Open Veterinary Journal, (2024), Vol. 14(10): 2497-2508
ISSN: 2226-4485 (Print)
ISSN: 2218-6050 (Online)

Review Article
DOI: *10.5455/OVJ.2024.v14.i10.1*

Submitted: 16/06/2024 Accepted: 05/09/2024 Published: 31/10/2024

Classical swine fever: Unveiling the complexity through a multifaceted approach

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Abstract
Classical swine fever (CSF), sometimes referred to as hog cholera, is a highly contagious, virally based, systemic illness that affects both domestic and wild pigs. The virus known as classical swine fever virus (CSFV) is a member of the Flaviviridae family, specifically the genus Pestivirus. This disease is thought to be endemic in many Asian countries that produce pork as well as in several countries in Central and South America, the Caribbean, and elsewhere. As previously indicated, depending on the virulence of the virus strain involved and several host circumstances, clinical indications of CSFV infection can vary greatly, ranging from abrupt fatality to an occult course. CSF diagnosis can be made by serological detection, antigen, RNA, and isolation. CSF's highly varied symptoms and post-mortem pathology resemble those of African swine fever (ASF). ASF, the kind of CSFV, the pig's age, and its susceptibility all affect the clinical symptoms. Pigs that contract CSFV, a highly infectious and economically significant virus. The great economic significance of the swine business makes the CSFV a potential bioterrorism threat. Live attenuated CSF vaccinations have been around for many years and are quite safe and effective. Controlling epidemics in CSFV-free zones requires quick action. Pigs that are impacted must be slaughtered, and the carcasses must be buried or burned.
Keywords: Classical swine fever, Disease, Pig, Vaccine, Virus.

Introduction

Classical swine fever (CSF), sometimes referred to as hog cholera, is a highly contagious, virally based, systemic illness that affects both domestic and wild pigs (Brown and Bevins, 2018). Acute forms of the disease are the most common, although there are also subacute, chronic, and clinically invisible variants. Classical swine fever virus (CSFV), the causal agent, is a member of the Flaviviridae family's genus Pestivirus (Blome *et al*., 2017). Along with these viruses, this genus also includes the HoBi-like virus, Border disease

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virus, Bungowannah virus, and Bovine viral diarrhea virus (BVDV-1 and BVDV-2) (Righi *et al*., 2021).

CSFV is a small RNA virus, very different from the large DNA virus that causes African swine fever (ASF), although both viruses produce similar clinical signs and lesions (Cabezón *et al*., 2017). It suppresses the immune system like other members of its genus, and afflicted animals may die from secondary infection (Muñoz-González *et al*., 2015). The virulence of the causing virus and the pig's immune system determine how this sickness manifests itself. Because of this, while pigs of all ages can have this disease, mature pigs often experience fewer severe symptoms and have a higher chance of surviving (Dharmawan *et al*., 2021).

The disease's epidemic was initially documented in Ohio in the United States in 1833 and the virus was later discovered in 1904 (Malik *et al*., 2020). The severity of the virus and the age of the animal both affect how long the disease takes to cure CSF disease, which has an incubation period of three to 10 days (Xie *et al*., 2018). Clinicopathological indicators of CSF include fever (>40°C), respiratory symptoms, conjunctivitis, diarrhea and constipation, skin bleeding, lethargy, and neurological symptoms infected animals such as seizures, clumsiness, and staggering gait (Brown and Bevins, 2018). Obstetric disease in pregnant pigs is typified by abnormalities, abortion, stillbirth, and fetal mummification (Choe *et al*., 2019).

Pigs can contract this disease directly from one another, as well as from infected feed and water, inanimate items, livestock equipment, transport trucks, and guests (Kameyama *et al*., 2019). In addition, sexual activity, artificial insemination, and contaminated wild boar sperm can all transmit this disease (Maes *et al*., 2008). Animals infected with extremely virulent CSFV isolates usually die from the infection, while isolates with moderate to low virulence cause long-term illness (Risatti *et al*., 2005). Testing in laboratories conducted by accredited, approved laboratories verifies suspected instances. CSF is challenging to diagnose due to its wide spectrum of clinical symptoms and similarity to other illnesses.

Since its inception, CSF has consistently resulted in significant financial losses for the pig farming sector. This is because of the virus's high rates of illness and death as well as the tight regulations placed on the trade in hog products and items derived from pork (Schettino *et al*., 2021). Furthermore, returning a country or territory to the CSF-free status that the Office International des Epizooties has recognized may need a difficult and costly procedure. Consequently, CSFV continues to be an endemic and reemerging virus in pigs, endangering global pork production as well as the food security of communities living in underdeveloped nations (Fan *et al*., 2021).

