Classical swine fever: the European experience and a guide for infected areas

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Submitted for publication: 31 March 1999
Accepted for publication: 28 July 1999

Summary
Classical swine fever (CSF) (hog cholera) virus infection is still of world-wide concern, either because of the direct effects of the disease on swine breeding in areas where the virus is epizootic or enzootic, or as a threat in areas where the virus has been eradicated.

The authors provide an overview of the characteristics of the disease. Special emphasis is placed on the chronic form of disease, particularly in the late stages of eradication programmes.

In the early 1980s, the European Union (EU) was composed of countries which were officially free of the disease (absence of infection and no vaccination) and countries in which vaccination was either permitted or was compulsory. To ensure free trade between the Member States, an eradication plan was agreed upon and implemented. Initially, the plan consisted of a combination of vaccination with the Chinese strain of the virus and slaughter and removal of infected herds. Consequently, when the number of infected herds was low, vaccination was abandoned and the control of CSF was conducted exclusively by eradication (removal and slaughter). The United Kingdom, Austria, Denmark, Ireland, Luxembourg, Finland and Sweden ceased vaccination before 1980. In the other countries, vaccination was useful in controlling the last epidemics and was finally ceased as follows: France in 1983, the Netherlands in 1986, Belgium, Spain and Greece in 1988, Germany in 1989 and Italy in 1990. From 1990 onwards, no vaccination against CSF has been performed in the EU.

New techniques for the diagnosis of CSF (for example, the enzyme-linked immunosorbent assay based on the detection of the p125 antigen of the virus) have been shown to be of value in the early detection of infected animals.

In enzootic areas, the use of vaccines based on the Chinese strain has been successful. Vaccines with at least 100 PD_{50} of virus per dose are able to significantly limit the replication of virulent virus in the tonsils. Consequently, shedding of virus after infection can be reduced considerably. In heavily infected areas, vaccination plays a crucial role. The European experience shows that eradication may be achieved when vaccination with highly effective vaccines is combined with effective identification of swine, movement control, early diagnosis and the rapid elimination of infected herds.

Keywords
Introduction

Classical swine fever (CSF) (hog cholera) remains of major world-wide concern in disease-free areas. Introduction of the disease is a constant threat and in contaminated areas, eradication is the ultimate target. In both cases, the basic characteristics of the CSF virus should be considered whether attempting to maintain or achieve official freedom from CSF.

The disease is induced by a small enveloped RNA (ribonucleic acid) virus named classical swine fever virus (CSFV), belonging to the Flaviviridae family, genus Pestivirus (36). The virus leads to a systemic disease and provokes a variety of symptoms in pigs. The most common signs in acute cases are high temperature (> 40°C) and haemorrhages on the ears and abdomen. These symptoms are accompanied by respiratory disease, encephalitis and central nervous disturbances. Symptoms of the chronic form are much less typical, for example, wasting and growth delay, particularly in cases where the other symptoms considered as typical are absent. Differences in strain virulence (9, 23, 34) and the immunological status of the pig affected seem to be the major factors influencing this varying clinical picture.

The presence of immunotolerant animals persistently infected with strains of low virulence may complicate early diagnosis of the infection. These animals do not express typical signs and fail to produce antibodies (13), making serological diagnosis problematic. This situation is similar to immunotolerance exhibited by ruminants infected with the pestiviruses bovine virus diarrhoea virus (BVDV) of cattle and bovine border disease virus (BDV) of sheep (8). Van Oirschot and Terpstra described the case of a carrier sow affected by a field outbreak (50). The animal gave birth to a litter of 11 piglets. All piglets had CSFV in their pre-colostral plasma. Six piglets were followed until death. At day two after birth, the piglets had high virus titres in the plasma although all had ingested colostrum with a high antibody titre against CSFV. Finally, all animals developed clinical signs, very late after birth, commonly known as 'late onset'. Signs such as increasing anorexia and depression, conjunctivitis, dermatitis and locomotion disturbances in varying degrees were noticed and death ultimately occurred at 323 days after birth. None of the piglets developed antibodies against CSFV. Vannier et al. experimentally reproduced immunotolerant animals from sows infected at 43 days of gestation (48). A similar syndrome was reproduced by Paton and Done in pigs congenitally infected with ruminant-type pestiviruses (38). Chronic infection with CSFV may occur after infection with moderately virulent virus types or with strains which provoke chronic cases of the disease (9, 34). The virus may transiently disappear from the serum before reappearance of clinical disease in a less clearly pronounced form. Such persistently infected animals play an important role in the epidemiology of the disease since the animals are not clearly affected clinically but harbour and may excrete the virus for several months. Wild boars can also act as a source of CSF infection (4, 11).

