NAHEMS GUIDELINES:
VACCINATION FOR CONTAGIOUS DISEASES
APPENDIX B: VACCINATION FOR CLASSICAL SWINE FEVER

FAD PReP
Foreign Animal Disease
Preparedness & Response Plan

USDA

NAHEMS
National Animal Health
Emergency Management System

the Center for Food Security & Public Health
Iowa State University

United States Department of Agriculture • Animal and Plant Health Inspection Service • Veterinary Services

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The Foreign Animal Disease Preparedness and Response Plan (FAD PReP)/National Animal Health Emergency Management System (NAHEMS) Guidelines provide a framework for use in dealing with an animal health emergency in the United States.

This FAD PReP/NAHEMS Guidelines was produced by the Center for Food Security and Public Health, Iowa State University of Science and Technology (ISU), College of Veterinary Medicine, in collaboration with the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service through a cooperative agreement. This Guidelines document has undergone review by USDA Legislative and Public Affairs.

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THE IMPERATIVE FOR FOREIGN ANIMAL DISEASE PREPAREDNESS AND RESPONSE

Why Foreign Animal Diseases Matter

Preparing for and responding to foreign animal diseases (FADs)—such as highly pathogenic avian influenza (HPAI) and foot-and-mouth disease (FMD)—are critical actions to safeguard the nation's animal health, food system, public health, environment, and economy. FAD PReP, or the *Foreign Animal Disease Preparedness and Response Plan,* prepares for such events and provides guidance for activities during a response.

Since 2014, three HPAI outbreaks in the United States have cost over $880 million, just for indemnity payments and response activities on premises. Studies have estimated a likely national welfare loss between $2.3–69 billion[1] for an FMD outbreak in California, depending on delay in diagnosing the disease.[2] The economic impact of an FAD outbreak results from lost international trade and disrupted interstate trade, as well as from costs directly associated with the eradication effort, such as depopulation, indemnity, disposal, and virus elimination. In addition, there are direct and indirect costs related to foregone production, unemployment, and losses in related businesses. The social and psychological impact on owners and growers can be significant. Diseases with zoonotic potential, such as HPAI and Nipah/Hendra, may also pose a threat to public health.

Challenges of Responding to an FAD Event

Responding to an FAD event—large or small—is complex and difficult, challenging all stakeholders involved. Response activities require significant prior preparation. There are imminent and problematic disruptions to interstate commerce and international trade.

A response effort must have the capability to be rapidly scaled up or down according to the needs of the specific incident. This involves many personnel, resources, and possibly veterinary countermeasures. Not all emergency responders have specific food and agriculture skills required in areas such as biosecurity, quarantine and movement control, epidemiological investigation, diagnostic testing, depopulation, disposal, and possibly emergency vaccination.

Establishing widely communicated and understood response goals and guidelines, as accomplished by the FAD PReP materials, helps to broaden awareness of common objectives as well as potential problems.

[1] Carpenter TE, O'Brien JM, Hagerman AD, & McCarl BA. 2011. "Epidemic and economic impacts of delayed detection of foot-and-mouth disease: a case study of a simulated outbreak in California." *J Vet Diagn Invest.* 23:26-33.
[2] Estimates based on models may vary: Ekboir (1999) estimated a loss of between $8.5 and $13.5 billion for an FMD outbreak in California. Ekboir JM. 1999. "Potential Impact of Foot-and-Mouth Disease in California: the Role and Contribution of Animal Health Surveillance and Monitoring Services." *Agricultural Issues Center.* University of California, Davis.

Lessons Learned from Past FAD Outbreaks

The foundation of FAD PReP is the lessons learned from past FAD incidents. FAD PReP is based on the following:

- Achieving rapid FAD detection and tracing.
- Providing processes for emergency planning that respect local knowledge.
- Integrating State-Federal-Tribal-industry planning processes.
- Ensuring that there are clearly defined, obtainable, and unified goals for response.
- Having a unified Incident Command that can act with speed and certainty.
- Employing science- and risk-based management approaches to an FAD response.
- Ensuring that all guidelines, strategies, and procedures are communicated effectively to responders and stakeholders.
- Identifying trained personnel and resources that are required for an effective incident response.
- Trying to resolve competing interests prior to an outbreak and addressing them quickly during an outbreak.

FAD PReP Mission and Goals

The mission of FAD PReP is to raise awareness, expectations, and develop capabilities surrounding FAD preparedness and response. The goal of FAD PReP is to integrate, synchronize, and deconflict preparedness and response capabilities as much as possible before an outbreak by providing goals, guidelines, strategies, and procedures that are clear, comprehensive, easily readable, easily updated, and that comply with the National Incident Management System.

In the event of an FAD outbreak, the three key response goals are to: (*1) detect, control, and contain the FAD in animals as quickly as possible; (2) eradicate the FAD using strategies that seek to stabilize animal agriculture, the food supply, the economy, and to protect public health and the environment; and (3) provide science- and risk-based approaches and systems to facilitate continuity of business for non-infected animals and non-contaminated animal products.* Achieving these three goals will allow individual livestock facilities, States, Tribes, regions, and industries to resume normal production as quickly as possible. They will also allow the United States to regain FAD-free status without the response effort causing more disruption and damage than the disease outbreak itself.

FAD PReP Documents and Materials

FAD PReP is not just one, standalone FAD plan. Instead, it is a comprehensive U.S. preparedness and response strategy for FAD threats, both zoonotic and non-zoonotic. The following section provides examples of the different types of FAD PReP documents available.

- Strategic Plans—Concept of Operations
  - *APHIS Foreign Animal Disease Framework: Roles and Coordination* (FAD PReP Manual 1-0): This document provides an overall concept of operations for FAD preparedness and response for APHIS, explaining the framework of existing approaches, systems, and relationships.
  - *APHIS Foreign Animal Disease Framework: Response Strategies* (FAD PReP Manual 2-0): This document provides significant detail on response strategies that will be conducted in an FAD outbreak.
  - *APHIS Foreign Animal Disease Framework: Information Management & Reporting* (FAD PReP Manual 3-0): This document explains how information is managed and reported in FAD incidents.

  - *FAD Investigation Manual* (FAD PReP Manual 4-0): This field-ready manual provides detailed information on completing an FAD investigation from start to finish.
  - *A Partial List of FAD Stakeholders* (FAD PReP Manual 5-0): This guide identifies key stakeholders with whom the National Preparedness and Incident Coordination (NPIC) Center collaborates.
- NAHEMS Guidelines
  - These documents describe many of the critical preparedness and response activities, and can be considered as a competent veterinary authority for responders, planners, and policy-makers.
- Industry Manuals
  - These manuals describe the complexity of industry to emergency planners and responders and provide industry a window into emergency response.
- Disease Response Plans
  - Response plans are intended to provide disease-specific information about response strategies. They offer guidance to all stakeholders on capabilities and critical activities that would be required to respond to an FAD outbreak.
- Standard Operating Procedures (SOPs) for Critical Activities
  - For planners and responders, these SOPs provide details for conducting critical activities such as disposal, depopulation, cleaning and disinfection, and biosecurity that are essential to effective preparedness and response to an FAD outbreak. These SOPs provide operational details that are not discussed in depth in strategy documents or disease-specific response plans.
- Continuity of Business Plans (commodity-specific plans developed by public-private-academic partnerships)
  - Known as the Secure Food Supply Plans, these materials use science- and risk-based information to facilitate market continuity for specific products in an outbreak.
- APHIS Emergency Management
  - APHIS Directives and Veterinary Services (VS) Memorandums provide important emergency management policy. These documents provide guidance on topics ranging from emergency mobilization, to FAD investigations, to protecting personnel from HPAI.

Most of these documents are available publicly, at http://www.aphis.usda.gov/fadprep.

PREFACE

The Foreign Animal Disease Preparedness and Response Plan (FAD PReP)/National Animal Health Emergency Management System (NAHEMS) Guidelines provide the foundation for a coordinated national, regional, state and local response in an emergency. As such, they are meant to complement non-Federal preparedness activities. These guidelines may be integrated into the preparedness plans of other Federal agencies, State and local agencies, Tribal Nations, and additional groups involved in animal health emergency management activities.

This Appendix B: Vaccination for Classical Swine Fever is a supplement to FAD PReP/NAHEMS Guidelines: Vaccination for Contagious Diseases, and covers the disease-specific strategies and general considerations of vaccination. Both documents are components of APHIS' FAD PReP/NAHEMS Guideline Series, and are designed for use by APHIS Veterinary Services (VS), and other official response personnel in the event of an animal health emergency, such as the natural occurrence or intentional introduction of a highly contagious foreign animal disease in the United States.

Appendix B: Vaccination for Classical Swine Fever, together with the Vaccination for Contagious Diseases Guidelines, provide guidance for USDA employees on principles of vaccination for classical swine fever for animal health emergency deployments. This Appendix B: Vaccination for Classical Swine Fever provides information for incident management personnel and other responders associated with vaccination activities. The general principles discussed in this document are intended to serve as a basis for understanding and making sound decisions regarding vaccination in a classical swine fever emergency. As always, it is important to evaluate each situation and adjust procedures to the risks present in the situation.

The FAD PReP/NAHEMS Guidelines are designed for use as a preparedness resource rather than as a comprehensive response document.