Worldwide, CSF is regarded as a disease with significant consequences (Blome *et al*., 2017). CSFV infections have no known cure. On the other hand, inoculation against CSFV with a live attenuated vaccine (LAV) stops the illness from occurring and is typically administered in regions where CSFV is prevalent (Augustyniak and Pomorska-Mól, 2023). Nations that are regarded as disease-free do not immunize. The aim of writing this review is to provide an overview of etiology, epidemiology, pathogenesis, diagnosis, differential diagnosis, clinical symptoms, post mortem lesions, transmission, economic impact, bioterrorism, vaccination, and control of CSF disease.

Etiology

The virus known as classical swine fever (CSFV) is a member of the Flaviviridae family, specifically the genus Pestivirus (Van Gennip *et al*., 2004). Other viruses in this genus include the Border disease virus (BDV), the BVDV-1 and 2 BVDV-2, and an increasing number of unclassified viruses known as atypical pestiviruses, which include the giraffe virus, HoBi-like viruses, the recently identified Bungowannah virus, and atypical swine pestivirus (Righi *et al*., 2021).

The four structural components that make up this enveloped virus particle are the envelope glycoproteins E1, E2, and Erns, as well as the core protein (C) (Schulz *et al*., 2017). A positive single-stranded RNA genome, measuring roughly 12.3 kb, is contained within the core and is translated into a single polyprotein (Shi *et al*., 2015). Non-translational regions encircle the coding area on both ends. Thirteen mature proteins are produced through co- and post-translational processing of precursor proteins by viral and cellular proteases. These include the structural proteins described above as well as the non-structural proteins Npro, p7, NS2-3, NS2, NS3, NS4A, NS4B, NS5A, and NS5B (Wang *et al*., 2015). These proteins serve a variety of purposes in the reproduction of viruses. For instance, NS5B is an RNA-dependent RNA polymerase, and NS3 is a protease (Wang *et al*., 2010).

In cell culture, viral replication often takes place in the cytoplasm following receptor-mediated endocytosis and does not result in cytopathic consequences (naturally occurring CSFV strains have been discovered to be non-cytopathic) (Summerfield and Ruggli, 2015). The proposed receptor is the porcine complement regulating protein differentiation (CD) group 46, which, together with heparan sulfate, has been demonstrated to be important for CSFV attachment (Dräger *et al*., 2015). Heparin sulfate was used more frequently for cell-virus interactions after cell culture adaption. The mutation that causes adaptation is found in the Erns coding region, specifically at amino acid 476 of the CSFV polyprotein's C terminus, where an Arg residue replaces a Ser residue (Hulst *et al*., 2000).

The degree to which CSFV survives in different environments varies greatly and is mostly determined by temperature as well as the matrix in which the virus is present. This virus typically has a longer survival period in cold, wet, and protein-rich environments (Edwards, 2000). It is commonly known that

temperature and virus survival are correlated. Stability of meat products and viability in excretion are crucial factors for controlling animal diseases. Survival periods for discharged CSFV have been reported to vary from a few days at ambient temperature to a few weeks at 5°C (Weesendorp *et al*., 2008). The survival duration is significantly shortened at temperatures above 35°C and inactivation happens in a matter of hours or even minutes at temperatures above 50°C (Edwards, 2000). This is a crucial consideration when talking about biogas power plants and other industrial sectors.

In line with this, Madera *et al*. (2018) were able to demonstrate that CSFV had a limited survival time at high temperatures and a prolonged infectivity period at low ones. Schulz *et al*. (2017) demonstrated that, in a lab setting, virus inactivation could be accomplished at 60°C for three minutes. Nonetheless, the temperature distribution and the homogeneity of the mixture to be inactivated are crucial. This indicates that the virus can endure in pig pens that are contaminated for a few days to a month during the winter (Muñoz-González *et al*., 2015). In laboratory settings, freeze-thawing negatively affects virus titers; however, certain chemicals, such as dimethyl sulfoxide, can stop this from happening (Ganges *et al*., 2020).

CSFV is reasonably stable in the pH range of pH 5 to pH 10 (Blome *et al*., 2017). Temperature affects the half-life at low pH levels; at pH 3, the average half-life is 10 times shorter at ambient temperature than it is at 4°C (70 hours at 4°C compared to 5 hours at 21°C) (Niederwerder, 2021). The matrix containing meat or downstream products is also significant. According to Kameyama *et al*. (2019), the virus can survive for years in meat that has been frozen at −70°C and for days to years in various meat products. Robert *et al*. (2023) also revealed that viruses might survive in frozen meat for up to 4.5 years. The virus is not much affected by pickling or smoking by itself, but it is readily inactivated by higher temperatures.