Vaccines are an efficient tool to limit the circulation of the virus in a swine population, on the condition that the vaccines comply with high safety and efficacy requirements and are properly applied.

In the early 1980s, some countries in Europe (United Kingdom, Ireland and Denmark) were already completely free of CSF; no vaccination or infection occurred in those countries. However, other countries in Europe were infected (5). This difference in health status of swine in regard to CSF hampered free trade of swine and swine products within the European Union (EU). Free trade of animals and animal products within the EU is only possible if trade does not represent a sanitary risk for countries which are free of disease. As a consequence, sanitary status in regard to CSF had to be harmonised within the EU.

Gaining official status of freedom from classical swine fever in the European Union


Some important definitions of the Directives are reproduced below:

1. Free of classical swine fever: no classical swine fever has been diagnosed during the last 12 months.

2. Officially free of classical swine fever: no classical swine fever has been diagnosed during the last 12 months, no swine vaccinated against classical swine fever are present and vaccination against classical swine fever has not been authorised for at least 12 months.

3. Region: a country can be divided into well-defined regions which may not all have an identical disease status. This system does not automatically block a whole country for trade if only some of these regions are affected by CSF (17).

According to this legislation, all EU Member States were expected to become officially free of CSF five years after having presented an eradication plan.

In areas infected with CSF, vaccination was initially intensified in order to cover the entire swine population. The general vaccination programme was accompanied by well-defined measures to be taken in case of suspicion or confirmation of the disease, financial measures for
compensation, and procedures for identification and tracing of infection. In the case of vaccination, only vaccines that were produced from the Chinese strain and that had at least 100 PD$_{50}$ (protective dose 50%) were allowed (7, 30). Vaccination was performed under official control. Veterinary Services controlled the vaccinations and assured that all swine in the area concerned were duly vaccinated with the officially-approved vaccines only. In parallel, presence of the disease was controlled through a system of surveillance by veterinarians and Veterinary Services. Every veterinarian had, and still has, the obligation to declare every minor suspicion of disease. After declaration, all movement of personnel, goods and animals, to and from the herd concerned and a defined area around the herd was stopped for a period determined by the veterinary authorities. Cessation of vaccination became possible in countries of the EU as indicated in Table I.

Cessation of vaccination against classical swine fever in the European Union

Twelve months after the last country in the EU ceased vaccination, the EU regarded itself as officially free from CSF. After that date, the legislation according to the Directive EEC/80/217 (14) was applied and in case of problems, special measures were taken by decision of the Commission. Those measures were based on tracing, identification, laboratory analysis and eradication of herds and contact herds.

Table I

<table>
<thead>
<tr>
<th>Member State</th>
<th>Date of cessation of vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>1 April 1988</td>
</tr>
<tr>
<td>Denmark</td>
<td>Before 1980*</td>
</tr>
<tr>
<td>Germany</td>
<td>1 January 1988</td>
</tr>
<tr>
<td>Greece</td>
<td>1 January 1988</td>
</tr>
<tr>
<td>Spain</td>
<td>1 July 1988</td>
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<tr>
<td>France</td>
<td>30 April 1983</td>
</tr>
<tr>
<td>Ireland</td>
<td>Before 1980*</td>
</tr>
<tr>
<td>Italy</td>
<td>1 January 1990</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Before 1980*</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>15 July 1986</td>
</tr>
<tr>
<td>Portugal</td>
<td>1 July 1989</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Before 1980*</td>
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<tr>
<td>Austria</td>
<td>Before 1980*</td>
</tr>
<tr>
<td>Finland</td>
<td>Before 1980*</td>
</tr>
<tr>
<td>Sweden</td>
<td>Before 1980*</td>
</tr>
</tbody>
</table>