APHIS DOCUMENTS

Key APHIS documents complement this "Appendix B: Vaccination for Classical Swine Fever, Strategies and Considerations" and provide further details when necessary. This document references the following APHIS documents:

- APHIS Foreign Animal Disease Framework documents
  - Roles and Coordination (FAD PReP Manual 1-0)
  - Response Strategies (FAD PReP Manual 2-0)

- Classical Swine Fever Response Plan (The Red Book)

These documents are available on the FAD PReP collaboration website at: www.aphis.usda.gov/fadprep.

For the full listing of all references, including other APHIS documents, see section 19. References.

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Summaries of each section can be accessed from the table of contents and are followed by more detailed descriptions of the material.

National Animal Health Emergency Management System

USDA

Appendix B: Vaccination for Classical Swine Fever
Strategies and Considerations

1. PURPOSE

This Appendix is intended to provide relevant information for Federal and State officials, and other interested parties, who will participate in decision-making related to vaccine use in an outbreak of classical swine fever (CSF) in the United States (U.S.). The following topics are presented and discussed:

- Important characteristics of CSF;
- Characteristics of vaccines;
- Strategies for vaccine use; and
- Various factors that must be considered when designing an effective vaccination program.

2. BACKGROUND

CSF (also known as hog cholera) is a highly contagious viral disease of swine. The U.S. eradicated its last case of CSF in August 1976.[1] However, a possible disease re-introduction continually threatens the U.S. swine herd. CSF virus (CSFV) could enter the U.S. through multiple routes. The intentional release of CSFV into the U.S. swine herd is a real concern. Unintentional introduction is also possible. Employees and owners of hog production systems, who travel all over the world, as well as visitors who arrive from countries with endemic CSF, could unintentionally expose pigs to the virus. The clinical signs associated with CSF resemble many endemic diseases, which may delay diagnosis and make control even more difficult. Industry estimates place over one million swine in trucks on the road every day.[2] During transport, any pig exposed to CSFV would have the potential to spread the disease to another location before it is diagnosed. Artificial insemination (AI) is a technology which has greatly benefitted the U.S. swine industry; however, if a boar stud becomes infected with CSFV, infected semen could be distributed throughout the country unknowingly.[3] Feral swine are now found throughout most of the southern U.S. and their range is ever expanding.[4] CSF would be even more difficult to eradicate from the U.S. if it was also found in feral swine. An appropriate and usable CSF response plan must be in place before a diagnosis is confirmed to enable an effective swine industry response.

CSF is endemic in many parts of the world. CSF is found in some areas of Asia, Africa, South and Central America, and the Caribbean islands.[5] Nearby threats specifically include Haiti, the Dominican Republic, and Cuba–where CSF has been found as recently as late 2016–and Mexico, where the last case was reported in mid-2009.[6] CSF has been eradicated from the U.S., Canada, New Zealand, Australia, and from domestic swine operations in most of western and central Europe.

Outbreaks in CSF-free countries have resulted in CSF infection on multiple farms and significant economic losses for swine industries in those countries. In 1994, Germany reported 117 farms infected, and Belgium reported 48 CSFV-positive farms.[7] Modeling of an outbreak that occurred from 1997–1998, involving 429 farms in the Netherlands, showed an estimated $423 million in losses for swine farmers and $596 million in losses for related industries.[7] Terpstra et al.[8] estimated greater losses in the Netherlands for the same outbreak totaling over $2 billion (direct losses only). Paarlberg et al.[9] calculated potential economic losses caused by a hypothetical CSF outbreak in the U.S. Eleven million hogs were

destroyed in this scenario, resulting in estimated losses ranging from $2.6 billion to $4.1 billion when considering the value of destroyed animals, the effect on breeding herd numbers, product demand, and effect on exports.

Controlling CSF in areas that are pig-dense has proven to be very challenging. Although the measures of stop animal movement, isolation, and stamping-out helped to control the outbreak in the Netherlands, it was at a great economic loss.[10] Measures to control CSF outbreaks in the Netherlands, England, and Belgium did not include CSF vaccination. For countries of the European Union (EU), utilizing CSF vaccination is prohibited unless the affected country requests and is granted permission to carry out emergency vaccination in addition to control measures already underway, according to Article 19 of EU Directive 2001/89/EC.[11] For example, beginning in 2006, Romania determined that in order to eradicate CSF, vaccination would be required. Contingency plans, including the use of CSF vaccine, were submitted by Romania to the Commission on November 9, 2006 for the control of CSF and approved under Directive 2007/19/EC.[12]

Stop movement orders could prevent or slow CSF spread during an outbreak, but may compromise animal welfare. With the management practices of the U.S. swine industry, many animals remain on a site until a specified weight or age. For example, pigs may be placed in a nursery from weaning, at about 3 weeks of age, until they reach about 50 pounds body weight. At that time, they are moved into a finishing building. If a stop movement were in place, animals in a nursery would continue to grow and become overcrowded. In addition, young animals that need to be weaned could not be transported to a new site or building if it has not been emptied. According to Pluimers et al.,[10] during the CSF outbreak in the Netherlands during 1997–1998, the welfare of the pigs during a stop movement was a concern. As animals became overcrowded and pigs began to suffer health problems, authorities implemented a buy-out plan and carcasses were destroyed. In 2004, participants in the World Organization for Animal Health (OIE) International Conference on the Control of Infectious Animal Diseases by Vaccination concluded that mass slaughter is no longer acceptable as the main technique for disease control and eradication due to ethical, ecological, and economic concerns.[13] They recommended that methods for disease prevention, control, and eradication be reviewed, and advised an increased emphasis on vaccination.

When initial control measures such as stamping-out, quarantine, and stop movement do not contain a CSF outbreak, the use of vaccine must be considered. According to DeHaven,[14] "The decision to use, or not to use, a vaccine in the face of a foreign animal disease outbreak can be complex and have far-reaching socio-economic consequences. Incorrect decisions or delays occurring during the actual outbreak can be costly." Factors that can influence the decision to vaccinate include the number of herds affected, how quickly the disease is spreading, personnel available to assist in the response effort, and the number of feral swine in the area.

3. OVERVIEW OF CSF

Summary

CSFV is a member of the genus *Pestivirus* and family Flaviviridae. The small, enveloped, single stranded RNA virus is closely related to ruminant pestiviruses that cause bovine viral diarrhea (BVD) and border disease of sheep. In recent years, atypical pestiviruses have been identified in several species including pigs. Only one CSF serotype exists; however, viral strains can be divided into three genotypes with three to four sub-genotypes that show a distinct geographical pattern.

All species of domestic pigs (*Sus scrofa domesticus*), feral pigs, and wild pigs—including European wild boar (*Sus scrofa scrofa*) and collared peccaries—are thought to be susceptible to CSFV infection.

Humans and other livestock species do not appear to be affected by CSF.

Virus shedding can begin before the onset of clinical signs, and occurs throughout the course of acute or subclinical disease. Chronically or persistently infected pigs can shed virus continuously or intermittently for months.

Sows can be infected with CSFV at any stage of gestation, and the virus can then cross the placenta and infect the fetuses. The outcome of prenatal infection depends on strain virulence and the time of gestation at which infection occurs. Sows infected with CSFV during gestation may deliver stillborn, aborted, or mummified pigs. Pigs born alive may be persistently infected.

Persistently infected pigs may appear asymptomatic at birth; however, congenital tremors may develop and stunting may become apparent over time. Persistently infected piglets may survive to 6 months, rarely up to a year, while shedding the virus and acting as a source of infection for other pigs. Cerebellar hypoplasia is evident more frequently in pigs born to sows infected with CSFV prior to 43 days of gestation.

Clinical signs vary depending on the stage of infection, type of disease (acute, subacute, chronic or persistent/late onset), and virulence of the strain. Clinical signs associated with acute infection with a highly virulent strain include a high fever, huddling, weakness, drowsiness, anorexia, conjunctivitis, and constipation followed by diarrhea. About 2–4 weeks after infection, purple discoloration of the skin on the abdomen, inner thighs, or ears may be visible, or hemorrhages may be evident. Vomiting bile may occur, or respiratory signs may develop. Some pigs show neurologic signs such as incoordination or unsteadiness, which may progress to posterior paresis or convulsions in the terminal stages. Clinical signs are generally less severe with the subacute form due to infection with lower virulence strains. Pigs that are chronically infected show mostly nonspecific clinical signs; weight loss can occur over time.

Transmission between pigs occurs mainly by the oral or oronasal routes via direct or indirect contact. Virus can be shed in saliva, lacrimal secretions, blood, urine, feces, and semen. Transmission may occur through ingestion of uncooked garbage containing infected pork products. Genital transmission and transmission via AI also occurs. CSFV can be transmitted on fomites and by mechanical vectors. Airborne transmission seems to be possible over short distances; however, the maximum distance the virus can travel is unclear.

The incubation period for acute disease can range from 2 to 14 days, depending on the virulence of the strain, the route of infection, and the dose.

CSFV is easily transmitted due to its ability to persist in the environment and in pork products. CSFV can survive in chilled pork up to 3 months, in frozen pork and pork products up to 4 years, and in salted or smoked meat up to 180 days.