Epidemiology

There are cases of CSF everywhere in the world. The disease is thought to be endemic in many Asian countries that produce pork as well as in several countries in Central and South America, the Caribbean, and elsewhere (Ganges *et al*., 2020). Countries with national pig herds that are free of this illness include Australia, New Zealand, Canada, America, and several European nations (Coronado *et al*., 2021). A common way for CSF infection to spread is through eating raw or infected pork products (Brown and Bevins, 2018). Due to inadequate or nonexistent surveillance, the status of CSF in some African countries may be unknown. In 2014, it was reported as endemic in Madagascar, suspected to have occurred in Equatorial Guinea in 2013 and is absent or eradicated in other reporting countries (Gonzalez and Macgregor-Skinner, 2014).

The primary issue in regions where CSFV is widespread is the disease's potential to spread through animal movement. The Suidae family of animals, including wild boars, is prone to CSFV infection (Moennig, 2015). The endemic CSFV virus in Europe is most likely the cause of documented CSF outbreaks in domestic pig populations (Postel *et al*., 2013). The virus can also spread to cattle through feeding, which can result in CSF outbreaks (Ribbens *et al*., 2004).

Given that heat (i.e., cooking) readily inactivates CSFV, heat treating swill feed prior to feeding to pigs is crucial (Edwards, 2000). However, several nations have outright outlawed the practice of swill feeding in order to reduce the possibility of disease epidemics. The disease's mechanical transmission across swine farms through cars, machinery, and personnel has also been linked to its spread (Juszkiewicz *et al*., 2023). It has been noted that CSFV persists in groups for extended periods of time.

Fetal in utero infection can result from CSFV strains that are minimal to moderately virulently infected in pigs during pregnancy (Jang *et al*., 2022). Because of this infection, newborn piglets are always infected with CSFV, which acts as a viral carrier and a source of future infections. Carriers that are persistently infected typically do not exhibit any clinical symptoms, but they continue to release CSFV into the environment (Manessis *et al*., 2024). Thus, when examining herds facing reproductive failure or piglets exhibiting inexplicable clinical indications, including tremors or other congenital anomalies, it is crucial to take CSFV infection into account.

The rise of fugitive CSFV variants, which are not completely neutralized by vaccine-derived immune responses, is thought to have been caused by the widespread use of CSFV vaccines in China (Luo *et al*., 2017). Sera from pigs inoculated with the LAV C strain less effectively neutralized CSFV isolates of genotype 2.1 than isolates of genotypes 2.2 and 2.3 (Tran *et al*., 2020). It is unclear how these findings relate to the possibility of vaccine failure.

Pathogenesis

As previously indicated, depending on the virulence of the virus strain involved and several host circumstances, clinical indications of CSFV infection can vary greatly, ranging from abrupt fatality to an occult course (Blome *et al*., 2017). The majority of clinical symptoms are nonspecific, and only laboratory diagnosis may distinguish this illness in pigs from several other infectious disorders. Viral hemorrhagic fever can have a catastrophic acute form that includes enhanced vascular leakage, pulmonary edema, petechial hemorrhages, and severe thrombocytopenia (Tamura *et al*., 2012). Numerous abnormalities found in acute CSF are described in relation to cytokine involvement. Primary replication of CSFV infection occurs in the tonsils, and then it spreads to the surrounding lymphoid tissue (Guo *et al*., 2023). The virus travels through lymphatic channels to local lymph nodes. At this point, the virus multiplies even more and travels

via the blood to secondary replication sites such as the spleen, bone marrow, and visceral lymph nodes (Liu *et al*., 2011). Certain subsets of macrophages exhibit apoptotic responses in addition to phagocytic and secretory activity. While direct viral damage is improbable in many of the lesions that arise after CSFV infection, these activated macrophages seem to be crucial to pathogenesis (Banete *et al*., 2022). Furthermore, pathogenesis is aided by the targeting of dendritic cells and the disruption of the interferon system (Carrasco *et al*., 2004). High serum levels of interferon (IFN)-α appear to be correlated with both the virulence of the implicated strain and the severity of the illness. Two days after infection, high amounts of IFN-α were detected prior to the manifestation of clinical signs (Summerfield and Ruggli, 2015). These findings were confirmed by microarray analysis of peripheral blood monocyte cells derived from CSFV-infected pigs (Zaffuto *et al*., 2007).