* Vaccination never applied or ceased before 1980

Source: Commission of the European Union

In the described situation, serological surveillance alone was demonstrated to be insufficient for tracing the infection (26). This is a further confirmation of the problem posed by chronically infected and immunotolerant pigs. Serological examination must be complemented by virological examination since persistently infected pigs are serologically negative and virologically positive. Furthermore, tracing of secondary outbreaks, clinical investigation of animals and routine laboratory investigation of clinically sick animals for CSF virus or antigens are essential (3). Epidemiological investigation will provide important information about the origin of outbreaks and possible existing risks. Genome analysis of strains together with computer analysis, as described by Greiser-Wilke et al., may be of considerable assistance (22). The financial contribution of the authorities must be stressed: farmers are compensated for all animals slaughtered within the framework of the eradication programme by the Member States and the EU (51).

Contacts by swine, transport vehicles and humans are the main channels for transmission of CSF. Identification and registration of animals are both essential in order to detect contacts among farms. Tracing forwards and backwards is necessary and probably the most difficult aspect of every eradication attempt.

Germany was also confronted with CSF outbreaks in 1993 and 1994, simultaneously with Belgium (39). Genome analysis (32, 44) of the isolates provided interesting data regarding the epidemiology. However, genomic differences cannot be related to different protective patterns among virulent strains and vaccine strains.

In 1997, CSF reappeared in the Netherlands, Germany, Belgium, Spain and Italy (1, 2, 35). The genomic profile of the isolates and tracing of infected and contact herds through the identification system revealed that all these epidemics were probably linked. Authorities in Belgium were successful in rapidly eradicating the seven infected herds and fifty-five contact herds as a preventive measure. As a consequence, the
country regained status of official freedom from CSF within 40 days (35). Eradication was equally successful in Italy.

In the EU, the control of CSF remains based on eradication without vaccination. The issue of the use of deleted vaccines, offering the possibility to differentiate between infected and vaccinated animals has been raised. Data currently available for deleted vaccines do not answer the questions of how to detect immunotolerant animals and pigs chronically infected with CSF viruses or whether deleted vaccines offer the same rapid protection in an emergency situation as presently available vaccines (7, 53). Furthermore, it is uncertain whether deleted vaccines will offer the same degree of efficacy (> 100 PD$_{50}$ per dose of vaccine). The Scientific Veterinary Committee of the EU identified several areas for further investigation, as follows (21):

- research on safety issues
- development of live marker vaccines in order to boost efficacy
- further testing of marker vaccines in the field of control
- further research on the companion discriminatory test
- further research on vaccination scenarios to be applied in practice
- economic cost-benefits
- further research on epidemiology of CSF in high density regions.

Currently, vaccination has been completely discontinued in countries of the EU. In contrast, the situation in countries in Asia can be compared with that of the EU before 1980. Experience and knowledge from both the EU and Asia should be shared for a better understanding of control measures in the future. Vaccination is still common practice in several countries in Central and Eastern Europe.

Vaccination and eradication

The situation in Member States of the EU ten to fifteen years ago, demonstrates that controlled vaccination and tracing of movement of pigs are vital steps towards control of the disease. Vaccination was undertaken under following conditions:

- high standards of safety and efficacy were maintained (7, 30)
- vaccines contained at least 100 PD$_{50}$ per dose of vaccine
- vaccines were administered under official control.

In an infected environment, vaccines are the basic tools for control and eradication. Vaccines can drastically reduce the circulation of virulent virus and prohibit or significantly minimise the economic losses due to CSF, on the condition that the vaccines used meet the highest standards of safety and efficacy and that administration is correctly performed.

