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Classical swine fever virus vaccines: An updated review

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Abstract
Classical swine fever (CSF) is one of the most devastating viral infectious disease affecting the members of Suidae family, which causes a severe impact on the global economy. The CSF aetiological agent is the Classical Swine Fever Virus (CSFV) an enveloped, single, positive stranded RNA virus belonging to Pestivirus genus and Flaviviridae family. The disease is notifiable to the World Organization for Animal Health (OIE) due to its enormous consequences on porcine health and the pig industry. Response policy to notification of an outbreak differs among different countries. In CSF endemic countries a mass vaccination approach is adopted for the disease control. Further, the negative aspects related with mass stamping out policies, including elevated costs and ethical issues, point out vaccination as the main control measure against future outbreaks. Thus, the current review enlightens information to acquire a clear understanding about the status quo regarding the vaccination against the disease in endemic areas.

Keywords: Classical swine fever, modified live vaccine, marker vaccine, DIVA vaccines

1. Introduction
Classical swine fever (CSF) is a highly contagious disease that affects domestic pigs and wild boars. The disease is notifiable to the World Organization for Animal Health (OIE) due to its normous consequences on porcine health and the pig industry (OIE, 2019) [20]. The CSF aetiological agent is the CSF virus (CSFV), an enveloped, single, positive stranded RNA virus within the Pestivirus genus into the Flaviviridae family. The viral genome, of around 12.3 Kb of length, codifies for a unique polyprotein that after proteolytic processing yields mature non-structural and structural proteins. Among the latter, E2 and Erns glycoproteins are the main targets for neutralising antibodies (Rumenaf *et al*, 1993; Borca *et al.*, 2019) [22,5].
Despite the implementation of extensive eradication programs, CSF remains endemic in Asia, South and Central American countries. Response policy to notification of an outbreak differs among different countries. In India, CSF is endemic, and for its control, a mass vaccination approach is being adopted. The European Union followed a non-vaccination policy, accompanied by culling of infected animals and severe trade restrictions in the way to successful eradication of the disease. However, this approach carries significant ethical and economic implications. The negative impact related with mass stamping out policies, including elevated costs and ethical issues, point out vaccination as the main control measure against future outbreaks. Generally, vaccination is an effective and safe method to control the disease. Following vaccination the pig's immune system develops antibodies that are significant part of the protection. Hence, it is imperative for the research community to continue with the active investigations for more effective vaccines against CSFV. Therefore the current review enlightens the information about the vaccines in use or under developing stages against CSFV to acquire a clear understanding on the available vaccines and the vaccination policy against CSFV towards controlling the disease.

Recent progress on vaccination strategies and CSF vaccines
Vaccination strategies against CSF depend on the epidemiology of the disease, animals affected domestic pigs and or wild boar and economic situation, resulting in different requirements for the vaccines to be used. For example, in endemic regions with domestic pigs and with little international trade, the priority is to protect against losses due to clinical disease. Such regions require safe, cheap, effective vaccines, easy to administer with long-lasting immunity. However, vaccination with the only live attenuated vaccines existing on the market that contain a whole CSF virus (CSFV) with reduced infectivity, leads to production of an antibody response that does not differ from the antibody response developed after infection.

Thus, implementation of these vaccines in case of outbreak will not give the possibility to differentiate infection in vaccinated animals (DIVA).In CSFV-free areas and where international trade in domestic pigs is important, emergency vaccination strategies that rapidly contain disease spread are important. This requires fast-acting vaccines, ideally with DIVA capacity, to minimise the impact on trade. Such DIVA vaccines are also desirable to assist in eradication programmes.

Modified Live Attenuated (non – DIVA) Vaccines

Mass vaccination using live attenuated vaccines has been implemented in several countries for many years as a mandatory control program. At present the mostly used live attenuated vaccines are based either on Chinese (C) strain, on the French cell culture adapted Thiverval strain or Japanese quinea-pig exaltation-negative strain (GPE-). The Thiverval strain has been obtained from the virulent Alfort strain and attenuated through more than 170 serial passages at a low temperature (29-30 °C). Among the many live attenuated CSF vaccines developed, the C-strain is the most widely used and can prevent 100% of CSF clinical signs, regardless of the genotype of the challenge strain (Graham *et al.,* 2012, Suradhat and Damrongwatanapokin, 2003) [11, 25]. However, the virus can persist even in areas where vaccination with these highly effective vaccines is mandatory (Zhou *et al.,* 2019) [31]. Various reasons contribute to the ongoing circulation of the virus in vaccinated populations, one of which is the ineffective application of vaccines in the field. Many C-strain variants are still produced in rabbits and efforts to produce vaccines in cell culture are encouraged. Good cell culture-adapted vaccines, such as the Riems strain used in the EU for wild boar vaccinations, exist but some lapinised versions of C-strain grow poorly in cell culture leading to poor productivity. Sequencing of cell culture passaged C-strain, identified eight amino acid mutations which, when re-introduced into the parental virus by genetic modification, resulted in a genetically stable virus with enhanced growth. This virus retained the ability to protect pigs from challenge at 4 weeks post-vaccination (Cao *et al.,* 2019) [6].