CSF causes immunosuppression, granulocytopenia, and severe lymphopenia, particularly in the acute-lethal stage (Ganges *et al*., 2020). Furthermore, severe thrombocytopenia develops quickly following infection. The reasons behind this decrease in platelets are yet unknown, although some theories include accelerated damage, bone marrow lesions, megakaryocyte degeneration, and disseminated intravascular coagulation (DIC) (Gomez-Villamandos *et al*., 2003). Additionally, phagocytosis and large activation of platelets have been proposed as etiological factors; however, no associations associated with DIC were found in infections with CSFV genotype 2.3 strains (Kameyama *et al*., 2019). Increased expression of pro-inflammatory and pro-coagulation factors is also observed in endothelial cells, at least *in vitro* (Dong *et al*., 2018). Hemorrhagic lesions are associated with many pathogenic pathways, such as endothelial cell injury, thrombocytopenia involvement, erythrodiapedesis, capillary vasodilation, and enhanced permeability (Gómez-Villamandos *et al*., 2000). Studies using various strains have produced contradictory outcomes, and some elements are still unknown.

Pigs recovering from CSFV infection exhibit a strong immunological response, with E2-specific antibodies showing up after 10–14 days, despite the immunopathogenesis of the majority of CSF-related lesions (Coronado *et al*., 2021). CSFV can be neutralized *in vitro* by E2 antibodies, which can also trigger a defensive immunological reaction (Zhao *et al*., 2021). These antibodies could endure a lifetime along with the defense against reinfection. Antibodies were also produced against the non-structural protein NS3 and Erns in addition to E2 (Yi *et al*., 2022). Live attenuated CSFV immunization can be effective 3–5 days after inoculation (Holinka *et al*., 2017). Therefore, protection can happen even in the absence of neutralizing antibodies and before a particular T cell response manifests. Though the exact mechanism of this first defense is yet unknown, T cells that secrete IFN-γ appear to play a part (Mair *et al*., 2014).

Diagnosis

Diagnostic tests to detect CSFV: CSF diagnosis is predicated on clinical manifestations, serological examination, tissue antigen identification, viral isolation, and CSFV RNA detection (Wang *et al*., 2020a). Laboratory confirmation of the disease is always required because clinical indications found in pigs infected with CSFV can also be seen in other swine infections. Clinically, the differential diagnosis changes according to how the CSF illness progresses. Due to the similar clinical symptoms of these infections, ASF is an important differentiator (Schulz *et al*., 2017). In addition, hemorrhagic lesions, pig systemic disease, and reproductive failure from various viral and noninfectious causes should be taken into account (Blome *et al*., 2017).

Serological testing: After the infection, 2–3 weeks later, antibodies against CSFV are found (Brown and Bevins, 2018). Virus neutralization tests and ELISA are frequently used to find CSFV-specific antibodies (Wang *et al*., 2020b). It is recognized that the viruses that cause border disease BDV and BVDV can infect pigs and cross-react on ELISA (Huang *et al*., 2021). Pigs with ruminant pestivirus antibodies may have difficulties with CSF serological diagnosis. Antibodies specific to BVDV and BDV have been found infrequently in the pig population (de Oliveira *et al*., 2020). For CSF surveillance, this approach is recommended.

Antigen detection*:* Direct immunofluorescence utilizing specific antibodies can identify CSFV antigens in frozen tissue sections, especially tonsil samples (Van Gennip *et al*., 2004). ELISA is another method for antigen identification; however, it is limited to group CSFV screening due to its low sensitivity (Watanabe *et al*., 2023).

Detection of CSFV RNA: CSFV RNA can be quickly found in tissue, blood, serum, or oronasal fluid using the RT-PCR and RT-qPCR tests (Dias *et al*., 2014). Tests that are appropriate to distinguish CSFV from BDV and BVDV. Scaling up standardized RT-PCR techniques allows for the screening of a large number of samples quickly and with great sensitivity (Jian *et al*., 2023). During CSF epidemics, this technique is quite helpful for screening pig herds.

Virus isolation: Cell cultures injected with tissue samples, white blood cells, or oronasal fluid from possible CSF cases are used to isolate CSFV (Lorena *et al*., 2001). Even if accurate, virus isolation can take days to weeks. Rather, there is widespread usage of preclinical and field fast detection assays.

Differential diagnosis

CSF's highly varied symptoms and post-mortem pathology resemble those of ASF. ASF is characterized by a hematoma-like swelling of the spleen and visceral lymph nodes; otherwise, the differences between the two diseases are more quantitative than qualitative (Cho

et al., 2023). Subpleural and interlobular pulmonary edema, as well as edema of the gallbladder wall and bile ducts, are uncommon in CSF but common in ASF (Sánchez-Vizcaíno *et al*., 2015).