The vaccines currently used are produced either using rabbits (lapanised vaccines) or cell cultures. In both cases the most widely used strain is the Chinese strain. The efficacy and safety of this strain have been proven world-wide (29, 30, 40, 45, 49). However, the system of production of the vaccine may significantly influence safety and efficacy. Vaccines produced using rabbits pose the problem of the standardisation of the vaccine viral content. The frequent use of these vaccines in sows has demonstrated that piglets from vaccinated sows may react anaphylactically when vaccinated themselves with lapanised vaccine (6). This problem has been solved by adapting the Chinese strain to cell culture and by elimination of all protein of rabbit origin from the final product. The latter vaccine has been adapted to an ovine continuous cell line. This vaccine has been scrutinised for safety in more than 15,000 swine, including pregnant sows, piglets and fattening swine. Safety of the vaccine has been confirmed by the use of millions of doses (internal Merial data).

The vaccine produced on ovine cell line meets the efficacy requirement (minimum 100 PD$_{50}$ per dose) and is an interesting tool for controlling the circulation of a virulent virus (7). This vaccine, with an antigenic content of 480 PD$_{50}$, was able to limit strongly, if not completely, the replication of virulent challenge virus in the tonsils, when pigs were infected oronasally at one week after vaccination performed in piglets at six weeks old. Long-term immunity using the same vaccine has been successfully demonstrated (41). This type of vaccine has been extremely useful in the eradication of CSF in the EU where vaccination was accompanied by elimination of infected animals and herds. However, in regions or countries where a policy of slaughter of infected animals does not exist, the situation is more complicated, as discussed below.

Vaccination in the presence of maternal antibodies

In an infected environment, sows may have high antibody titres due to infection with virulent virus. Their offspring may have higher maternal antibodies than offspring of vaccinated non-infected sows. In these herds, revaccination of piglets is recommended at the age of nine weeks, or even later in some cases, because of interference of maternal antibodies with vaccination at a younger age. As stated earlier, persistently infected animals pose an important risk and are difficult to detect. In a vaccinated environment, these animals should be found and eliminated.

Persistently infected animals: response to vaccination

Immunotolerant animals are unlikely to respond to vaccination (33). Animals that have been chronically infected with CSF do not always demonstrate a clear antibody response following a CSF infection. It is not known how these animals react to vaccination, however, chronically infected pigs shed CSF virus.
The usefulness of precolostral vaccination

Although technically proven, the practicability of precolostral vaccination is an important obstacle (28, 29).

Diagnosis

The clinical signs that are typical of CSF consist of petechiae on the skin, reddening of ear tops, anorexia and fever, accompanied by central nervous disturbances and diarrhoea. The incubation period of CSFV is approximately six days. Early signs, such as anorexia and fever, appear from the second day after infection. The symptoms of CSF may be confused with salmonellosis, actinobacillosis, erysipelas, African swine fever, porcine reproductive and respiratory syndrome and other diseases. In utero infections may give rise to abortions, stillbirths and foetal anomalies.

Typical anatomo-pathological lesions are necrotic tonsils, congested, swollen and haemorrhagic lymph nodes, necrosis of the ileocaecal valve and petechial haemorrhages in organs such as the epiglottis, larynx, renal cortex, urine bladder and small intestine.

In cases of congenitally persistent infection and chronic CSF, typical clinical signs as described above may be completely or partially absent. Symptoms are commonly limited to fever, anorexia and poor performance. Concurrent infections occur fairly frequently, which further complicates establishment of a clinical and pathological diagnosis of CSF. The difference in clinical signs and pathology between typically virulent strains and the more chronic type of strains has been described by Kamolsinpinchaiporn et al. (23, 24).

Given the various difficulties in establishing a reliable clinical and anatomo-pathological diagnosis, laboratory diagnosis is an essential tool in control of the disease. As mentioned before, persistently infected animals appear healthy for some time, although these animals are continuously infecting the environment. Identification of persistently infected animals is an important part of all control measures.

