Veterinary Microbiology 172 (2014) 1–6

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Review

Classical swine fever in China: A minireview

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ARTICLE INFO

Article history:
Received 8 January 2014
Received in revised form 26 March 2014
Accepted 1 April 2014

Keywords:
Classical swine fever
Epidemiology
Diagnosis
Vaccine
Control
China

ABSTRACT

Classical swine fever (CSF), caused by Classical swine fever virus (CSFV), is an OIE-listed, highly contagious, often fatal disease of swine worldwide. Currently, the disease is controlled by prophylactic vaccination in China and many other countries using the modified live vaccines derived from C-strain, which was developed in China in the mid-1950s. This minireview summarizes the epidemiology, diagnostic assays, control and challenges of CSF in China. Though CSF is essentially under control, complete eradication of CSF in China remains a challenging task and needs long-term, joint efforts of stakeholders.
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1. Introduction

China is the biggest pork producer in the world, with a record output of pork of 54.93 million tons in 2013, accounting for about 48% of the world pork products. On the other hand, the productivity of the Chinese pig industry is relatively low, with 715.57 million pigs slaughtered and 474.11 million pigs registered in the total stocks including around 50 million breeding sows in 2013 (National Bureau

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http://dx.doi.org/10.1016/j.vetmic.2014.04.004
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of Statistics of China, 2014), providing around 14 pigs per sow per year (PSY), far below the productivity of developed countries (PSY > 22). Numerous factors are responsible for the low productivity, but swine infectious diseases definitely have the greatest impact.

Classical swine fever (CSF) is an Office International des Epizooties (OIE)-listed, highly contagious, often fatal disease of swine. It is distributed almost worldwide. The disease is caused by classical swine fever virus (CSFV), a member of the *Pestivirus* genus within the *Flaviviridae* family. CSFV is genetically and serologically related to other pestiviruses, including bovine viral diarrhea virus (BVDV)-1, BVDV-2, and border disease virus (BDV). Pigs can be infected by other pestiviruses. Currently, CSF is controlled by a non-vaccination, stamping-out policy or prophylactic vaccination.

Several modified live vaccines (MLV), such as the Chinese lapinized vaccine (C-strain), the Japanese GPE$^-$ strain and the French Thiverval strain, have been developed and used in different countries. These vaccines are generally safe and effective (Beer et al., 2007).

C-strain was developed jointly by China Institute of Veterinary Drugs Control and Harbin Veterinary Research Institute (HVRI) in China in 1956. It was attenuated from a highly virulent strain (disputably Shimen strain) after at least 480 passages in rabbits (Zhou, 1980a,b). Generally, C-strain is considered a nearly perfect vaccine. The vaccine is genetically stable and safe to pigs of all ages, and it can induce sterile immunity and provide rapid, long-lasting and complete protection against CSFV of different genotypes (Research Group of CSF Vaccine, 1979; Qiu et al., 2006).

C-strain was firstly gifted to Hungary via Dr. Mészáros at Veterinary Research Institute, Hungarian Academy of Sciences, in 1958, and then spread in other European countries and worldwide. There exist different "versions" of C-strain in the world, such as Riems strain, Chinese strain, HCLV strain, etc, which have been widely used. Undoubtedly, C-strain has played a critical role in the control or eradiation of global CSF (Vandeputte and Chappuis, 1999; Qiu et al., 2006).

2. Epidemiology of CSF in China

The first CSF outbreak in China has not been documented. It was recorded that therapeutic hyperimmune antisera to CSF were first tried in 1925 in the Southeast University of China (Yin and Liu, 1997). The first highly virulent Shimen strain was isolated in China in 1945, which has been used as the reference challenge virus for vaccine evaluation. For many years, CSF had been the No. 1 swine disease in China, causing numerous pig deaths and huge economic losses (Fang, 1956; The Veterinary Bureau of Ministry of Agriculture China, 1957). This situation had not been changed until the development of C-strain in 1954 (Ning, 1956; The Veterinary Bureau of Ministry of Agriculture China, 1957; Shen, 1958). Currently, CSF has not been completely controlled since it is sporadic or endemic in many regions of China (Lv et al., 2001; Tu, 2003; The Veterinary Bureau of Ministry of Agriculture China, 2013). According to a report from the Veterinary