3.1 Serotypes and Strains

CSFV is a member of the genus *Pestivirus* and family Flaviviridae.[15] The small, enveloped, single stranded RNA virus is closely related to the ruminant pestiviruses that cause BVD and border disease of sheep.[16] In recent years, atypical pestiviruses have been identified in several species including pigs.[17-25] Only one CSF serotype exists; however, viral strains can be divided into three genotypes with three to four sub-genotypes that show a distinct geographical pattern.[26] The viral particle is composed of four

structural proteins: the core protein (protein C) and envelope glycoproteins Erns, E1, and E2.[27] CSFV strains can vary considerably in virulence.

3.2 Species Affected

All species of domestic pigs (*Sus scrofa domesticus*), feral pigs, and wild pigs—including European wild boar (*Sus scrofa scrofa*) and collared peccaries—are thought to be susceptible to CSFV infection. Humans and other livestock species do not appear to be affected by CSF.

3.3 Pathogenesis

The most common form of CSFV transmission in pigs is oronasal.[28] Following intranasal inoculation with CSFV, the virus replicates primarily in the tonsils before spreading to other lymphoid organs,[29-31] including regional lymph nodes, and then the peripheral blood, bone marrow, and visceral lymph nodes.[28] Spread of the virus within the animal usually occurs in 5–6 days.[32] Virus shedding can begin before the onset of clinical signs, and occurs throughout the course of acute or subclinical disease.[33] Chronically or persistently infected pigs can shed virus continuously or intermittently for months.[34,35]

3.3.1. Persistent Infection

Infection with CSFV during pregnancy leads to persistent infection where affected pigs do not mount an adequate immune response.[26] Persistent infection is sometimes referred to as the prenatal course or "late onset CSF." Experimentally, when sows were infected with CSFV on either day 22 or 43 of gestation, pigs born showed a variety of clinical signs including tremors.[36] Of those with tremors, 83% of those pigs had cerebellar hypoplasia. Several piglets died within a few days of birth. Pigs from sows infected after day 72 of gestation did not exhibit severe tremors, although a majority of these piglets were either mummified or stillborn.[36] Tremors became less evident as pigs grew older and continued to shed virus.

Van Oirschot et al.[37] produced different results after infecting 4 sows at days 40, 65, and 90 of gestation with a low virulence CSFV strain. Transplacental transmission did not occur in 2/4 sows infected at 40 days gestation and 2/4 sows infected at 90 days gestation. Two different sows infected at 40 days gestation gave birth to pigs which all tested positive for virus at birth, and 1/4 sows infected at 65 days gestation also gave birth to pigs all of which tested positive at birth.[37] Concerning persistently infected animals, it was concluded from this experiment that sows infected with a low virulence strain of CSFV, at an earlier stage of gestation, will produce a greater number of persistently infected pigs.[37] Dahle et al.[38] inoculated sows between 70 and 90 days gestation and observed persistently infected pigs born to these sows. Persistent infection has also been experimentally induced by infecting newborn piglets within 8 and 48 hours after birth.[39,40]

3.4 Clinical Signs

Pigs infected with CSFV may show a variety of clinical signs depending on the stage and type of infection (acute, subacute, chronic or persistently infected) and virulence of the strain.

3.4.1 Acute Infection

Clinical signs associated with acute infection include high fever, huddling, weakness, drowsiness, anorexia, conjunctivitis, and constipation followed by diarrhea.[28,41,42] Approximately 2–4 weeks later, purple discoloration of the skin on the abdomen, inner thighs, or ears may be visible, or hemorrhages may be evident. Vomiting bile may occur, or respiratory signs may develop. Pigs may show neurologic signs such as incoordination or unsteadiness, which may progress to posterior paresis or convulsions in the terminal stages.[5,42] Secondary infections can complicate the clinical diagnosis.[26] If bloodwork is conducted, severe leukopenia is usually seen. Pigs with acute CSF often die within 10–20 days post-infection.[33]

3.4.2 Subacute Infection

Moderately virulent strains of CSFV can cause subacute disease in which the clinical signs are less severe. However, fever may persist for 2–3 weeks. Survival of pigs with subacute CSF varies as some survive for longer periods, while others die within a month.[33]

3.4.3 Chronic Infection

Chronic infection is linked to CSFV strains of moderate virulence.[34,43] When the immune system cannot eliminate the virus, pigs develop the chronic form of CSF. Nonspecific clinical signs (e.g., fever, depression, wasting, and diffuse dermatitis) are most commonly seen.[26] Chronically infected pigs lose weight as severe lesions develop in the ileum and rectum.[42] Chronically infected pigs can shed CSFV for 1–3 months.[44] Pigs developing the chronic form of CSF may survive 2–3 months before they die.[28]

3.4.4 Persistent Infection

Sows can be infected with CSFV at any stage of gestation, and the virus can then cross the placenta and infect the fetuses leading to persistent infection. Persistent infection is sometimes referred to as the prenatal course or "late onset CSF." The outcome of prenatal infection will depend on the virulence of the strain and the time of gestation.[42] If infected in early pregnancy with a strain of moderate or low virulence, pigs may be aborted, stillborn, or mummified. Infection of the sow around 50–70 days of gestation may result in persistently infected pigs, depending on the strain virulence.[42] When persistently infected pigs are born alive, some develop a congenital tremor while others are asymptomatic at birth.[37,42] Persistently infected animals may not show signs, such as stunted growth, for several months following birth.[42,45] Some pigs will survive for more than 6 months, but rarely past one year, while shedding the virus and potentially spreading the disease.[35]

The differential diagnosis for CSF includes both endemic and foreign animal diseases such as African swine fever, salmonellosis, porcine dermatitis and nephropathy syndrome, erysipelas, porcine circovirus-associated disease, hemolytic disease of the newborn, porcine reproductive and respiratory syndrome, pasteurellosis, actinobacillosis, *Haemophilus suis* infection, thrombocytopenic purpura, anticoagulant (e.g. warfarin) poisoning, salt poisoning, pseudorabies, parvovirus infection, and eperythrozoonosis.[5,42]

3.5 Transmission

3.5.1 Incubation

The OIE listed incubation period for CSF ranges from 2 to 14 days.[46] Pasick reports 3 to 4 days may be typical.[47] Chronic infection may not appear until up to 3 months following virus exposure.[46] Under field conditions, the disease may not be diagnosed in a herd for weeks as the clinical signs resemble domestic diseases. For example, in the Netherlands, on January 15, 1997, a practitioner observed atypical clinical signs in finishing pigs.[48] He suspected pneumonia and prescribed antibiotics. When the pigs did not respond to treatment, the practitioner suspected porcine reproductive and respiratory syndrome (PRRS) and submitted two pigs to the diagnostic laboratory on January 21. The laboratory diagnosed CSF on February 4, 1997, more than 2 weeks after the pigs began to show clinical signs.

3.5.2 Transmission Routes

CSF is highly contagious. Virus can be shed in saliva, lacrimal secretions, blood, urine, feces and semen.[3,37,49-51] Transmission between pigs occurs mainly by the oral or oronasal routes via direct or indirect contact.[28,42,52,53] Some experts regard direct contact as the most important route of CSF transmission.[54] Feral swine roam in many states throughout the U.S. If CSFV were to infect feral swine, the health of the U.S. domestic swine herd would be threatened. In Germany, direct or indirect contact with CSFV-infected wild boar was found to be the cause of CSFV transmission to domestic swine.[53]

CSFV can also be spread by genital transmission or AI as boar semen may contain the virus.[3] In the 1997–98 CSF outbreak in the Netherlands, two AI studs became infected. Because the boar studs were

allowed to continue shipping semen, they were suspected of potentially infecting 21 sow herds.[8] Infected carrier sows may give birth to persistently infected pigs.

Pigs can acquire CSFV through ingestion of uncooked garbage containing infected pork products.[53] Pork products may be smuggled into the U.S. from countries with endemic CSF, enabling long-distance transmission of CSF. Garbage feeding has been suspected in other countries as a means of CSF introduction. For example, in Bulgaria, non-vaccinated pigs fed uncooked table scraps tested positive for CSFV in March 2000.[55] CSFV can survive in chilled pork up to 3 months,[56-58] in frozen pork and pork products up to 4 years,[59] and in salted or smoked meat up to 180 days.[5,57,59-62] According to Kleiboeker,[63] a hiker feeding part of a ham sandwich to a sow herd may have introduced CSFV into the United Kingdom in 2000.

Fomites and mechanical vectors can also play a role in CSFV transmission. Dorset et al.[64] reported that stable flies and house flies can transmit CSFV from sick pigs to healthy pigs. It is still unclear if birds play a role in CSF transmission.[54] The role of cats, dogs, and rodents in CSF transmission has also been questioned. Research by Dewulf et al.[65] showed that cats, dogs, and rats do not serve as reservoirs of CSFV; however, mechanical transmission may still be possible.

Dewulf et al.[66] demonstrated that airborne transmission is possible under experimental conditions, although the maximum distance the virus can spread is unclear. While aerosol transmission was documented only within a radius of 250 meters in some studies, transmission occurred up to 1 km in another.[54]

Fomites such as transportation vehicles pose a threat in transmitting CSFV when not properly cleaned and disinfected. Although it has not been proven, transportation vehicles originating from Germany are thought to have introduced CSFV into the Netherlands during the 1997–1998 CSFV outbreak.[48] The very cold weather made properly cleaning and disinfecting of the transport vehicles difficult.