Laboratory diagnosis starts with the collection of appropriate material. The most frequently applied methods are the fluorescent antibody test on organ sections and virus isolation in cell culture. Samples should be as fresh as possible and submitted rapidly to the laboratory. Indeed, if samples are not fresh, cell destruction may render immunofluorescence on these tissues in the case of less virulent strains isolated from these tissues in the case of less virulent strains (24). Irrespective of the type of tissue taken, viruses of low virulence yield less virus per sample than virulent viruses, so that the risk of false negative results is real. Nevertheless, virus isolation remains the most reliable, ‘gold standard’ and the most useful method to test single animals.

The number of samples that can be examined may be increased by the use of less labour-intensive enzyme-linked immunosorbent assay (ELISA). The use of these kinds of tests is based on knowledge of the molecular structure of CSF virus.

From a molecular point of view, ruminant pestiviruses and CSFV are very closely related: three major structural glycoproteins, gp44/48(E<sub>m</sub>), gp33(E<sub>c</sub>) and gp55(E<sub>c</sub>) have been determined in CSFV (42). These are very similar to analogous glycoproteins determined in ruminant pestiviruses. All pestiviruses share a non-structural protein, p125/80 (now commonly called NS2-3), which represents the most conserved protein within the genus (12). Identical epitopes are present on p125 and p80 (NS-3) and monoclonal antibodies have been produced that react uniformly with these two non-structural proteins (12).

Non-cytopathic pestiviruses only express the non-structural protein (p125) (36). Most, if not all, CSF strains are non-cytopathic and only express the non-structural protein p125. These non-structural proteins are of major importance as diagnostic tools for pestiviruses in general and CSF in particular (10, 25, 46). Until now, a clear distinction among pestiviruses as serological groups has not been possible. Distinctions can only be made with monoclonal antibodies against different epitopes of these structural proteins (27).

Extensive pathogenesis studies determined the key role of persistently infected animals in pestiviruses in cattle (8). The detection and elimination of persistently infected animals, followed by vaccination are the main tools for control of pestiviruses in ruminants. Non-cytopathic virus types typically replicate in cell cultures without showing cytopathic effect, therefore complicating detection. Persistent infection results from infection during early pregnancy; when infection takes place during the first third of pregnancy, the infecting
antigen is not recognised as a foreign antigen but as a
self-antigen (47), thus, no antibodies are developed against
the antigen. The diagnosis of persistently infected, and in
particular, immunotolerant animals can only be achieved by
virus isolation or by detection of the p125 antigen which is
produced during virus replication.

The p125 antigen detection kit was used by Koenen and
Lefebvre in pigs (25). Results of a contact challenge
experiment are reported where pigs of different ages were
placed in different degrees of contact with one pig
intramuscularly or intranasally infected with a moderately
virulent strain of CSF. The clinical symptoms of the pigs in
direct contact were more pronounced than pigs in non-direct
contact. Older pigs did not always exhibit clear symptoms of
CSF although the presence of virus could be directly
confirmed by virus isolation as well as indirectly confirmed by
p125 antigen detection with an ELISA antigen capture test.
Similar results have been described by Lipowski et al. (31)
using a pi25 detection test on blood, leukocytes and organs.
These trials indicate the interest of using the p125 antigen
capture test. The test is less time-consuming than virus
isolation, easier to perform and particularly indicated for
screening large numbers of animals. In adult animals,
viraemia can be short-lived, therefore sampling of sick
animals and/or animals with fever is highly recommended. In
a vaccinated environment, the p125 test may be of particular
interest since negative results are obtained for CSF vaccine
produced on an ovine continuous cell line (7), similar to the
results obtained using immunofluorescence at one week after
vaccination (conjugate supplied by the National Veterinary
Institute in Brussels).

The p125 tests detect swine and ruminant pestivirus antigens
which is an advantage in an eradication programme.
Ruminant and swine pestiviruses are very closely related and
ruminant pestiviruses can provoke signs very similar to
chronic forms of CSF, particularly in sows infected early
during pregnancy (38). In trying to differentiate between
ruminant and swine pestiviruses, extremely precious time
may be lost for the implementation of the appropriate control
measures.