Marker vaccines

Marker vaccines (live or inactivated) is either based on deletion mutant or isolating antigenic proteins that allows the distinction between vaccinated and infected animals on the basis of identifiable differences in antibody responses. The concept of marker vaccines arises from the need to differentiate infected animals from those vaccinated. Associated with the DIVA concept explained above, each marker vaccine must be coupled with a discriminatory test, which must be able to selectively determine which vaccinated herds are or not free to circulating field strains (Dong, *et al.,* 2007) [9]. In general, the development and manufacturing of the marker vaccines have covered, so far, four main strategies including subunit vaccines, viral vectors (chimera vaccines and replicons), immunogenic CSFV peptides, and DNA vaccines (Dewulf *et al,* 2000) [8].

E2 subunit vaccine

Marker vaccines emerged using the E2-protein, which is considered the most immunogenic viral protein of CSFV in non-replicating systems (Greiser-Wilke *et al.,* 2004) [10]. This first generation of genetically engineered vaccines is recognized as E2-subunit vaccine (Dewulf *et al.,* 2000; Sánchez *et al,* 2007; Van Rijn *et al.,* 1996) [8, 23, 29]. E2 is highly immunogenic and it is linked to the induction of neutralizing antibodies, which have a protective role against the viral infection. Based on the described characteristics of E2, the whole protein or regions from the main epitopes of E2, have been used coupled with different expression systems to generate several commercial vaccine candidates. The first commercial subunit vaccines were launched in baculovirus-expressed E2 protein in insect cell line (Sánchez *et al,* 2007; Van Rijn *et al.,* 1996) [23, 29]. Two marker subunit DIVA vaccines, Porcilis Pesti (MSD Animal Health) and BayoVac (BAYER AG), both based on the immunogenic E2 protein expressed in baculovirus systems were developed (Van Oirschot, 2003) [28]. These vaccines are safe and were shown to provide clinical protection and limit the spread of CSF. However, compared with the live attenuated vaccines, the disadvantages of the two subunit vaccines are lower efficacy with a later onset of immunity, incomplete protection against transplacental transmission, and the requirement for a two-dose inoculation regime (Zhou *et al.,* 2014; Reimann, *et al.,*2016) [31, 21]. Thus, these vaccines are unsuitable for emergency vaccination in CSFV-free countries and they are also not compatible with oral delivery to wild boars. At present, only Porcilis® Pesti is still commercially available. Promising enhancement of immunity to E2 subunit vaccine has been achieved in the past by inclusion of immunomodulatory proteins, such as IFN-α, together with E2 (Toledo *et al.,* 2010) [26]. This concept has been extended recently to investigate the impact of the inclusion of IFN-γ as an immunoadjuvant (Zhang *et al.,* 2018) [30].

Live attenuated DIVA vaccines

Live attenuated vaccines are widely used to control CSF disease in many areas and have paved the way to successful eradications, but these vaccines have the disadvantage that they lack DIVA. A promising vaccine candidate has been developed by genetic elimination of a highly conserved CSFV-specific epitope of the E2 glycoprotein and the inclusion of a Flag epitope in E1 as a positive marker (Holinka *et al.,* 2014) [12]. This virus induces effective immunity against challenge as early as 3 days after vaccination (Holinka *et al.,* 2017) [13]. With extensive efforts the European medicine agency licensed a novel CSF marker vaccine, Suvaxyn, in 2014 (Blome *et al.,* 2017b) [4]. This vaccine, also referred to as CP7_E2Alf, is a chimeric pestivirus constructed in a BVDV virus backbone in which the E2 gene is replaced by the E2 gene from the CSFV strain Alfort/187. This vaccine is safe and as efficacious as the classical live attenuated vaccines but with the added benefit of DIVA capability. During development of the CP7_E2Alf vaccine, studies to assess protection from vertical transmission used early challenge with a highly virulent virus**.** Another live attenuated chimeric DIVA vaccine, Flc-LOM-BErns, has been described recently and is applied in South Korea (Lim *et al.,* 2019) [15]. The Flc-LOM-BErns vaccine is based on an infectious clone of the LOM (low virulence of Miyagi) vaccine strain in which the 3′ -end of the capsid gene and the full Erns gene were replaced with the equivalent sequences from a BVDV-1 virus. DIVA capacity is therefore possible with the Flc-LOM-BErns vaccine, with detection of antibodies against CSFV Erns being indicative of a field virus infection.

