Introduction to classical swine fever:
virus, disease and control policy

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Abstract

Classical swine fever virus is a spherical enveloped particle of about 40–60 nm in diameter with a single stranded RNA genome of about 12,300 bases with positive polarity, classified as a pestivirus within the family Flaviviridae. Natural hosts are domestic and wild pigs. The virus causes one of the most severe diseases in pigs world wide with grave economic consequences. The clinical picture of classical swine fever is variable, depending on the age of the affected animals and viral virulence. The virus is well characterised and reliable laboratory diagnostic procedures are available. In many parts of the world live attenuated vaccines are being used as a safe and efficient prophylactic tool. However, in EU Member States and several other countries vaccination is prohibited and CSF is controlled by a strict stamping out policy. In order to overcome the disadvantages of conventional vaccination inactivated marker vaccines have been developed that enable the distinction between vaccinated and infected animals. Whether these vaccines will be accepted as an additional tool in the framework of the stamping out policy is not yet decided. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: CSF; Control; Eradication; Wild boar; Marker vaccine; Epidemiology

1. Introduction

Classical swine fever (CSF, syn. Hog cholera, European swine fever) is probably the economically most important viral infectious disease of domestic pigs. It is classified as an OIE List A disease, i.e. every suspected case has to be investigated and once it is confirmed, the outbreak has to be notified. After implementation of strict control measures, several countries, including Australia, Canada, New Zealand, United States of America (USA), and some Member States of the European Union (EU), succeeded in
eradicating the virus. In most other parts of the world with significant pig production the CSF virus is present, causing substantial economical damage (Edwards et al., 2000).

The disease probably emerged in the 1830s in the Midwestern States of the USA and its viral aetiology was revealed early this century when body fluids of diseased pigs that had been passed through porcelain filters proved infectious. Natural hosts of CSFV are members of the Suidae, i.e. not only domestic pigs but wild boar are also fully susceptible to the virus. In the 1940s and the following years three disorders of ruminants were attributed to viruses that share a great number of virological properties with CSFV: Bovine viral diarrhoea, mucosal disease of cattle and border disease of sheep. Based on their common features, e.g. sequence homologies and genome organisation, these viruses make up the genus Pestivirus in the family Flaviviridae. CSFV’s devastating economical impact on the pig industry has always been a stimulus for research. However, like the other pestiviruses, CSFV was a difficult virus to work with, and major progress only became possible with the development and the availability of sophisticated virological methods especially during the last 15 years. Before this, many details concerning the virion remained obscure. However, despite all recent progress, there are still open questions concerning, e.g., the molecular markers of virulence and details on the functional role of viral nonstructural proteins.

Parallel to the growing understanding of viral structure and pathogenesis of CSF, sensitive and reliable laboratory diagnostic techniques have been developed during the last decades and efficient vaccines are available.

2. Virus

The causative agent of CSF is a small (40–60 nm) enveloped ribonucleic acid (RNA) virus with a single stranded RNA genome with positive polarity. CSF virus belongs to the pestivirus genus of the Flaviviridae family (Wengler, 1991) and it is related to the bovine viral diarrhoea (BVD) virus and the border disease (BD) virus of sheep. The genomic sequence of about 12,300 bases is known and infectious complementary deoxyribonucleic acids (cDNAs) have been produced in several laboratories (Meyers et al., 1996; Moormann et al., 1996; Ruggli et al., 1996). The viral RNA codes for four structural and seven nonstructural proteins (Elbers et al., 1996; Meyers and Thiel, 1996). The virus is relatively stable in moist excretions and fresh meat products, including ham and salami type sausages (Savi et al., 1965). However, it is readily inactivated by heat, detergents, lipid solvents, proteases and common disinfectants (Edwards, 2000).

3. Disease

The diagnosis of CSF based on clinical signs is often difficult, because it is an exotic disease, unfamiliar to both farmers and most veterinarians, and because symptoms may vary considerably, depending on the age and/or breed of the affected animals and viral virulence (Moennig and Plagemann, 1992; Depner et al., 1997; Van Oirschot, 1999). Under natural conditions the most frequent route by which the CSF virus enters its host is...
oronasal. Typically the incubation period is 7–10 days. Infected pigs develop pyrexia and leukopenia. Petechial haemorrhages of the outer skin and mucosae are the most typical sign although they are not seen consistently. Central nervous system disorders and constipation followed by diarrhoea may also be characteristic clinical findings. The severity of clinical signs largely depends on the age of the animal and viral virulence. Usually young animals are affected more severely than older animals. In older breeding pigs the course of the infection is often mild or even subclinical. Mortality rates may reach 90% in young pigs.