3.5.3 Survival

Estimates of CSFV survival in pens and on fomites under field conditions vary. Weesendorp et al.[67] found that CSFV was no longer detectable in the feces after 42 days (when pigs were infected with the moderately virulent Paderborn strain) and after 64 days (when pigs were infected with the highly virulent Brescia strain). Neither strain of the virus could be detected in urine after 18 days post infection.[67] While initial concentrations and strain of the virus in feces will affect the survival time, at 20°C (68°F), the virus was inactivated in feces within 3 (Paderborn strain) to 5 days (Brescia strain) and in 15–20 hours at 30°C (86°F).[67] Information on CSFV survival in animal products can be found in section 18.3.

3.5.4 Vaccination and Virus Transmission

Effective vaccination can decrease transmission between animals by 1) decreasing the susceptibility of animals to infection, and 2) reducing virus shedding, if a vaccinated animal becomes infected.

4. DETECTION OF INFECTED ANIMALS

Summary

Diagnosis of CSF based on clinical signs alone is almost impossible. Several OIE-approved tests are available; preferred diagnostic samples include serum (for live animals) or tissues such as tonsil and ileum (for dead animals).

Diagnostic tests that detect virus, viral nucleic acid, or viral antigen include virus isolation, reverse transcription polymerase chain reaction (RT-PCR), real-time (or quantitative) PCR (rRT-PCR or qRT-PCR), direct immunofluorescence (fluorescent antibody test, FAT), immunoperoxidase staining, and antigen-capture enzyme linked immunosorbent assay (ELISA).

Virus isolation is the test of choice to confirm CSFV infection; however, it is slow and labor intensive. After growing virus in PK-15 cells (or another porcine line), cultures are examined by FAT after 24 to 72 hours, or in 4- to 5-day-old cultures by immunoperoxidase staining. Samples shipped for virus isolation should be refrigerated but not frozen.

RT-PCR is a fast and sensitive diagnostic method that can detect CSF nucleic acids in pigs throughout the course of disease, from the preclinical stage to recovery. Blood samples from live pigs or tissues samples collected during necropsy can be tested with results in 48 hours or less.

CSFV antigen can be rapidly detected using the FAT. This test uses frozen tissue sections which are stained directly with an anti-CSF immunoglobulin conjugated to a fluorescence marker, or indirectly with a fluorescent conjugate, and examined by fluorescence microscopy.[45] Detecting CSF virus in the tonsil is more likely 2 to 15 days post infection when animals are showing clinical signs of CSF. Vaccine administration and infection with ruminant pestiviruses may affect FAT results in some cases.

Immunoperoxidase staining is a test that uses monoclonal antibodies (MAbs) and can differentiate field strains of CSFV, vaccine strains of CSFV, and other pestiviruses including those from ruminants.

Antigen-capture ELISA is a good tool for early diagnosis of CSFV at the herd level; however, sensitivity is low and the assay is not appropriate for CSFV surveillance purposes or detection of CSFV in individual animals.

Serology is used for diagnosis and surveillance. Antibodies cannot be detected until at least 21 days post infection and persist for life. Serological tests include virus neutralization (neutralizing peroxidase-linked assay, fluorescent antibody virus neutralization test, comparative neutralization test) and various ELISAs.

Diagnostic tests with the ability to detect infection in vaccinated animals (DIVA) have been developed, but to date, most are useful only at the herd level because of less than optimal sensitivity and specificity.

Many countries, including those in the EU, accept the use of rRT-PCR for screening and confirmation of suspected cases of CSF. However, a positive result must always be confirmed by another test such as virus isolation.

Diagnosis of CSF based on clinical signs alone is almost impossible. The clinical presentation of CSF is similar to U.S. endemic diseases and foreign animal diseases. Diagnostic testing is required to confirm

CSF. Several OIE-approved tests are available; preferred diagnostic samples include serum (for live animals) or tissues such as tonsil and ileum (for dead animals).[45] An overview of CSF diagnostic methods, as described in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2017[45] is given below.

4.1 Detecting Infected Animals by Identifying Virus, Nucleic Acids, or Antigen

4.1.1 Identification of the Virus

4.1.1.1 Virus Isolation

Virus isolation is a highly sensitive method of CSF diagnosis. It is the test of choice to confirm CSFV infection; however, in an outbreak situation, virus isolation may be too slow and labor intensive to test large numbers of samples.[28] The tonsil is preferred for testing, although spleen, kidney, ileum, and lymph nodes can also be used.[45] In live animals, blood, plasma, and tonsil scrapings can be tested.[68] PK-15 cells or other porcine cells lines can be used, though they must be free of other pestiviruses and pestivirus antibodies. Viral growth does not cause a cytopathic effect. Viral antigen must be detected via the fluorescent antibody test (FAT) after 24 to 72 hours, or in 4- to 5-day-old cultures by immunoperoxidase staining (described in section 4.1.2.2).[45] Samples for virus isolation should be refrigerated but not frozen; they should be kept cold during shipment to the laboratory.[69]

4.1.1.2 Reverse Transcription Polymerase Chain Reaction (RT-PCR)

RT-PCR is a fast and sensitive diagnostic method that can detect CSF nucleic acids in pigs throughout the course of disease. RT-PCR can also be used to detect CSFV in tissues that are autolyzed.[70] It is accepted for CSF testing by the EU and other nations for screening and confirmation of suspected cases of disease.[45,70] Because false positive may occur, primary outbreaks must be confirmed by other tests. RT-PCR protocols, both standard and real-time, have been widely published and are also available from the OIE Reference Laboratories for CSF. Blood samples from live pigs or tissues samples, including tonsil, spleen, ileum and lymph node, collected during necropsy can be tested[28] with results in 48 hours or less.[70]

RT-PCR assays can differentiate CSFV from ruminant pestiviruses.[45] Novel pestiviruses that infect pigs, known as atypical porcine pestiviruses, have recently been characterized in Australia,[71] the U.S.,[17,18] Germany,[19,20] the Netherlands,[21] Austria,[22,24] and China.[23,25] Concerns about cross-reactivity in genome detection between CSF and atypical porcine pestiviruses have been raised. However, limited data indicate that RT-PCR assays used for CSF diagnosis cannot detect the genomes of atypical porcine pestiviruses.[72]

4.1.1.3 Real Time RT-PCR (rRT-PCR)

rRT-PCR, also known as quantitative RT-PCR (qRT-PCR), is a variation where nucleic acids are detected as they are being amplified (i.e., in “real time”) by an automated process. This makes rRT-PCR a more rapid test compared to standard RT-PCR, and results can be available within 2 hours after the samples are prepared. rRT-PCR can be used when confirming a test result or for surveillance purposes.[68]

Tonsil scrapings, tonsil, spleen, lymph node, blood, and nasal swabs can be tested by qRT-PCR.[73] A protocol published by Hoffmann et al.[74] is widely in use according to the OIE.[45] There are a number of other rRT-PCR systems as reported by Blome et al.,[26] including those that allow differentiation between vaccine and field virus strains. Methods that involve sample pooling must be validated in individual laboratories, and quality control is essential to prevent contamination that may cause false positives. qRT-PCR has gradually been replacing other antigen detection methods,[26] although virus isolation will remain necessary for further testing.[68]

4.1.1.4 Genetic Sequencing

Following amplification by RT-PCR, sequence data can be obtained in order to compare the genomes of different CSFV isolates. This is particularly important for primary outbreaks, where CSFV isolates should be sent to an OIE Reference Laboratory for analysis. According to the OIE,[45] the regions that are sequenced most frequently are the 5‟-nontranslated region (5‟NTR) and the E2 major glycoprotein gene.

4.1.2 Identification of Viral Antigen

4.1.2.1 Fluorescent Antibody Test (FAT)

CSFV antigen can be rapidly detected using FAT. This test uses frozen sections of tonsils, spleen, kidney, lymph nodes or distal portions of the ileum which are stained directly with an anti-CSF immunoglobulin conjugated to a fluorescence marker, or indirectly with a fluorescent conjugate and examined by fluorescence microscopy.[45] Detecting CSF virus in the tonsil is more likely 2 to 15 days post infection when animals are showing clinical signs of CSF compared to animals that have been infected for a longer period of time.[49,75] Testing the ileum will provide more accurate test results for subacute and chronic cases.[28] If a FAT result is negative and CSF is still suspected, RT-PCR or virus isolation in cell culture should be attempted.[45] Only laboratories that perform the FAT on a regular basis should be used to minimize the risk of false positives.[45]

Vaccine administration and infection with ruminant pestiviruses may affect FAT results in some cases. Administration of the live attenuated virus vaccine may cause pigs to test positive on the FAT for 2 weeks following vaccination. Ruminant pestiviruses can also interfere with CSFV testing causing false-positive FAT reactions. Pigs infected with ruminant pestiviruses from congenital infections can have the same clinical signs and lesions as pigs with chronic CSF.[76,77] To differentiate CSFV infection from infection with ruminant pestiviruses, animals can be tested for neutralizing antibodies to the virus.[45] It may also be possible for atypical porcine pestivirus infection to confound FAT results.