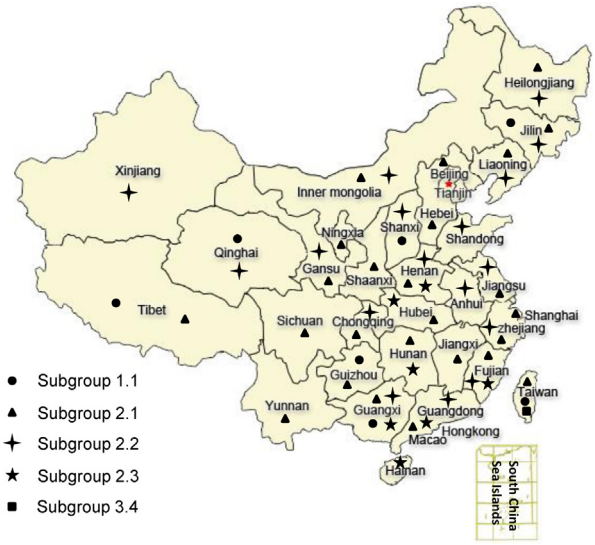

Fig. 1. Distribution of CSFV genotypes in China.

Bureau of Ministry of Agriculture (MOA), China (2013), 285 CSF outbreaks occurred in 12 provinces and autonomous regions of China in 2011, which is believed to be grossly underestimated, because most cases were not notified to the government by farmers in fear of inadequate compensation. Based on the documents currently available, no regions can be declared free of CSF, and there is a long way to go to control and ultimately eradicate CSF in China.

To date, several subgroups/subgenotypes of CSFV including 2.1, 2.2 and 1.1, and occasionally 2.3 have been identified in Mainland China, and group 3 was only found in Taiwan from pig samples collected in 1994 (Tu et al., 2001; Tu, 2003; Deng et al., 2005; Wang, 2006; Li et al., 2006; Chen et al., 2008; Shen et al., 2011; Jiang et al., 2013) (Fig. 1). Subgroup 2.1, particularly clade 2.1b, has long been predominant in China (Tu et al., 2001; Chen et al., 2008, 2010; Luo et al., 2011). Recently a new clade 2.1c has been identified in South China (Jiang et al., 2013). Fortunately, C-strain provides complete protection against any subgroups identified (Qiu et al., 1997; Wang and Ning, 2003). In the field, CSF is often manifested as subclinical infections or co-infections with other viruses and/or bacteria (Jiang et al., 2010; Liu et al., 2011; Xu et al., 2012), making it difficult to reach a definitive diagnosis simply based on clinical signs and pathology. Limited surveys have been conducted to determine CSFV infections in wild boars (not domesticated ones), and the investigated feral pigs were suspected of CSFV infections merely according to clinical findings (Wang, 1990) or negative for CSFV based on RT-PCR and antigen-capture ELISA (Chen et al., 2007). A German group, however, isolated CSFV from a frozen meat sample of wild boars imported from China in 1993 (Krassnig et al., 1995). Further large-range surveillance is needed in the future.

3. Diagnostic assays in China

Different assays (Table 1), such as RT-PCR, RT-nested PCR, RT-nested PCR based restriction fragment length

Table 1
Diagnostic assays for CSFV developed/used in China.

Assays	Usage	References
RT-PCR	Viral RNA detection	Luo et al. (2004)
RT-nested PCR	Detection and differentiation of wild-type and C-strain of CSFV	Li et al. (2007b)
RT-LAMP	Detection of wild-type CSFV	Zhang et al. (2010)
Multiplex real-time RT-PCR	Quantitative detection and differentiation of wild-type and C-strain of CSFV and BVDV-1	Zhao et al. (2008), Zhang et al. (2012)
RT-nested PCR based restriction fragment length polymorphism (RFLP)	Detection and differentiation of wild-type and C-strain of CSFV and subtyping of the isolates	Chen et al. (2010)
Multiplex PCR	Simultaneous detection of CSFV and other porcine viruses	Liu et al. (2013), Xu et al. (2012), Jiang et al. (2010)
E2-based blocking ELISA	Antibody detection	IDEXX blocking ELISA kit; Liang et al. (2008)
E2-based indirect ELISA	Antibody detection	Sun et al. (2008)
E^{rns}-based indirect ELISA	DIVA compatible assay	Li et al. (in preparation)
Antigen-capture ELISA	Antigen detection	IDEXX Antigen ELISA kit
Immunochromatographic test	Detection of wild-type CSFV antigens	Wang et al. (2010)