Acute and chronic courses of CSF are known. All courses of the infection have in common that the animals are viraemic at least as long as they show clinical signs. Death occurs 2–3 weeks after infection (acute course) or after up to three months (chronic course).

The outcome of transplacental infection of foetuses depends largely on the time of gestation (Van Oirschot and Terpstra, 1977) and may result in abortions, stillbirths, mummifications, malformations or the birth of weak or persistently viraemic piglets (Meyer et al., 1980). Although persistently infected offspring may be clinically normal at birth, they invariably die from CSF. Survival periods of 11 months after birth have been observed. This course of infection is referred to as ‘late onset CSF’ (Van Oirschot, 1999).

Major target cells for the virus are endothelial cells, lymphoreticular cells, macrophages, and some kinds of epithelial cells. Pathological findings vary according to clinical signs (Moennig and Plagemann, 1992; Van Oirschot, 1999). Prenatally, at the early phases of ontogenesis, the virus affects organ differentiation and leads to malformations. In postnatal infections, lesions are generally caused by widespread thrombosis and/or endothelial damage, inducing haemorrhagic diathesis and petechial bleedings. Bronchopneumonia is another common feature. In a high proportion of fatal cases, histopathology of the brain shows a non-suppurative encephalitis with severe vasculitis. Substantial thrombocytopenia is a consistent finding. The terminal stage of acute infection is associated with a marked depletion of B-lymphocytes in the circulatory system as well as in lymphoid tissues (Susa et al., 1992).

Like all pestiviruses, CSFV virus is immuno-suppressive during acute infection. Pigs that have recovered are protected against CSF for several years or even for their lifetime (Van Oirschot, 1999). Neutralising antibodies are detectable 2 weeks after infection at the earliest. In pigs with chronic CSF, neutralising antibodies are detectable at the end of the first month postinfection for a few days and disappear afterwards (Mengeling and Packer, 1969; Depner et al., 1996). Persistently viraemic, in utero infected pigs seldom produce specific antibodies (Van Oirschot, 1999). Maternal antibodies have a half-life of approximately 14 days. Passive immunity generally protects piglets against mortality during the first 5 weeks of life, but not against virus replication and shedding. Little is known about cell-mediated immunity against CSF.

4. Epidemiology

Both structure and density of pig populations have a considerable influence on the epidemiology and control of CSF. The structure of the European pig industry displays a
wide variation between regions and countries. In some countries domestic pigs are kept preferably in small and medium-sized farms while in others they are predominantly kept in bigger operations. In recent years high pig concentrations with respect to animal and farm density have built up in several regions of Europe that offer favourable production conditions. The probability of spreading the disease after a primary outbreak in those areas is much higher than in areas with lower densities of pigs. Factors influencing the ‘neighbourhood risks’ for the spread of the infection are either not known or they are at best ill defined. In parallel long distance animal trade has intensified considerably and contributes to the problem. Therefore, it is very important to obtain quick, reliable and complete information about trade movements and contact farms.

At present the EU Member States are practically free of CSF in domestic pigs. However, sporadic or massive new outbreaks were observed in domestic pigs in recent years (1990–1998). Outbreaks in areas with a high density of pigs often led to extensive epidemics with most severe economic losses. During the last 4 years CSF outbreaks in domestic pigs have been observed in Austria, Belgium, Germany, Italy, The Netherlands, Spain and Switzerland. The most recent and probably most costly epidemic started at the end of 1996 in a pig herd in western Germany due to illegal swill feeding. The virus was subsequently spread to several regional pig farms (1997) and presumably from Germany to The Netherlands and subsequently to Spain, Italy and Belgium. More than 550 confirmed outbreaks could be attributed to this epidemic (De Smit et al., 2000; Stegeman et al., 2000).