4.1.2.2 Immunoperoxidase Staining

Immunoperoxidase staining is a test that can be used to differentiate field strains of CSFV, vaccine strains of CSFV, and other pestiviruses including those from ruminants. Immunoperoxidase staining has been used in the investigation of an atypical porcine pestivirus (Bungowannah virus) in Australia.[71]

The test uses monoclonal antibodies (MAbs) that are tagged with an enzyme; a chemical reaction occurs following CSFV antigen and antibody binding and produces a colored product.[68] In a given geographic region, MAbs must be specific to the CSF strains in circulation and vaccine strains being used, if any.

4.1.2.3 Antigen-Capture Enzyme Linked Immunosorbent Assay (ELISA)

Antigen-capture ELISA is a good tool for early diagnosis of CSFV at the herd level; however, sensitivity is low and the assay is not appropriate for CSFV surveillance purposes or to detect CSFV in individual animals.[28] Blood, tissues, plasma, or serum specimens can be tested.[68] Most commercially available tests detect the CSFV glycoprotein Erns.[78]

4.2 Detecting Infected Animals by Serological Assays

Serology is used for diagnosis and surveillance, especially when infection with a CSFV strain of low virulence is suspected.[45] It is also useful in the final phase of CSF eradication when trying to detect positive animals that might remain in a breeding herd.[45]

Antibodies cannot be detected until at least 21 days post-infection and can be present for the life of the animal.[45,78] Congenitally infected pigs are immunotolerant and do not produce antibodies that are detectable via serology.[36]

4.2.1 Virus Neutralization Tests (VNTs)

Compared to ELISA, VNT is more sensitive, especially when detecting antibodies in samples 10–14 days post infection.[75] VNTs cannot differentiate between antibody titers produced from a field strain of CSFV versus those produced following administration of a live attenuated virus CSF vaccine.[78] High biocontainment facilities must be used when performing VNTs.

4.2.1.1 Neutralizing Peroxidase-Linked Assay (NPLA)

The NPLA is favored according to the OIE.[45] It is performed in microtiter plates using the constant-virus/varying-serum method. The test uses cell cultures; however, CSFV is noncytopathic and must be detected by an indicator. Immunoglobulin conjugated with horseradish peroxidase reacts with a chromogen-substrate solution to allow visualization of infected cells. An inverted light microscope is necessary to determine results, although a crude assessment of titer can be made with the naked eye according to the OIE.[45]

4.2.1.2 Fluorescent Antibody Virus Neutralization Test (FAVN)

The FAVN is similar to the assay described above and involves the observation of infected cells. However, the conjugate used causes fluorescence of infected cells and infected cells must be detected by fluorescence microscopy.

4.2.1.3 Comparative Neutralization Test

The comparative neutralization test can be useful for differentiating CSFV strains from ruminant pestiviruses. Protocols are similar to those for the NPLA and FAVN tests. Strains of CSFV, bovine viral diarrhea virus (BVDV), and border disease virus are used that are representative of the geographic region; cell lines must be suitable for growth of both swine and ruminant pestiviruses. It may be necessary to test several pigs from an infected herd according to the OIE.[45]

4.2.2 Antibody Detection ELISAs

Many techniques (e.g., competitive, blocking, and indirect) can be used as long as they minimize cross reactions with ruminant pestiviruses.[45] Most commercially available ELISAs detect antibodies to the envelope glycoprotein E2.[26] Antibody detection ELISAs are suitable for testing serum or plasma from individual pigs.[45]

4.2.3 Serological Assays in Development

In recent years, the development of assays with DIVA capabilities has been prioritized. The companion DIVA tests for E2 subunit marker vaccines (described in section 5.1.2) are ELISAs which detect antibody to the Erns protein.[79,80] Having received approval from the European Commission,[81] these tests have been used to determine if a herd vaccinated with an E2 marker vaccine may also have been exposed to field virus. According to the OIE, Erns-specific ELISAs should not be used for diagnosis of CSF in individual animals due to reduced sensitivity and specificity (compared to conventional E2 ELISAs).

DIVA tests designed for use with newer marker vaccines, such as the CP7_E2alf chimeric vaccine (described further in section 5.1.3), have also shown promise.[82,83] One assay that is commercially available, the PrioCHECK CSFV Erns ELISA (Prionics BV), has been shown to have DIVA potential;[84,85] however, use is currently recommended only at the herd level because of less than optimal sensitivity and specificity.[85] Other commercially available CSFV ELISAs are not recommended for DIVA testing since they may cross-react with ruminant pestivirus antibodies.[84] A double-antigen ELISA[86] and a microsphere immunoassay[87] with potential DIVA applications have also been recently described.

4.3 The Use of Diagnostic Tests in Outbreaks

Many countries, including those in the EU, accept the use of rRT-PCR for screening and confirmation of suspected cases of CSF.[45,70] However, positive results must always be confirmed by other tests, since false positives and negatives can occur. The OIE recommends that CSFV isolates from primary outbreaks be sent to an OIE Reference Laboratory for sequencing and phylogenetic analysis.[45]

Serological tests have limitations when used during a CSF outbreak. Antibodies may not be detected until at least 21 days post infection, but persist for the life of the animal.[45,78] Serology is not appropriate for the identification of early cases; however, it is useful for herd monitoring and/or surveillance programs.[70]

4.3.1 Outbreak Testing: Real World Examples

In the 1997–98 CSF outbreak in the Netherlands, over 2 million samples were tested for CSF using several diagnostic tests.[88] FAT was used on tonsils to detect 74% of the positive tests. Over 140,000 blood samples were tested using virus isolation. In Korea in 2003,[89] antibody and antigen ELISA and RT-PCR tests were used to detect CSFV-positive animals.

4.4 Use of Diagnostic Tests in Feral Swine

rRT-PCR assays have been developed that show great potential to differentiate CSFV field strains from either CP7_E2alf[90-92] (discussed in section 5.1.3) or the C-strain "Riems" when used to immunize feral swine.[90] In European countries that are trying to eliminate CSFV from their wild boar populations, DIVA technology may become more widely used.

5. CSF VACCINES

Summary

Inactivated whole virus vaccines are not effective or available for use. Live attenuated virus (LAV) vaccines, also known as modified live virus (MLV) vaccines, are made from attenuated CSFV strains. They are the most widely used vaccines in countries with endemic CSF. However, CSF free countries may not allow the use of LAV vaccines because it is impossible to differentiate vaccinated animals from animals infected with the field strain using serology.

LAV vaccines can be administered parenterally or orally. In Europe, oral administration has been effective in reducing CSF prevalence in wild boar. A large number of LAV vaccines are commercially available in different parts of the world.

Marker vaccines induce antibodies that can be distinguished from those produced by animals infected with a field strain via serology. E2 marker vaccines, which produce the CSFV glycoprotein E2 using a baculovirus recombinant system, are the most widely used. Only one commercial formulation (Porcilis® Pesti, MSD Animal Health) is currently available.

A number of other CSFV vaccines have been developed in recent years. The pestivirus chimera CP7_E2alf (Suvaxyn CSF Marker, Zoetis), which is based on an infectious cDNA clone of the cytopathic BVDV strain CP7, has been recently licensed by the European Medicines Agency. This vaccine is safe, efficacious, and has DIVA capability when combined with the PrioCHECK CSFV Erns (Thermofisher) or CSF Marker (Qiagen) assays.

Other vaccine constructs have shown promise but remain experimental at this time. This includes additional subunit vaccines/immunogenic peptides, DNA vaccines, viral vector vaccines (such as adenoviral or pseudorabies virus vectors), and trans-complemented deletion mutants (replicons).

Conditions for the production of LAV vaccines are addressed in the OIE Manual of Diagnostic Tests and

Vaccines for Terrestrial Animals. Additional regulatory considerations may be applicable when discussing vaccines produced through biotechnology. The U.S. does not currently have a market for CSFV vaccine. However, the National Veterinary Stockpile program, administered by USDA APHIS, maintains contracts with biologics manufacturers to provide limited quantities of CSF vaccine within 2 to 4 days (if needed during an U.S. outbreak).

For a vaccine to be given a full product license, the manufacturer must conduct extensive efficacy, purity, and safety testing. Steps in the U.S. vaccine licensing process include review of manufacturer data to support the product and label claims; inspection of manufacturing processes and practices; confirmatory testing of the biological seeds, cells, and product; post-licensing monitoring including inspections and random product testing; and post-marketing surveillance of product performance.

5.1 Types of CSF Vaccines

Inactivated whole virus vaccines are not effective or available for use.[45] Live attenuated virus (LAV) vaccines have been available in other countries for decades.[26] Only one E2 marker vaccine is currently commercially available. Experimental vaccines continue to be developed and evaluated.

5.1.1 Live Attenuated Virus (LAV) Vaccines

LAV vaccines, also known as modified live virus (MLV) vaccines, are made from attenuated CSFV strains[45] and are the most effective and widely used vaccines in countries with endemic CSFV according to Blome et al.[75] As of 2016, areas practicing CSF vaccination include China, some countries of South and Central America, Trans-Caucasian countries, and some parts of Eastern Europe.[26]

Examples of attenuated vaccines include the Chinese lapinised strain, sometimes called the C, K or LPC strain; the Japanese guinea pig cell-culture-adapted (GPE-) strain; the Thiverval strain (the French PK-15 cell-adapted strain); and the Mexican PAV strain (the most common being the PAV-250 strain, from the 250th passage of the A-PAV-1 strain).[47,75] According to Blome et al.,[75] the most widely used strain is the Chinese strain. Japanese GPE- strain vaccines are used in Asian and Pacific countries, Thiverval strain vaccines are produced in France, and the Mexican PAV strain vaccine is licensed in Mexico.

