990). In the 1990s, so-called 'first-generation' DNA vaccines were tested in mice inducing antibody responses against viral or non-viral antigens (Tang et al., 1992; Ulmer et al., 1993; Fynan et al., 1993). The prospects of DNA vaccination caused excitement to the scientific community and early technologies were tested against two of mankind's most challenging pathogens: *Human Immunodeficiency virus* (HIV) and *Plasmodium* spp. (the cause of Malaria), but with limited success (MacGregor et al., 1998; Wang et al., 1998). 'Second-generation' DNA vaccines, developed over the following years, are characterized by improved uptake of the plasmid by the cells and more robust immune responses (Kutzler and Weiner, 2008; Yager et al., 2009). These advancements are attributed to the optimization of antigen coding, resulting in enhanced transfection efficiency, improved formulation, inclusion of adjuvants and exploitation of different delivery approaches (Ferraro et al., 2011). Original concerns regarding DNA vaccine safety focused on possible integration of the plasmid in the genome of the host cells and anti-DNA immune responses (Ferraro et al., 2011). So far, the platform appears to be at least as safe as conventional vaccines with little evidence of plasmid DNA integration and no significant increase of autoimmunity markers reported in clinical trials (Ledwith et al., 2000; Wang et al., 2004; Sheets et al., 2006; Tavel et al., 2007). Currently, DNA vaccines against *Canine Melanoma Virus*, *West Nile Virus* and *Fish Infectious Haematopoietic Necrosis Virus* are licensed and commercially available (Ferraro et al., 2011).

Foot-and-Mouth disease has been in the forefront of DNA vaccine research. Over 20 DNA vaccines have been tested, some offering partial to full protection (Fowler and Barnett, 2012). There is also an increased interest in Small ruminant Lentiviruses, against which a number of DNA vaccines have been tested with promising results, especially when combined with attenuated or viral vector vaccines in a prime/boost strategy (Reina et al., 2013). *Bluetongue Virus* and *Rift Valley Fever Virus* vaccines have also been developed for use in small ruminants (Lagerqvist et al., 2009; Bhardwaj et al., 2010; Jabbar et al., 2013; Calvo-Pinilla et al., 2009, 2014). As in the case of DNA vaccines against *Small ruminant lentiviruses*, a prime/boost strategy has been suggested. In recent years, due to the controversial safety profile of attenuated vaccines, DNA vaccine platforms have also been tested against *B. melitensis* and *B. abortus*. These vaccines appear to elicit both antibody and strong cell-mediated immune responses in different animal models, thus appearing as promising candidates to replace the current vaccines (Clapp et al., 2011; Al-Mariri and Abbady, 2013; Riquelme-Neira et al., 2013; Olsen, 2013).

3. Recombinant viral vector vaccines

Viruses have been characterized as obligate intra-cellular parasites. They cannot grow or reproduce by themselves; instead, they 'hijack' the endocytic machinery of their host cell, in order to produce progeny viral particles (Lopez and Arias, 2010). Until recently, viruses were only thought of as pathogens that could harm humans and animals. However, advances in molecular virology, already from the 1980s, enable us to manipulate them

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