Wild boar and domestic pigs are equally susceptible to CSF virus infection (Depner et al., 1995; Laddomada, 2000). The occurrence, density and behaviour of wild boar populations are important for the epidemiology of CSF. The population of wild boar appears to have increased all over Europe and the present population in EU Member States is an estimated 800,000 to 1 million. In countries that are free of CSF in domestic pigs epidemics in wild boar are typically initiated by the uptake of swill. Depending on viral virulence, geographical profile, the density and the size of the population, CSF epidemics in wild boar are not always self-limiting. Endemic CSF in wild boar represents a permanent virus reservoir that poses a constant threat to domestic pigs.

In recent years CSF was observed in Western European Countries in wild boar in Austria, France, Germany, Italy and Switzerland. In some areas the infection has been endemic for several years. In parts of Germany a number of primary outbreaks in domestic pigs were linked to the occurrence of CSF in local wild boar populations (Fritzemeier et al., 1998). Almost all Western European countries where CSF occurred during the last few years run a monitoring program for CSF in wild boar. The introduction of CSFV into a susceptible wild boar population usually occurs via contaminated food. Apparently the animals are occasionally exposed to material contaminated with CSFV, e.g., garbage that had been thrown away at rest places and dumping sites. In other cases — ignorant of the risk — still feed wild boar with swill. From wild boar the virus may be transmitted directly (animal contact) or more often indirectly to domestic pigs (contaminated equipment belonging to farmers who are hunters as well, feed contaminated by wild boar excretions or carcasses, illegal swill feeding, contact of pigs with wild boar excretions etc.).
With CSF having become an exotic disease for many countries with a non-vaccination policy, epidemiological investigations and information are of utmost importance for the control of an outbreak, e.g. thorough tracing back and forth. The ‘molecular epidemiology’ based on techniques that will be described later has become a useful tool and may well support epidemiological investigations (Greiser-Wilke et al., 1998; Greiser-Wilke et al., 2000; Paton et al., 2000a). Typing of CSF virus isolates of at least each primary outbreak in domestic pigs and isolates originating from wild boar is desirable, in order to obtain a comprehensive picture of the epidemiological situation.

5. Laboratory diagnosis and vaccination

A modern and efficient laboratory diagnosis is an essential tool for CSF control. Monitoring of the status of pig populations in ‘peace time’ and early detection of CSF outbreaks depend on reliable diagnostic methods and adequate laboratory facilities.

5.1. Detection of virus and viral antigen

Although much progress had been made in the development of new methods for the direct detection of CSFV, the ‘gold standard’ is still the isolation of the virus in cell culture. CSFV can be isolated from buffy coat cells or organ suspensions of viraemic animals. Suitable organs are spleen, tonsils, lymph nodes, parotid glands and kidneys (Anonymous, 1980, 1996). The samples are incubated on susceptible cell cultures of porcine origin. Since CSFV is noncytopathogenic, CSFV specific antibodies are used for detecting the virus in cell culture. Differentiation of the CSFV from ruminant pestiviruses is usually done using monoclonal antibodies (mAbs) (Anonymous, 1980, 1996; Cay et al., 1989). Virus isolation takes about 3 days and is labour intensive. A rapid, though less sensitive test for CSFV is based on the demonstration of viral antigen in organ tissue sections using fluorescent antibodies. For the screening of large numbers of animals in herds suspect of being recently infected by CSFV, virus antigen capture enzyme-linked immunosorbent assays (AgC-ELISAs) may be used. This test is also less sensitive compared with virus isolation.

Recently, detection of viral RNA has become an additional option for laboratory diagnosis (Paton et al., 2000b). In particular, the 5’nontranslated region of the genome has been used for amplification by the reverse transcriptase polymerase chain reaction (RT-PCR). Subsequent nucleotide sequencing of the respective region allows discrimination between different CSFV isolates (Hofmann et al., 1994; Lowings et al., 1996; Greiser-Wilke et al., 1998). The EU/OIE Reference Laboratory for CSF in Hannover, Germany, keeps a large computer data base on CSF virus isolates including epidemiological and virus type information data (Greiser-Wilke et al., 2000).