LAV vaccines for CSF are safe and efficacious, and there are many formulations commercially available. A major drawback of LAV vaccines is that antibodies caused by vaccination cannot be differentiated from antibodies caused by natural infection. This is not a problem in countries with endemic CSF. However, countries free of CSF may not allow the use LAV vaccines because of this issue.[45] Additionally, inability to detect natural infection in vaccinated animals may result in strict international trade restrictions on pork and pork products.[68] LAV vaccines may be used if CSF eradication is not possible to prevent the spread of the virus on a production site.

LAV vaccines can be administered orally or parenterally. Oral vaccination has been investigated primarily in countries where CSF is endemic in feral swine. German field trials from the 1990s showed that bait vaccines can reduce CSFV prevalence in wild boar and increase herd immunity.[93,94] Oral vaccination campaigns have since improved CSF control in wild boar in the EU; however, LAV vaccines delivered via bait lack DIVA capability.[95] See section 13 for specific field experiences with oral vaccine in Germany and Romania. In countries with many backyard pigs, oral vaccination has also been investigated as an adjunct method of CSF control.[96,97]

5.1.2 E2 Marker Vaccines

Marker vaccines contain protective antigen(s), but do not contain viral antigen(s) that induce antibodies when vaccinated animals are exposed to wild-type virus. Marker vaccines must have an accompanying serological test that can distinguish antibodies that result from infection vs. vaccination.[45]

The CSFV major envelope glycoprotein E2, which is strongly immunogenic in pigs,[98-101] has been used to produce the E2 marker vaccine using a baculovirus recombinant system.[99,102] Companion discriminatory tests detect antibodies to the Erns glycoprotein, which is found only in wild-type virus.[79,103]

Marker vaccines are known to be safe[45] and highly stable when stored properly.[104] However, as reported by Blome et al.,[26] drawbacks include lack of early protection and reduced protection against transplacental transmission. Marker vaccines continue to be developed and improved.[45] Only one E2 marker vaccine is commercially available (Porcilis® Pesti, MSD Animal Health). Currently, DIVA tests are not sufficiently sensitive to reliably detect individual animals that are infected, and they are used only on a herd basis.

E2 marker vaccines require double parenteral administration. Because of this, E2 marker vaccines are not suitable for oral use in wild boar populations.[105]

5.1.3 Pestivirus Chimeric Vaccines

The pestivirus chimera CP7_E2alf (Suvaxyn CSF Marker, Zoetis) has been recently licensed by the European Medicines Agency. This vaccine was constructed based on an infectious cDNA clone of the cytopathic BVDV strain CP7[106] in which the E2 encoding region was replaced with the CSFV strain Alfort/187.[107]

According to Blome et al.,[105] testing has shown the pestivirus chimera CP7_E2alf to be as safe and efficacious as conventional LAV vaccines. Vaccinated animals carry antibodies to CSFV E2 but not CSFV Erns. There are two commercially available ELISAs that can be used with CP7_E2alf for DIVA purposes: PrioCHECK CSFV Erns (Thermofisher) and CSF Marker (Qiagen). Because cross-reactivity has been observed with both BVDV and border disease virus strains, additional test systems are in development[105] (see section 4.2.3 for more information on diagnostic testing).

A single intramuscular injection of CP7_E2alf confers immunity within 1 week of administration.[105] Oral administration of CP7_E2alf in wild boar has been found to be safe and effective.[108] However, CP7_E2alf licensing for oral use in wild boar is not yet approved.

Another pestivirus chimera, CP7_E2gif, containing the backbone from BVDV strain CP7 and E2 from the border disease virus strain Gifhorn, has also been developed.[109] CP7_E2gif has been tested as a DIVA vaccine[110] but is not commercially available. Additional chimeric pestiviruses, such as flc11 and flc9, have shown promise and are described by Blome et al.[105]

5.1.4 Additional Subunit Vaccines/Immunogenic Peptides

In addition to the E2 marker vaccine, additional "subunit" peptide vaccines have been developed and described in depth by Blome et al.[105] To date, most candidates have contained one or more peptides that belong to the antigenic domains of E2. In particular, E2 marker vaccines that use expression systems (such as the E2his vaccine produced in the mammary gland of goats after adenoviral transduction[111] or the yE2 yeast-expressed vaccine[112]) have shown promise.

Peptide vaccines are safe and, when paired with an accompanying diagnostic test, have DIVA capability. However, no current candidates confer protection that is superior to classical E2 marker vaccines.[105] Most peptide vaccines are administered parenterally and require multiple vaccinations.[105] As described by Blome et al.,[105] at least one baculovirus-expressed E2 subunit vaccine can induce protection after a single injection, and some E2 formulations are being explored for potential oral administration. At this time,

peptide CSFV vaccines are mostly experimental[105] and no licensed products are available in the U.S. Luo et al. reports that the yeast-expressed vaccine yE2 is being evaluated for licensing in China.[113]

5.1.5 DNA Vaccines

DNA vaccines described in the literature are based on plasmid constructs that express the CSFV glycoprotein.[105] They are high cost and require multiple vaccinations, which precludes their widespread use at this time.[105] There are no licensed CSFV DNA vaccines.

5.1.6 Viral Vector Vaccines

Vaccinia virus and pseudorabies virus vector vaccines have been described since the 1990s. Most express the CSFV glycoprotein E2 and are capable of DIVA (when combined with serological assays that detect Erns or NS3).[105] According to Blome et al., additional viral vector systems have been tested in recent years, including porcine and human adenoviral vectors, swinepox vectors, parapox vectors, fowlpox vectors, and canarypox vectors.[105] Some vector vaccines confer full protection; however, their drawbacks include the need for multiple vaccinations, safety concerns (particularly for vaccinia virus), and interference with serological surveillance programs (for example, when pseudorabies virus vectors are used in a country that is pseudorabies-free).[105] According to Luo et al., a recombinant human adenoviral vaccine expressing E2 (rAdV-E2) is being evaluated for licensing in China.[113]

5.1.7 Trans-Complemented Deletion Mutants (Replicons)

Trans-complemented deletion mutants (also known as replicons or virus replicon particles) are infectious virions that contain subgenomic RNA with specific deletion(s) in at least one of the genes encoding the viral structural proteins.[114] Several trans-complemented CSFV Erns or E2 deletion mutants have been developed as described by Blome et al.[105]

Trans-complemented deletion mutants are not transmissible and cannot revert to virulence because they contain defects in at least one envelope protein.[114] They are also DIVA-capable. Efficacy varies by route of administration. Intradermal injection (with the replicons A187delErns and Flc23) has been shown to confer full protection; however, oral, intranasal, and intramuscular administration may result in partial or no protection.[105] Trans-complemented E2 deletion mutants are less potent than conventional LAV vaccines.[105]

Newer trans-complemented deletion mutants include the DNA-based Semliki Forest virus replicon pSFV1CS-E2 (which expresses CSFV glycoprotein E2) and its successor, the adenovirus/alphavirus replicon chimeric vector-based vaccine rAdV-SFV-E2 (a replication-defective adenovirus 5 vector that delivers a Semliki Forest virus replicon expressing CSFV E2). In particular, rAdV-SFV-E2 is safe and fully protective against CSFV challenge following double vaccination (6.25×10^5 $TCID_{50}$) or single vaccination ($10^7 \times TCID_{50}$).[115] In addition, pre-existing maternally derived CSF antibodies do not interfere with vaccine efficacy, and the vaccine does not induce anti-vector immunity.[115] As reported by Blome et al.,[105] further studies have shown that maternally derived antibodies provide some protection to 5-week-old piglets, and antibodies to similar viruses such as BVDV do not interfere with efficacy. Luo et al. reports that RAdV-SFV-E2 and the alphavirus replicon-vectored vaccine pSFV1CS-E2 are two vaccines being evaluated for licensing in China.[113]

5.1.8 Additional Approaches

As described by Blome et al.,[105] additional approaches continue to be explored in the search for a safe and efficacious CSFV marker vaccine.

5.2 Production of CSF Vaccines

In the U.S., CSFV is found on the Select Agents and Toxins List. According to 9 CFR §121.3, CSF poses a potential threat to animal health. Vaccine production tends to be driven by market demand, and

currently, the U.S. does not have a market for CSF vaccine. Therefore, CSF vaccine is not currently manufactured in the U.S.

5.2.1 LAV Vaccines

Conditions for the production of LAV vaccines are addressed in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. The OIE states that the production of LAV vaccines must be based on a seed-lot system that has been validated with respect to virus identity, sterility, purity, safety, non-transmissibility, stability and immunogenicity.

5.2.2 Vaccines Produced Through Biotechnology

E2 marker vaccines do not contain live CSFV.[45] However, additional regulatory considerations may be applicable when discussing vaccines produced through biotechnology.