Conclusions

The method of control of CSF will primarily depend on the
disease situation and legislation in the country concerned. In
areas where the disease frequency and/or pig density is low,
Peste porcine classique : l’expérience européenne et un guide pour les régions infectées

J. Vandeputte & G. Chappuis

Résumé
La peste porcine classique reste un problème mondial, du fait de ses conséquences directes sur la production porcine lorsque la maladie est enzootique ou épizootique et du fait de la menace qu’elle représente lorsque la maladie a déjà été éradiquée.


Pour les zones enzootiques, la vaccination avec la souche chinoise semble extrêmement efficace. Des vaccins contenant au minimum 100 PD50 de virus par dose sont capables de limiter de façon significative la réplication du virus sauvage au niveau des amygdales, ce qui réduit considérablement la diffusion du virus dans l’environnement. Dans les régions très infectées, la vaccination joue un rôle crucial. L’expérience européenne montre qu’il est possible d’éradiquer la maladie si l’emploi de vaccins d’une grande efficacité est accompagné d’une bonne identification des porcs qui permette le contrôle des mouvements des animaux, d’un système de diagnostic précoce et d’une élimination rapide des troupeaux infectés.

Mots-clés
Peste porcina clásica: experiencia europea y guía para zonas infectadas

J. Vandeputte & G. Chappuis

Resumen
La peste porcina clásica sigue constituyendo un problema en todo el mundo, tanto por sus repercusiones directas sobre la producción porcina, en zonas donde la enfermedad es epidémica o enzoótica, como por la amenaza que supone en zonas donde ya ha sido erradicada.

Los autores repasan las características generales de la enfermedad, haciendo hincapié en su forma crónica, que plantea problemas sobre todo en las etapas finales de los programas de erradicación.

A principios de los años 1980, los Estados Miembros de la Unión Europea (UE) se repartían en dos grupos: países donde no se practicaban vacunaciones y que estaban libres de infección (esto es, países oficialmente libres de la enfermedad); y países donde se permitía u obligaba a vacunar a los animales. Con el fin de hacer posible el libre comercio entre todos los países de la UE, se implementó un plan de erradicación. En su primera fase, el plan combinaba campañas de vacunación (con la cepa china del virus) con campañas de erradicación (sacrificio sanitario de los rebaños infectados). Posteriormente, cuando la tasa de rebaños infectados cayó a un nivel lo bastante bajo, se abandonaron las vacunaciones para fiar la lucha contra la peste porcina clásica exclusivamente a la erradicación (sacrificio sanitario). El Reino Unido, Austria, Dinamarca, Irlanda, Luxemburgo, Finlandia y Suecia ya habían interrumpido las vacunaciones antes de 1980. Los demás países continuaron con sus campañas a fin de controlar los últimos brotes epidémicos, y después fueron interrumpiéndolas progresivamente en el orden siguiente: Francia en 1983, Países Bajos en 1986, Bélgica, España y Grecia en 1988, Alemania en 1989 e Italia en 1990. A partir de 1990 no se han realizado vacunaciones contra la peste porcina clásica en el seno de la UE.

Nuevas técnicas de diagnóstico de la peste porcina clásica, como el ensayo inmunoenzimático para la detección del antígeno p125 del virus, han demostrado ser de gran utilidad para la detección precoz de animales infectados.

En zonas donde la enfermedad es endémica, el uso de vacunas con la cepa china parece sumamente eficaz. Las vacunas con un mínimo de 100 PD_{50} de virus por dosis son capaces de contener de forma significativa la replicación del virus virulento en las amígdalas, lo que reduce considerablemente la excreción de virus y su difusión en el entorno. En zonas con elevada tasa de infección, las vacunaciones desempeñan un papel crucial. La experiencia europea demuestra que es posible erradicar la enfermedad combinando el uso de vacunas de gran eficacia con una identificación eficiente de los animales que permita controlar sus desplazamientos, establecer un sistema de diagnóstico precoz y eliminar con rapidez los rebaños infectados.

Palabras clave
References