5.2. Serology

Considering the progress in antigen detection methods the importance of serology in the control of acute outbreaks has somewhat decreased. However, serological diagnosis of CSF is still important for surveys and the detection of hidden clusters of CSF, especially in wild boar.
The virus neutralisation test is the most sensitive and specific method for CSF antibody detection. Porcine serum samples are incubated with a CSF reference virus. In case the serum contains antibodies to CSFV the test virus will be neutralised. However, cross-neutralising antibodies specific for ruminant pestivirus infections of pigs are often also registered by this test. Differential diagnosis for ruminant pestiviruses should therefore be carried out using a second neutralisation test using ruminant pestiviruses. The neutralisation test takes at least 2–3 days or longer if comparative testing is required and it is labour intensive. Large numbers of serum samples are, therefore, processed using ELISA tests. Positive or unclear results should be retested using the neutralisation test.

6. Vaccines

From the beginning of the century attempts have been made to develop vaccines against CSF. However, the safety and efficacy of the first generations of vaccines were poor. In the 1940s first experiments were made to attenuate CSFV by adapting it to rabbits (Baker, 1946; Koprowski et al., 1946). After initial setbacks, this development ultimately led to a very efficient and safe generation of live vaccines. Most attenuated vaccines are based on the China-strain (C-strain) of lapinized CSF virus. C-strain vaccines were and are still being used world-wide for the control of CSF in domestic pigs. It is also used at least on an experimental basis for the oral immunisation to control CSF in wild boar (Kaden et al., 2000). C-strain vaccines induce high titres of neutralising antibodies and they are safe when used on pregnant animals. Their efficacy is demonstrated by the observation that vaccinated pigs are protected against infections with virulent CSF virus as early as five days after vaccination. The animals are immune throughout their economic life. However, with respect to today’s global trade policy there is a severe disadvantage in using live attenuated vaccines against CSF: Vaccinated and field-virus-infected animals cannot be distinguished because the antibody pattern induced by the vaccine virus resembles that of reconvalescent animals.

A way out of this dilemma may be the development and use of so-called marker vaccines, e.g., subunit vaccines consisting of single viral surface proteins, which are sufficient for the induction of protective immunity. At present two subunit vaccines containing the viral glycoprotein E2 are under scrutiny. The respective gene is expressed in baculoviruses grown in insect cells (Van Rijn et al., 1996). Since these cells are able to glycosylate proteins, the resulting viral glycoprotein is expressed in a ‘natural’ way. CSF subunit vaccines are safe and so far their protective potency is promising, though inferior to live vaccines. Vaccinated animals may be distinguished from infected pigs using an ELISA based on a different viral protein as diagnostic antigen, e.g., the surface glycoprotein E\textsubscript{ms} or the nonstructural protein NS2-3. However, not all criteria for the emergency use of marker vaccines are well defined yet, and the technical merits of these vaccines have not yet been established. More data are expected to be available during the year 1999.

Technically there is the potential for further improving CSF marker vaccines by developing, e.g., viral vector vaccines (Rümenapf et al., 1991; Van Zijl et al., 1991; Hooft van Iddekinge et al., 1996), DNA vaccines and molecularly altered infectious cDNA clones of CSF virus (Meyers et al., 1996, Moormann et al., 1996, Ruggli et al., 1996).
7. Control policies

The control policy for CSF depends on the incidence and prevalence of the infection in the domestic and wild pig populations, respectively. In countries with CSF endemic in domestic pigs it is common practice to vaccinate against the disease, thereby, avoiding serious losses. However, the simultaneous eradication of field virus is improbable because serological methods are no longer applicable for the detection of field virus infections. It is acknowledged that field virus may be hidden under a ‘blanket’ of general vaccination. Taking this risk into account, importing countries in general do not allow the introduction of pigs or pig products from countries that vaccinate against CSF. The preventive measures adopted by the EU for trade with Third Countries stipulate that live pigs and fresh pig meat can only be imported from regions or countries where no CSF has occurred for 12 months and no vaccination against CSF was applied during the same period. Nevertheless a policy of consistent and systematic prophylactic vaccination in endemic situations may ultimately lead to a favourable starting point for a non vaccination policy and the eradication of the virus. After the cessation of general vaccination, eventual local outbreaks of residual field virus must be dealt with by strict measures to ensure prevention of virus spread and eradication of the virus.