Even though it is uncommon, congenital BVDV infection in pigs can result in post-mortem lesions and clinical symptoms that are identical to those of chronic CSF infection (de Oliveira *et al*., 2020). The conjugate used in the immunofluorescence test, which is made from anti-CSFV hyperimmune serum, is unable to distinguish between BVDV and CSFV antigens (Leifer *et al*., 2012). The conjugate also failed to distinguish between the fluorescence produced by the Chinese vaccine strain (C), which was tailored for the rabbit and was detected in the tonsils for up to 2 weeks following immunization, and the fluorescence induced by the field CSFV strain (de Smit *et al*., 2000).

If anamnesis and clinical signs point to a potential BVDV infection or vaccination, group serology for CSFV and BVDV neutralizing antibodies, respectively, or rabbit inoculation can be used to differentiate between the two infections (Falkenberg *et al*., 2021). The necessity for a diagnosis as soon as feasible is not addressed by either procedure because they take several days to complete. The issue has been resolved by conjugates made from specific monoclonal antibodies raised against CSFV, which enable instantaneous, unambiguous distinction between vaccinated and field CSFV strains as well as between CSFV and BVDV (Mi *et al*., 2022).

The parasites on a blood smear or by bacterial culture can be used to distinguish other septicemic disorders such as salmonellosis, eperythrozoonosis, pasteurellosis, *Haemophilus suis*, babesiosis, and *Erysipelothrix insidiosa* infections from CSF (Benninger and Steiner, 2017). In piglets, widespread bleeding without fever might result in thrombocytopenia or, in all age groups, dicumarol or other poisoning (Choe *et al*., 2019). Stunting, diarrhea, and stunted growth can be brought on by conditions such as vibrionic dysentery, chronic CSF, starvation, and enterotoxicosis caused by *Escherichia coli* or *Clostridium perfringens* (Kameyama *et al*., 2019). Congenital myoclonia might be mistaken for a piglet's trembling caused by an intrauterine CSFV infection (Barman *et al*., 2021).

Clinical symptoms

The kind of CSFV, the pig's age, and its susceptibility all affect the clinical symptoms. While there have been instances of very virulent viral strains in the past, most outbreaks these days are brought on by moderately virulent virus strains, and the clinical signs are frequently less severe and less distinctive. The incubation time is typically 3–7 days in acute instances, but it can range from 2 to 15 days (Brown and Bevins, 2018). The disease may not show symptoms in the herd for 2– weeks or more in a pasture setting (Robbins *et al*., 2014).

In vulnerable populations, highly virulent CSFV strains frequently cause acute and serious illness. In the acute form, common clinical indications include high fever, anorexia, and conjunctivitis, which can cause severe crusting of the eyes, lethargy, curling up, weakness, and more (Benninger and Steiner, 2017). Hard fecal pellets passing through the stool are typically followed by watery diarrhea, either continuously or sporadically. Pigs can walk with an unstable, tottering, or stumbling gait or lack of coordination, which frequently leads to posterior paresis (Kumar *et al*., 2015). Certain pigs may vomit yellow liquid that contains bile or develop respiratory ailments. Hyperemia may set in, accompanied by bleeding (particularly in the stomach, inner thighs, and ears) or cyanotic purple staining (usually on the snout, ears, and tail) (Helke *et al*., 2015). A frequent anomaly in laboratories is severe leukopenia (Shimizu *et al*., 2020). In the last stages, seizures may happen, and pigs with acute CSF frequently pass away in 1–3 weeks (Choe *et al*., 2019). The subacute form is comparable, but it has fewer severe symptoms, a longer illness course, and a lower death rate (Izzati *et al*., 2021). There have been reports of both subacute and chronic cases of ear spotting.

Certain animals may be the sole ones affected by chronic disease, which is more common in populations with partial immunity or less virulent strains. Early symptoms of the disease include anorexia, sadness, fever, leukopenia, and spells of diarrhea or constipation (Brown and Bevins, 2018). These symptoms can mimic those of other kinds. Pigs with the condition often get better in a few weeks, although these symptoms could come back later when they start to act more normally. Additional symptoms include skin sores, baldness, and thin or stunted growth. Immunosuppression may also result in concomitant infections (Büttner and Ahl, 1998). Over weeks to months, clinical symptoms may wax and wane, and the outcomes are frequently fatal.