Viral vectored CSFV vaccines

The use of viral vectors to deliver CSFV antigens can retain the advantages that live vaccines have over subunit vaccines by targeting multiple aspects of the immune response to provide greater efficacy. A number of recent studies have continued investigations into the use of viral vectors as candidate DIVA vaccines. Constructs expressing the CSFV E2 and Erns proteins in a Newcastle disease vaccine (NDV) strain have been produced (Kumar *et al.*, 2019) [14]. NDV has advantages as a delivery vector in that it can grow to high titres in embryonated eggs and in cell cultures, which allows cost-effective vaccine production. The vector is also able to infect *via* the intranasal route, thereby targeting induction of responses at the primary site of CSFV entry and replication. Another interesting study has investigated the use of recombinant baculovirus vectors as a vehicle to deliver DNA encoding CSFV E2 in pigs (Liu *et al.*, 2017) [18]. A recombinant swine pox virus construct rSPV-E2, expressing the E2 protein, has also been produced (Lin *et al.*, 2017a, 2017b) [16, 17]. Like other poxviruses, the swinepox virus can encode large amounts of recombinant proteins and is a potent stimulator of both, cellular and humoral immunity. Pigs immunised intramuscularly with two doses of the rSPV-E2 candidate were clinically protected against CSFV challenge.

Alternative Approaches

Other DIVA vaccines, such as peptide vaccines and DNA vaccines have also been generated against CSFV. Studies with these candidates were reviewed previously (Blome *et al.*, 2017a) [3]. Briefly, peptide vaccine candidates generally contained either one peptide or a mixture of different peptides covering different parts of the antigenic domains of the E2. However, none of the evaluated candidates were able to confer complete protection upon CSFV challenge. As for DNA vaccines, all the vaccine candidates described so far are based on plasmid constructs that express the E2 protein. The high costs associated with DNA preparation and the inefficient delivery make DNA vaccines economically non-viable for CSFV control. Thus, these vaccines have not been under investigation for use.

Existing vaccines against Classical Swine Fever in India

Classical swine fever disease was first documented in India in the year 1962 (Sapre *et al*.,1962) [24]. Since then, the disease is endemic disease in India in all pig-producing areas, most often reported from the northeast states, where the majority of the pig population exists (Deka *et al*.,2012) [7]. For CSF, killed vaccines have been used. However, these vaccines were able to prevent the clinical manifestations of the disease but not the infection. India has a lapinized swine fever virus vaccine to protect the pigs from the disease but vaccine produced is not sufficient to meet out the demand for many Indian farmers (Bett *et al.*, 2012) [2]. Thus, the inactivated vaccines were replaced by the modified-live attenuated vaccines. Keeping the prioritization for the CSF control in the country, the Ministry of Fisheries, Animal Husbandry and Dairying, Govt. of India has initiated the Classical Swine Fever Control Programme (CSF-CP) in the year 2014–2015 to control the CSF in pigs by mass vaccination using the live attenuated vaccines. The lapinized vaccine using the Weybridge strain of the virus, which belongs to the sub-genogroup 1.1, has been used since 1964 (Dong *et al.*,2007) [9]. The lapinized vaccines are produced mostly by the Institute of Veterinary Biologicals located in different states of the country to meet the local demand of the vaccines. A few of the Institute of Veterinary Biologicals have lately shifted to producing local CSFV strain based cell culture attenuated live vaccines (Bardhan *et al.*, 2017) [1]. The systematic vaccination using a live-attenuated vaccine appears to be the best way forward for elimination/eradication of the CSF. The present domestic pig population of India is 9.06 million, as per the 20th livestock census of the government of India. The vaccination coverage of all the domestic pigs twice in a year requires about 20 million doses per annum, and only 1.2 million doses are produced per year by the lapinized vaccine. To meet out the demand and overcome the constraints in producing a large quantity of the lapinized vaccine, attempts are underway to produce a cell-culture-based vaccine using either the lapinized vaccine strain or the local CSFV isolates (Nath *et al.*, 2016) [19]. There are reports on developing effective cell-culture-based live attenuated vaccines against CSFV, using Weybridge strain by the Indian Veterinary Research Institute (IVRI) of the country. The vaccine was reported to be safe, efficient and provide immunity for a period of one year (Tomar *et al.*, 2018) [27]. A commercial Bovine Kidney cell culture adapted vaccine for CSFV (Himmvac Hog Cholera (T/C) Vaccine) is also available from KBNP Inc. Korea through Panav Bio-Tech, India. Veterinary and human vaccines maker, Indian Immunologicals Limited (IIL), has launched the Classical Swine Fever (CSF) vaccine under the brand name 'Raksha Class' (Press Information Bureau, 2020).

Summary

Classical swine fever disease continues to pose a threat to pig production worldwide. Vaccination with safe and highly efficacious live attenuated vaccines has been practiced for decades to control the disease and has paved the way to successful eradication of the disease. These vaccines have usually outstanding efficacy and safety but lack differentiability of infected from vaccinated animals, DIVA or marker strategy. Also, great progress has been made in development of live attenuated DIVA vaccines, viral vector vaccines and subunit vaccines. Together with good surveillance and biosecurity, these vaccine candidates are promising for disease control and eradication in endemic areas. Though, conventional vaccines are a standard in terms of efficacy, only vaccines with DIVA or marker strategy will allow improved eradication strategies

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