Based on the above mentioned disadvantages of vaccination and a cost benefit analysis the EU banned vaccination against CSF at the end of the 1980s. Whereas most neighbours of the EU have also adopted a similar policy, vaccination is allowed and mostly routinely applied by many Central and Eastern European countries (Edwards et al., 2000). In some of the latter countries only sick or clinically suspect animals are destroyed in case of CSF outbreaks whereas all other animals of the infected herd, herds in the neighbouring area and contact herds are vaccinated.

In case of an outbreak of CSF, all EU Member States and the other Western European countries execute eradication measures according to the Council Directive 80/217/EEC (Anonymous, 1980; Edwards et al., 2000). These are based on stamping out (depopulation) of infected pig herds and possibly infected contact or (partially) neighbouring herds, epidemiological investigations, clinical and virological investigations, movement restrictions for live pigs, pig meat and other vectors which can transmit CSF within zones surrounding the infected farm and restrictions on contact farms outside these zones (Anonymous, 1980). Especially in areas with dense pig populations very high numbers of pigs had to be destroyed in the course of the eradication measures dealing with the outbreaks mentioned above. Only a minority of animals were killed due to direct involvement with the infection. Most of the pigs had to be killed because of welfare measures. The direct and indirect costs of recent CSF outbreaks in several EU Member States so far amount to several billion Euro, and in the course of the CSF epidemic in the Netherlands in 1997 approximately 10 million pigs were destroyed (Saatkamp and Horst, 2000; Stegeman et al., 2000). Whereas in areas with a low density pig population, the present control policy works very well it may well be questioned whether it is sustainable in areas with a high density of pigs. There is a general consensus that a number of measures must be introduced in order to reduce the vulnerability of regions at risk, e.g., structural changes in the pig industry including trade. However, implementation of appropriate programs might be difficult. Several parties, notably some
national farmers’ associations requested the reintroduction of a general or at least regional vaccination.

In principle, emergency vaccination is in agreement with EU legislation (Anonymous, 1980). Requirements related to emergency vaccination campaigns against CSF virus have been defined in the document ‘Guidelines for a Classical Swine Fever Emergency Vaccination Programme’ (Anonymous, 1994). However, by using conventional vaccines and applying the mentioned guidelines, the Scientific Veterinary Committee of the Commission has calculated that vaccinated animals would be excluded from the market for up to 600 days (Anonymous, 1997). This is economically unacceptable and so far emergency vaccination has never been used.

With the development of a first generation marker vaccine against CSF the possibility of an amendment of the existing EU emergency vaccination regulations seems feasible. A restricted application of a marker vaccine would require extensive serological testing in the vaccinated population in order to detect hidden field virus infections. At present no marker vaccine has been licensed within the EU and EU Member States demand well-documented data on the safety and efficacy of the vaccine before its potential use in emergency situations. It is understood that the criteria for the use of the marker vaccine will be very stringent. Provided that all safety requirements are met, the period of exclusion from the market could be considerably shortened at least for pig products after a CSF outbreak (Anonymous, 1997). As soon as marker vaccines are sufficiently investigated and licensed, the ‘Guidelines for a Classical Swine Fever Emergency Vaccination Programme’ (Anonymous, 1994) are to be amended. The possible use of an emergency vaccination with marker vaccines is expected to avoid the ethically questionable and expensive large scale pre-emptive slaughter of pigs. Thereby, the public acceptance of the eradication policy will increase and costs will decrease. Under these circumstances the use of emergency vaccination using marker vaccines could be a useful tool of the non-vaccination policy.

A still unresolved problem is the control of CSF in wild boar (Laddomada, 2000). Both the prolonged persistence of virus in wildlife populations and the constant threat of domestic pig holdings in the respective areas require an efficient control strategy. Comprehensive information about the current situation in wild boar populations is essential and new strategies have to be devised. They have to take into account current knowledge about factors influencing CSF epidemiology, e.g., wild boar behaviour; population dynamics; influence of hunting strategies; influence of geographic profiles.

An efficient surveillance system must be an integral part of the control strategy. The EU Commission has held a workshop dedicated to this topic (Anonymous, 1998) and a working group of the Scientific Committee on Animal Health and Animal Welfare will prepare a recommendation.

8. Additional reading

Forschungsprojekt 96HS022, Institute of Virology, Hannover Veterinary School, Buenteweg 17, D-30559 Hannover, Germany.

References