The only indication that certain cattle are infected with less virulent strains of CSFV may be poor reproductive performance (Blome *et al*., 2017). These sows have the ability to abort or give birth to dead, malformed, mummified, stillborn, or weak piglets (Choe *et al*., 2019). Congenital tremors or anomalies of the central nervous system or visceral organs may occur in some piglets at birth (Barman *et al*., 2021). Others might have a chronic infection yet not exhibit any signs from birth. After a few months, these piglets get sick, exhibiting "late onset" symptoms such as depression, diarrhea, conjunctivitis, dermatitis, ataxia, and posterior paresis in addition to the inability to eat (Moennig *et al*., 2003). Pigs that are congenitally sick often die within a year, while they may live for 2 months or more.

The clinical signs and symptoms of wild boars are comparable to those of domestic pigs. Wild boars that are experimentally infected also get sick, sometimes rather badly, with fever, anemia, delayed clotting times during blood draws, diarrhea, and conjunctivitis (Artois *et al*., 2002). Despite virological and serological indications of infection, the majority of experimentally

infected boars in the same study did not exhibit any clinical signs (Kameyama *et al*., 2019). A wild boar has moderate-to-severe diarrhea (Moennig, 2015). Collared peccaries vaccinated with CSFV have been observed to exhibit nonspecific symptoms and a short-term fever (Brown and Bevins, 2018).

Post mortem lesions

The CSF lesions might differ greatly. In an outbreak, examining 4 or 5 pigs increases the likelihood of finding distinctive necropsy lesions. Hemorrhage is the most frequent lesion in acute illness (Izzati *et al*., 2021). There could be purple patches on the skin and swollen, bleeding lymph nodes (Malswamkima *et al*., 2015). Serous and mucosal surfaces frequently exhibit petechial hemorrhages or ecchymoses; these are particularly common in the kidneys, intestines, epiglottis, larynx, bladder, epicardium, trachea, subcutaneous tissue, and spleen (Blome *et al*., 2017).

Lesions in the gastrointestinal system include button ulcers in the colon, mild to moderate catarrhal enteritis in the small intestine, and hemorrhagic lesions in the stomach (Sudo *et al*., 2021). There is straw-colored fluid in the pericardial sac, thoracic cavity, and peritoneum (Blome *et al*., 2017). Severe tonsillitis is frequent, perhaps accompanied by necrotic foci. Though splenic infarction, a bulging, black, wedge-shaped lesion, is rare with the CSFV strains now in circulation, its detection raises serious suspicions (Giangaspero and Zang, 2023). There is a chance of brain encephalitis, lung blockage, and bleeding (Izzati *et al*., 2021). Lesions may not appear at all or may not be easily seen in certain acute situations.

Lesions from chronic diseases are less severe and can become more problematic due to secondary infections. Necrotic foci, often known as "button" ulcers, are present in the larynx, epiglottis, and intestinal mucosa (Ganges *et al*., 2020). Intestinal button ulcers may be associated with widespread diphtheria necrotizing enteritis. Bone lesions can also develop at the growth plates of the long bones and the costochondral junction of the ribs in growing pigs that have lived for more than a month (Gomez-Villamandos *et al*., 2003).

Common abnormalities in pigs with congenital infection include thymic atrophy, cerebellar hypoplasia, ascites, and head and foot deformities (Blome *et al*., 2017). Skin and internal organs may exhibit edema and petechial hemorrhages (Oh *et al*., 2022).

Transmission

Pigs are thought to be infected with CSF via the oral or oronasal route (Olesen *et al*., 2017). In addition, CSFV can enter the body through skin abrasions and other mucous membranes, including the genitalia through semen (Guo *et al*., 2023). The virus can be expelled by urine, feces, semen, and oronasal and ocular secretions (Brown and Bevins, 2018). According to a study, oronasal secretions are the primary way that low pathogenicity strain-infected pigs shed the virus (Weesendorp *et al*., 2008). Transmission may start before to the manifestation of symptoms. CSFV is easily transmitted through raw food containing tissue from infected pigs because it can linger in blood and tissue after death (Cai *et al*., 2017). Experimental evidence of aerosol transfer involving many strains. This is most likely to happen when there are a lot of animals around and nearby mechanically ventilated buildings (Ribbens *et al*., 2004). Piglets and boars that contract the virus during pregnancy or soon after may remain infected for a long time without producing an antibody against CSFV (Coronado *et al*., 2021). These animals have a months-long capacity to spread the virus either constantly or sporadically.