The National Environmental Policy Act (NEPA) of 1969 requires the review and approval by the appropriate federal agency to evaluate the potential impact of an organism containing recombinant DNA on the environment.[116] The Institutional Biosafety Committee (IBC) reviews experiments performed for licensure when they are performed within a facility; the USDA Center for Veterinary Biologics (CVB) must give approval when those experiments are field trials conducted prior to licensure that involve environmental release.[116]

5.3 Vaccine Banks

Vaccine banks (also known as antigen banks or strategic reserves) store a variety of vaccines which can be used if an outbreak occurs. Banks may contain either ready-to-use vaccines or vaccine antigens that will be formulated, if needed, into complete vaccines. Some experts agree that when a contingency plan includes the possible use of CSF vaccine in an emergency vaccination protocol, CSFV vaccine banks should be established.[102,117]

5.3.1 National Veterinary Stockpile

The National Veterinary Stockpile program, administered by USDA APHIS, maintains contracts with biologics manufacturers to provide limited amounts of CSF vaccine within 2 to 4 days (if needed during an U.S. outbreak).[118] If CSFV vaccine use is desired, it must be requested at the State level and approved by APHIS leadership.

In 2008, the National Veterinary Stockpile (NVS) Classical Swine Fever Countermeasures Working Group (CSFCWG) expressed their desire for adding a second-generation CSF vaccine that is as effective as LAV vaccine strains but has DIVA capabilities. A second long term goal for the NVS would be to have a pen-side test kit available for use during an outbreak, to rapidly detect any CSFV field strain.

5.3.2 International Examples

For the European Union Vaccine Bank, recommendations include at least 2 million doses of LAV vaccine, possibly E2 marker vaccine or a new modified live marker vaccine provided the vaccines prove effective.[117]

5.4 CSF Vaccines from Commercial Manufacturers

A large number of LAV vaccines are commercially available in different parts of the world. One E2 marker vaccine, Porcilis® Pesti (MSD Animal Health), is also commercially available. The pestivirus chimera CP7_E2alf (Suvaxyn CSF Marker, Zoetis) has been recently licensed by the European Medicines Agency. A list of commercially available vaccines can be found on the Center for Food Security and Public Health website at *http://www.cfsph.iastate.edu/Vaccines/disease_list.php?disease=classical-swine-fever&lang=en*. Blome et al.[105] have recently published a review of experimental CSF vaccines.

5.5 Vaccine Licensing

The USDA CVB, NVS, and other agencies may be involved in evaluating and purchasing vaccine antigen concentrates and/or finished routine or emergency use vaccines.[119] Vaccines may be licensed by the CVB and distributed with a full product license, or they may receive a conditional biologics license for use in specific conditions (e.g., if the product will be used by or under the supervision of the USDA in an emergency animal disease outbreak).[119]

For a vaccine to be given a full product license, the manufacturer must conduct extensive efficacy, purity and safety testing.[119,120] Steps in the U.S. vaccine licensing process include review of manufacturer data to support the product and label claims; inspection of manufacturing processes and practices; confirmatory testing of the biological seeds, cells and product; post-licensing monitoring including inspections and random product testing; and post-marketing surveillance of product performance.[119]

In an animal disease emergency, it may not be possible for a vaccine to achieve a full product license. The USDA has mechanisms for expedited product approval, and can exempt products from some of the regulatory requirements for full product approval during emergencies.[119] However, every attempt is made by the CVB to establish a reasonable expectation of purity, safety, potency and efficacy prior to the use of any vaccine. In addition to potential harm to animal, human and environmental health, the risk of lawsuits if problems occur must be considered.[119]

6. VACCINE MATCHING, EFFICACY, AND SAFETY

Summary

Vaccine matching for CSF is not necessary since only one serotype exists. Vaccine efficacy is estimated in vaccinated animals by evaluating their resistance to live virus challenge.

Overall, CSF LAV vaccines (Chinese lapinised strain [C, K or LPC]), GPE strain and the Thiverval strain) are considered safe for intramuscular or oral administration in all ages of pigs including neonatal and pregnant swine.

Marker vaccines are generally considered to be low-risk for animal safety, aside from occasional tissue reactions at the injection site.

6.1 Vaccine Matching

Vaccine matching is used to determine whether a given vaccine is likely to provide good protection against a field strain. It is important for pathogens with a high degree of genetic variability, such as foot-and-mouth disease virus. Vaccine matching for CSF is not necessary since only one serotype exists.

6.2 Vaccine Efficacy and Effectiveness

Vaccine efficacy is the term for relative reduction in the transmission rate among vaccinated animals under optimal conditions (i.e., under laboratory conditions). According to the OIE,[45] vaccine efficacy is estimated in vaccinated animals directly, by evaluating their resistance to live virus challenge, and is expressed by the number of 50% protective doses (PD_{50}) for pigs contained in the vaccine dose. Piglets 6–10 weeks-of-age are vaccinated with different dilutions of the vaccine in question (1/40 and 1/160), along with controls, and challenged with a virulent strain of CSFV fourteen days later.[45] The PD_{50} content of the vaccine is calculated from the number of animals protected in each group using the Spearman-Kärber method; the vaccine complies with the test if the minimum dose corresponds to not less than 100 PD_{50}.[45] Protection against transplacental infection is assessed in a similar way. Details can be found in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals.

The term vaccine effectiveness is used to describe the reduction in cases (among vaccinated animals) that occurs in real world (i.e., not under controlled laboratory conditions). In the field, many factors can affect vaccine effectiveness. For example, animals are exposed to field viruses at different times after vaccination, rather than at a defined interval. When vaccines are administered to domestic pigs, animals are often crowded in a tight pen and the vaccine is administered without individual animal restraint. When this occurs, not all animals may receive the correct dose as animals may move while the vaccine is being administered. Vaccine effectiveness can also be reduced by failure to maintain an effective cold chain. The immune status of each individual animal, which may be compromised by parasitism, poor nutrition, stress, or other factors, is also related to vaccine effectiveness.

Anytime vaccines are used in a manner that is not in accordance with the approved label directions, problems may occur. In Thailand, the C-strain vaccine was used in combination with a live gI-deleted pseudorabies (PRV) vaccine and administered as a single dose.[121] Pigs were protected against CSF if they were immunized with the combination PRV/CSF vaccine; however, they demonstrated a reduced CSF-specific cellular immune response compared to those pigs which were vaccinated with the CSF product only. More pathological changes following the CSF challenge were also documented in these pigs when compared to pigs receiving the CSF vaccine only.[121]

6.3 Vaccine Safety

In general, safety assessments for vaccines vary with the type of vaccine (inactivated or live, bacterial or viral), the adjuvants used, the history of similar products in use, the dose, vaccine claims, the usage regimen, and animal factors such as species.[122] The “worst case” scenario is usually assessed even if it is unlikely, assuming that the product will be used at its maximum potency and quantity, in animals of the highest sensitivity. Safety concerns include both manufacturing errors, such as vaccine contamination, and user errors that could cause problems.[122] According to the OIE, CSFV vaccine safety assessment includes testing in young animals, testing in pregnant animals, non-transmissibility testing, and reversion-to-virulence testing.[45]

Overall, CSF LAV vaccines (Chinese lapinised strain [C, K or LPC]), GPE strain and the Thiverval strain) are considered safe for intramuscular or oral administration in all ages of pigs including neonatal and pregnant swine.[123,124] Marker vaccines are generally considered to be low-risk for animal safety,[122] aside from occasional tissue reactions at the injection site.[102,104,125,126] CSF E2 marker vaccines, however, are given only parenterally, not orally.[124]

In the U.S., the USDA CVB determines the recommended ages for vaccine administration, whether it is approved for use in pregnant swine, and recommended revaccination frequency. This information will accompany the vaccine.

Risks to people who administer or contact the vaccine should be assessed. The LAV CSF vaccine will not replicate in humans. However, local reactions from oil adjuvants, other ingredients, or infection at the injection site may occur.[122]

7. EFFECTS OF VACCINATION ON VIRUS TRANSMISSION

The main purpose of emergency vaccination is to end or reduce virus transmission. This can be accomplished by vaccines that increase the minimum infectious dose of virus, and/or decrease virus shedding from animals that become infected.

The reproduction ratio or R value estimates the ability of a vaccine to reduce transmission of the virus in a field situation. If vaccination decreases R to less than one, the epidemic will die out and only minor outbreaks are expected (however, some transmission is still expected to occur until the epidemic ends).[127] If R remains higher than 1, there can be major outbreaks and the epidemic may continue to grow. Reproduction ratios can be estimated within herds (R0) and between herds (Rh). R value can be affected by the density of animals and their interactions, as well as the infectivity and susceptibility of individual animals (as cited in Orsel et al.[128]).