polymorphism (RFLP), real-time RT-PCR, and RT-LAMP have been developed in China for detection of CSFV or/and differentiation of wild-type CSFV and C-strain (Li et al., 2007b; Chen et al., 2010; Zhao et al., 2008; Zhang et al., 2010). A triplex TaqMan real-time RT-PCR assay has been established for differential detection of wild-type and vaccine strains (C-strain) of CSFV and BVDV-1 (Zhang et al., 2012). Considering frequent co-infections of CSFV with other viruses in the field, several multiplex PCR assays have been developed in China, allowing simultaneous detection of CSFV and other porcine viruses including porcine reproductive and respiratory syndrome virus (PRRSV), porcine circovirus type 2 (PCV2), suid herpesvirus 1 (SuHV-1) (also called pseudorabies virus, PRV), Japanese encephalitis virus (JEV), porcine teschovirus (PTV) and porcine parvovirus (PPV) (Liu et al., 2011, 2013; Xu et al., 2012; Jiang et al., 2010). Several commercially available ELISA kits, imported or homemade, mainly IDEXX blocking ELISA kit, have been licensed and used for detection of serum antibodies and evaluation of vaccines. In addition, some promising antibody ELISA kits are being developed and registered in China. Also, an anti-E^{rns} ELISA for DIVA strategy has been developed and evaluated (Li et al., in preparation). Currently, detection of CSFV antigens relies on the IDEXX CSFV Antigen ELISA kit or fluorescent antibody test (FAT).

For the diagnostic tests for CSF, RT-PCR and ELISA including antigen-capture ELISA are routinely performed in most diagnostic laboratories in China. However, real-time RT-PCR, FAT, virus neutralization test (VNT) and virus isolation in susceptible cell lines of porcine origin, such as PK-15 cells, can only be performed in some professional laboratories for definite diagnosis.

A big problem is the lack of standardization of the diverse methods, resulting in discrepancy in diagnosis and different explanations of the clinical samples.

4. CSF control in China

For decades, a compulsory vaccination policy has been carried out in China, in which farmers are demanded to carry out immunization of pigs with vaccines paid by the Chinese government. On the other hand, farmers would rather buy commercial vaccines from the market because of the concern of the quality guarantee of free vaccines due to the vicious price war for a bid among crowds of biological companies.

To completely control CSF, some larger pig farms are practicing CSF elimination programs with the support of scientists and officials, and CSF has been eradicated in some farms and regions. For many farmers, more attention is paid to vaccination rather than other measures, such as biosecurity procedures. Even though CSF is one of the key diseases to be vaccinated and controlled, China suffers from incomplete vaccination coverage, especially in remote villages and backyard farms, following the general requirements for compulsory vaccination against CSF that vaccination coverage in the swine population shall be kept at over 90% all year through, and the seroconversion should be maintained at over 70% throughout the year (The Veterinary Bureau of Ministry of Agriculture China, 2013).

China MOA issued National Animal Disease Surveillance Plan—2011, demanding surveillance of CSF, according to five basic principles: combining national surveillance with local surveillance, sentinel surveillance with comprehensive surveillance, regular surveillance with emergency surveillance, antibody surveillance with pathogen surveillance, and disease surveillance with epidemiological investigation. The surveillance results should be announced on the Veterinary Bulletin monthly, quarterly, semiannually, and annually. Surveillance timing includes: (1) regular monthly surveillance by local authorities according to the local situation; (2) spring and autumn surveillance, completed by the end of June and December, respectively; (3) sample collection and immediate testing whenever suspect cases are detected. Serological test, including indirect hemagglutination test (IHA) or blocking or indirect ELISA to detect anti-CSFV antibodies, and pathogen test, such as FAT, RT-PCR, or antigen-capture are performed for the surveillance.

In China, commercially available vaccines against CSF are exclusively C-strain-based ones. The vaccines are produced in either primary bovine testicle (BT) cells, rabbits or continuous swine testicle (ST) cells. The vaccines are tested for quality and efficacy in rabbits according to the Chinese Veterinary Pharmacopoeia (The Ministry of

Agriculture of the People's Republic of China, 2000), based on the regular fever induced by C-strain in rabbits inoculated intravenously with the vaccines. This protocol is not objective but labor- and time-consuming. To simplify the vaccine testing, a real-time RT-PCR method was developed, which is correlated well with the rabbit fever test (Ge et al., 2011). To date, more than 50 bio-companies are involved in CSF vaccine production, resulting in variable types and quality, which makes more multiple but difficult choices for pig farmers.