In addition to spreading through external objects, CSFV can also be carried by mechanical live vectors like insects (Li *et al*., 2022). The initial virus concentration and the existence of organic materials are two factors that affect estimates of its survival in the environment. According to certain research, CSFV inactivates on various materials and in urine and feces in a matter of days to 2 weeks at room temperature (e.g., 20ºC) (Weesendorp *et al*., 2008). Other research reports survival at 4°C–5ºC for 1–3 months under materials like pig excrement (Edwards, 2000). According to a study, this virus could also endure at least 70 days at 17ºC in pig feces (Davies *et al*., 2017). Infectious CSFV can linger in meat that has been chilled for almost 3 months and frozen for more than 4 years (Schulz *et al*., 2017). It does not appear to be inactivated by smoking or salt pickling in this proteinaceous environment. Depending on the method, reported viral survival durations in cured and smoked meats might range from 17 days to more than 180 days (Hempel *et al*., 2019).

All or most of the pig family (Suidae) appears to be susceptible to infection by CSFV. Both farmed pigs and wild boars have clinical instances. CSFV has been identified in white-lipped peccaries (*Tayassu pecari*), while common boars (*Phacochoerus africanus*), wild boars (*Potamochoerus larvatus*), and collared peccaries (*Tayassu tajacu*) have all been reported to have experimental infections (Martínez *et al*., 2018). Although reports of experimental infections in cattle, sheep, goats, and deer without clinical signs exist, there is no proof that these species are naturally infected (Clemmons *et al*., 2021). Additionally, CSFV strains can adapt to rabbits (Zhao *et al*., 2021). There is no proof that humans can contract CSFV.

Economic impact

Pigs that contract CSFV, a highly infectious and economically significant virus. The severity of the disease varies depending on the type of virus, age of the pig, and immune status of the animal. Acute infections are likely to be identified promptly since they are caused by extremely virulent isolates and have high mortality rates in naïve groups (Kleiboeker, 2002). However, particularly in older pigs, infections caused by less virulent viruses can be more challenging to diagnose (Brown and Bevins, 2018). CSF can be challenging to

diagnose due to its wide spectrum of clinical symptoms and similarity to other illnesses.

Even though CSF was historically common, the illness has been eliminated from farmed pigs in many nations. Reintroducing the virus may result in negative outcomes. An infection that began in the Netherlands in 1997–1998 spread to over 400 cattle and required $2.3 billion to contain (Elber *et al*., 1999). Approximately 12 million pigs were killed, largely for epidemic-related welfare concerns but also as a part of eradication operations. There have been outbreaks in other European nations as well, and there is a chance that domestic pigs could be exposed to the virus again due to its existence in wild boar (Sauter-Louis *et al*., 2021). Additionally, there is a chance that CSF, which is still widespread in South and Central America, will spread to North America (Schulz *et al*., 2017).

Bioterrorism

The great economic significance of the swine business makes the classical swine fever virus a potential bioterrorism threat. The virus's strong stability, clinical sickness it causes, endemic status in many countries worldwide make acquiring it an easy option, as the virus's presence in an environment high in proteins, and its disastrous effects on global trade (Brown and Bevins, 2018). Thus, it is important to regularly check both domestic and wild pigs for disease and to set up quick diagnosis procedures.

Vaccination

Live attenuated CSF vaccinations have been around for many years and are quite safe and effective. Through repeated passage in animals (rabbits) or cell culture, the underlying virus strain (e.g., C strain of CSFV, Lapinized Philippines Coronel, Thiverval, or Japanese guinea-pig exaltation GPE negative strain) is attenuated (Qiu *et al*., 2006). These vaccinations were included in mandated control programs that, along with stringent hygienic practices, resulted in the complete eradication of CSF from many parts of the globe. The CSF vaccine is still in use today in a number of Asian nations, including China, Eastern Europe, Trans-Caucasian nations, and South and Central American nations (Coronado *et al*., 2021). In an effort to contain the CSF outbreak, 22 nations formally confirmed having to conduct vaccine efforts in 2016 (Blome *et al*., 2017).

Furthermore, this vaccine has been modified for oral immunization of wild boars and has been investigated recently for vaccination of farm-raised domestic pigs (Bazarragchaa *et al*., 2021). The primary drawback of these vaccinations is the absence of conceptual serological markers that enable discrimination between viruses infected in the field and immunized animals, despite the fact that these shots typically offer advantages in terms of immunity onset, spectrum, and persistence (Greiser-Wilke and Moennig, 2004). This is typically less significant in endemic nations because vaccination campaigns are conducted in advance to prevent illness and guarantee product safety.

For emergency vaccination situations, there is typically no legal requirement to administer a specific vaccine. However, only the differentiated infected and vaccinated animals (DIVAs) vaccine is regarded as a practical choice for domestic pigs because trade limitations are placed on pigs inoculated with conventional LAV (Zhang *et al*., 2022). To date, only E2 subunit marker vaccines (including DIVA) are available on the market (currently, one E2 marker vaccine is commercially available, Porcilis® Pesti, MSD Animal Health, Unterschleißheim, Germany) (Li *et al*., 2022). These vaccinations have been shown to be safe, offer clinical protection, and stop the spread of CSF. However, there are issues with this vaccination, particularly with regard to early protection and protection against transplacental transmission (Coronado *et al*., 2021). These issues make it challenging to administer emergency vaccinations to farmed pigs. As a result, numerous research teams are trying to create next-generation marker vaccination candidates that, in theory, satisfy every need in terms of marketability, safety, efficacy, and DIVA potency.

Various vector vaccines, including vaccinia virus, pseudorabies virus, and adenovirus, are among the ideas that have been studied. Additional vaccine designs consist of RNA/DNA vaccines, subunit vaccines based on various expression systems, and attenuated recombinant vaccines containing chimeric constructions (Yuan *et al*., 2022). One of these vaccines, the chimeric marker vaccine candidate "CP7_E2alf," was licensed by the European Medicines Agency in 2014 following thorough testing conducted as part of a research effort sponsored by the EU (Leifer *et al*., 2009). Investigations into this novel marker vaccine are ongoing, but it has the potential to be a potent tool for the immunization of wild boars and domestic pigs in an emergency.

It has been demonstrated that oral emergency immunization of wild boar is successful in safeguarding domestic pigs and controlling CSF illness in wild animals. For this reason, several European nations, notably Germany and France, have adopted the aforementioned C strain formulation (Postel *et al*., 2013). To enhance this approach even more, DIVA vaccinations, like "CP7_E2alf," which have been tested on wild boar in both lab and field settings, maybe a viable medium-term solution (Leifer *et al*., 2009).

Control

Controlling epidemics in CSFV-free zones requires quick action. Veterinarians should adhere to local and national illness reporting rules if they encounter or suspect the presence of CSF (Acosta *et al*., 2023). Notification must be made right away to state or federal animal health authorities (Shimizu *et al*., 2020). There is currently no known treatment for this illness. Pigs that are impacted must be slaughtered, and the carcasses must be buried or burned.

CSF can be kept out of a herd in nations where the disease is endemic by buying animals from herds that

are CSFV-free, quarantining new stock for 4 months, and testing the animals before letting them interact with other herds (Blome *et al*., 2017). Vaccines can be used to lower the prevalence of infection during eradication campaigns as well as to shield animals from clinical signs (Coronado *et al*., 2021). The production of modified components (markers) and live vaccinations. Typically, killing confirmed cases and animal contact, cleaning and disinfecting contaminated sites, properly disposing of carcasses, movement control or quarantine, and surveillance are used to end outbreaks in CSFV-free areas (Schettino *et al*., 2021). Emergency vaccinations can also be administered, as well as the preventive slaughter of animals at surrounding farms. Some nations do routine virological surveillance for CSFV, such as routinely collecting tonsils from deceased pigs, because presently circulating viruses are frequently more difficult to identify based only on clinical symptoms (Kameyama *et al*., 2019). It is difficult to control endemic infections in wild populations. In Europe, wild boars are vaccinated orally (Rossi *et al*., 2015). It is best to prevent domestic animals and wild boar from coming into contact.

Conclusion

CSF is a highly contagious, virally based, systemic illness that affects both domestic and wild pigs. There are cases of CSF everywhere in the world. There is currently no known treatment for this illness. Pigs that are impacted must be slaughtered, and the carcasses must be buried or burned. Vaccines can be used to lower the prevalence of infection during eradication campaigns as well as to shield animals from clinical signs.

Acknowledgments

The authors thank Universitas Airlangga and Badan Riset dan Inovasi Nasional.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This study was funded in part by the Skema Airlangga Article Review (AAR) Universitas Airlangga Year 2024, with grant number: 323/UN3.LPPM/PT.01.03/2024.

Author's contributions

ARK, MHE, and IBM drafted the manuscript. KAF, KHPR, YP, and IM revise and edits the manuscripts. RR, OSMS, SMY, and SW took part in preparing and critical checking this manuscript. MKJK, AH, SRA, and BPP edit the references. All authors read and approved the final manuscript.

Data availability

All references are open access, so data can be obtained from the online web.

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