Vaccination schedules are mostly based on simple empiricism, and only partially based on serological data, which cause improper vaccination timing thus often leads to vaccination failure of CSF vaccines due to the interference by maternally derived anti-CSF antibodies (MDA). Other factors, such as unqualified vaccines, co-infections with viruses or bacteria, interference by other modified live vaccines (e.g. PRRSV MLV) or immunosuppressive antibiotics, or intake of moldy feed, may also account for the frequent vaccination failure in the field in China.

Several marker vaccines against CSF are being evaluated and undergoing the licensing procedures, including the chimeric adenovirus/alphavirus vector-based vaccine rAdV-SFV-E2 (Sun et al., 2011, 2013a), the yeast-expressed E2 subunit vaccine (Lin et al., 2009, 2012), adenovirus-vectored vaccines (Sun et al., 2010, 2013b) and the alphavirus replicon-vectored vaccine pSFV1CS-E2 (Li et al., 2007a) in China, in competition with the chimeric pestivirus-based vaccine CP7_E2alf (Koenig et al., 2007; Gabriel et al., 2012) and the baculovirus-produced E2 subunit vaccine (Bouma et al., 1999) in Europe. rAdV-SFV-E2 was shown to be able to induce sterile immunity comparable to C-strain, and its efficacy was not interfered by anti-CSF MDA, anti-BVDV antibodies, or co-administered PRV or PRRSV MLV vaccine, in sharp contrast to C-strain (Sun et al., 2011, 2013a). It is a very promising vaccine with the potential to be included in CSF eradication in China. An accompanying DIVA ELISA, an indirect ELISA based on the yeast-expressed E^{rns} protein, has been developed and evaluated (Li et al., in preparation).

Animals with low antibody levels should be revaccinated in time, and infected animals should be culled according to the regulations. The Chinese government aims to control CSF step by step, starting from reduced economic losses and national control to regional eradication, and finally national eradication. China MOA continues to strictly operate the regulation system. Measures such as regular supervision, surprise inspection, in-place supervision and lot release were adopted to ensure manufacturers to conduct vaccine quality inspection fully in compliance with laws and regulations. A veterinary legal system has been built and put into practice, including national laws such as the Animal Disease Control Law of China (The Veterinary Bureau of Ministry of Agriculture China, 2013).

5. Problems and challenges in CSF control in China

Control of CSF remains a big challenge in face of the following problems and challenges in China: (1) too many vaccine producers and insufficient regulation, leading to inconsistent and unqualified vaccines; (2) "inherent" shortcomings of C-strain-based vaccines (non-DIVA, interference by MDA, and possible BVDV contamination); (3) incorrect immunization schedules, resulting in immunization failure; (4) co-existence of modern and smallholder pig farms. You may see several "clean" big farms in the background of numerous "dirty" small farms; (5) non-strict restricted animal movement. Diseased animals are sometimes transported by illegal traders, leading to far-ranging spread of some diseases.

6. Prospects

To facilitate the control and eradication of CSF in China and worldwide, we have many things to do. First, safe and effective marker (DIVA) vaccines and accompanying DIVA tests should be developed. Second, regional or national-wide eradication campaign should be initiated and implemented. Third, vaccination should be carried out together with other comprehensive measures, such as serological and virological surveillance, and biosecurity procedures, because vaccination alone can never eliminate a disease. The government should bring together all stakeholders (farmers, veterinarians, scientists, vaccine producers, officials and the community) to fight against CSF jointly. To achieve this end, we should learn more from the EU and the USA, where CSF and pseudorabies are successfully eradicated long time ago. Fourth, multiplex assays for simultaneous detection of diverse pestiviruses (existing and emerging pestiviruses) and other swine viruses should be developed, considering the widespread BVDV from infected bovine sera and contaminated biologicals and concurrent viral co-infections (Deng et al., 2012; Tao et al., 2013). Lastly, we need to know more about the virus: how does it replicate/infect and establish persistent infection? How does it interact with the host? This may lead to more efficient intervention strategies for CSF. Some groups in China are investigating the CSFV-host interactions and several cellular proteins regulating the CSFV replication have been identified (Li et al., 2013a,b; He et al., 2014; Shi et al., 2013). These proteins are potential targets for the CSF control.

Acknowledgments

This work was supported by the European Union's Seventh Framework Programme LinkTADs (no. 613804) and the National 863 Projects of China (no. 2011AA10A208).

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