Another concern during an outbreak is the infectivity of rendered animals. When animals are vaccinated with a LAV vaccine, then infected at least 4 days later with CSFV, the carcass has very little risk of infecting other animals with CSFV.[124]

7.1 Examples of R Values for CSFV Vaccines

A baculovirus vector E2 marker vaccine produced by Moormann et al.[129] administered as a single dose prevented virus transmission to unvaccinated in-contact animals when challenged 3 weeks after vaccination. A transmission experiment was designed to estimate the R value of the virus. At 1 week after vaccination, the R value was >1, whereas in another challenge 2 weeks after vaccination, the R value was <1. Transplacental transmission of the challenge CSFV was prevented in 8 out of 9 animals when a single vaccination was administered; however, transmission to offspring was prevented when the sow received two vaccinations, then challenged 70 days after the second vaccination.[129]

Dewulf et al.[41] compared a C-strain LAV vaccine and an E2 marker vaccine in preventing illness and virus transmission at 7 days after vaccination. The C-strain vaccine prevented illness and virus transmission in all pigs challenged via CSF inoculation, and prevented illness in vaccinated pigs in contact with CSFV-inoculated animals. However, all the pigs vaccinated with the E2 marker vaccine became clinically ill when challenged at 7 days and many of the vaccinated pigs in contact with the CSFV-inoculated animals became viremic.[41]

8. ONSET OF PROTECTIVE IMMUNITY

The onset of protective immunity varies according to vaccine type. LAV virus vaccines have a rapid onset of immunity; E2 marker vaccines have a slower onset of immunity.[45] Specifically, protective immunity can be induced within a few days when LAV vaccine strains C, GPE, Thiverval and PAV-250 are used.[68] A single vaccination may protect animals by day 5–6[123,130] with neutralizing antibodies detectable by day 7–10 post vaccination.[123] E2 marker vaccines may not protect animals from challenge until 2–3 weeks after vaccination with a single injection,[68,104,129,131] and a second injection is recommended. As described by Blome et al.,[105] the chimeric vaccine CP7_E2alf has repeatedly been shown to confer protection within 1 week after a single intramuscular injection.

9. DURATION OF IMMUNITY

Duration of immunity for LAV vaccines varies from 10 months with oral administration[132] to lifelong CSF immunity with a single intramuscular vaccination.[68,102,123] E2 marker vaccines, however, induce a shorter immunity of approximately 6 to13 months.[68,104,129,131,133] Immunity conferred by the chimeric vaccine lasts at least 6 months as reported by Blome et al.[105]

10. MATERNAL ANTIBODIES

Maternal antibodies may complicate CSF control during an outbreak. Coggins[134] reported that when pigs are not exposed themselves to CSFV, maternal antibodies decline with approximately a two week half-life. Therefore, some pigs may not clear their maternal antibodies until 12 to 14 weeks-of-age.

Bironet al.[50] challenged piglets born from vaccinated and non-vaccinated dams. CSFV was found only in piglets vaccinated in the presence of maternal antibodies, following vaccination at 2 weeks-of-age and challenge 1 week later. No CSFV was isolated from 23 of 25 pigs vaccinated in the absence of maternal antibodies, following vaccination and challenge at the same time. This study and another conducted by Terpstra[135] both demonstrated that pigs with maternal antibodies may survive a CSF infection. Bironet al. suggests that these pigs may also shed CSFV for a limited time.

The amount of maternal antibody may also affect vaccination response. Vandeputte et al.[136] determined that when vaccinated, pigs with a high maternal antibody level had a stronger inhibition than pigs with a low level of maternal antibody. Virus was detected for a greater length of time in animals vaccinated in the face of high maternal antibody versus their unvaccinated counterparts; virus replication was prevented in vaccinated animals with low maternal antibody levels.[50] When maternal antibodies are a concern, a general recommendation may include delaying the vaccination of young pigs until 6 weeks-of-age or older.[102]

When immunizing pigs with an E2 marker vaccine, two doses may be needed to protect pigs with a low level of maternal antibody. In Thailand, Damrongwatanapokin et al.[137] vaccinated pigs with a low level of maternal antibody using E2 marker vaccine. Following CSFV challenge, 14 days post-vaccination, the pigs developed clinical signs of CSF infection and all died within 18 days post-inoculation.

11. VACCINE WITHDRAWAL TIMES IN MEAT

In general, vaccination does not result in harmful residues in meat.[122] Other vaccine components, such as adjuvants and excipients, may require withdrawal periods.[122]

The E2 marker vaccine marketed internationally (Porcilis® Pesti, MSD Animal Health), and another previously marketed E2 marker vaccine, both listed zero withdrawal times. However, in the U.S., withdrawal times following vaccination with specific products are established by the USDA CVB, and will be found on the vaccine label. Due to regulatory requirements, all vaccines for food animals in the U.S. must be labeled with a minimum slaughter withdrawal time of 21 days.

12. STRATEGIES FOR VACCINE USE

Summary

To control and eradicate CSFV in an outbreak, the U.S. will consider three strategies: stamping-out with modified emergency vaccination-to-kill, stamping-out with modified emergency vaccination-to-slaughter, and stamping-out with emergency vaccination-to-live. All types of vaccination decrease virus transmission and the short-term resources needed for carcass disposal, but will require resources to implement, manage and maintain a vaccination, movement, and permitting system for the vaccinates. All other factors being equal, vaccination-to-live would result in the most benefits for animal survival and domestic continuity of business. However, the detrimental effect on exports is likely to be greater.

Approaches to the application of CSF vaccination include prophylactic vaccination, emergency vaccination (which may be protective or suppressive), targeted vaccination, ring vaccination, barrier vaccination and blanket vaccination. Consideration should be given to establishing a vaccination surveillance zone around the vaccination zone.

12.1 CSF Vaccination Strategies in the U.S.

To control and eradicate CSFV in an outbreak, the U.S. may use three strategies that involve stamping-out (depopulation) plus emergency vaccination. These strategies are defined in the Foreign Animal Disease Preparedness and Response Plan (FAD PReP) *Classical Swine Fever Response Plan*[138] (also known as the Red Book) as follows:

- *Stamping-out modified with emergency vaccination-to-kill:* depopulation of clinically affected and in-contact susceptible animals and vaccination of at-risk animals, with subsequent depopulation and disposal of vaccinated animals. Depopulation and disposal of vaccinated animals may be delayed until logistically feasible, as determined by IC and the VS Deputy Administrator (U.S. CVO).
- *Stamping-out modified with emergency vaccination-to-slaughter:* depopulation of clinically affected and in-contact susceptible animals and vaccination of at-risk animals, with slaughter and processing of vaccinated animals, if animals are eligible for slaughter under USDA FSIS authority and rules and/or State and Tribal authority and rules.
- *Stamping-out modified with emergency vaccination-to-live:* depopulation of clinically affected and in-contact susceptible animals and vaccination of at-risk animals, without subsequent depopulation of vaccinated animals. Vaccinated animals intended for breeding, slaughter, or other purposes live out their useful lives.

As previously described, the National Veterinary Stockpile program, administered by USDA APHIS, maintains contracts with biologics manufacturers to provide CSF vaccine within 2 to 4 days (if needed during an U.S. outbreak).[118] CSFV vaccine use must be requested at the State level and approved by APHIS leadership.

According to the NVS,[118] both the LAV vaccine and the E2 marker vaccine could be used in a potential U.S. outbreak of CSF. If the outbreak is focal, using an inner ring vaccination program, the LAV vaccine could be administered to animals with the vaccinate-to-kill approach. The DIVA vaccine could be used in the outer vaccinate-to-live zone. The approach would be different if the CSF outbreak were widespread. In a widespread outbreak, the LAV vaccine may be administered to terminal market swine, with breeding stock receiving the DIVA vaccine. Specific terminology regarding vaccination zones is discussed in section 12.3.

12.2 CSF Vaccination Strategies in the EU

While several strategies can be used, EU member countries tend to use three different strategies:[68]

- CSF LAV vaccines, particularly C strain, are used in endemic areas with feral swine and many backyard swine producers.
- E2 marker vaccination programs are an option during a disease outbreak.
- E2 marker vaccines and LAV vaccines are used in combination during a disease outbreak. Animals in the infected area are vaccinated with LAV vaccine as it provides protection more quickly, and E2 marker vaccines are used in animals surrounding the area with a possible vaccination-to-live approach.

12.3 Vaccination Terminology and CSF Applications

12.3.1 Prophylactic Vaccination

Prophylactic (routine) vaccination is generally used only in endemic areas or regions at high risk for CSFV introduction, because it is a significant trade barrier for countries exporting animal products. LAV vaccines are often used.

12.3.2 Emergency Vaccination

Emergency vaccination (vaccination in the face of an outbreak) is usually conducted as reactive vaccination.

12.3.3 Protective Emergency Vaccination

Protective emergency vaccination, which is conducted among animals in uninfected areas, creates a zone of animals with reduced susceptibility around the infected area.

12.3.4 Suppressive (or "Damping Down") Emergency Vaccination

Suppressive (or "damping down") emergency vaccination is conducted in the infected area where the virus is already circulating. It is intended to reduce virus transmission, aid control efforts and prevent CSFV from spreading beyond the infected zone. Suppressive vaccination is likely to face a more severe virus challenge than protective vaccination: infected animals may already be present on a farm in areas where this form of vaccination is used. In contrast, animals in uninfected areas (protective vaccination) are likely to be exposed to smaller amounts of virus in aerosols and on fomites.

12.3.5 Targeted Vaccination

Targeted vaccination attempts to protect specific groups of animals. Stamping out, as the sole eradication strategy, risks the destruction of rare species, rare breeds and high value genetic stock.[139] Targeted vaccination may be directed at uninfected animals of high value, which can include livestock with particularly valuable, rare, or unusual genetic backgrounds; long-lived production animals; zoo animals; or endangered species. Targeted vaccination can also be directed at uninfected areas where there is a high density of susceptible animals.

12.3.6 Ring Vaccination

Ring vaccination refers to a strategy of immunizing animals within a defined area around infected premises or infected zones. Its purpose is to reduce or prevent virus transmission from a focal outbreak to surrounding uninfected areas. Ring vaccination is most likely to be successful if foci of infection can be identified rapidly, before the virus can spread. It may not be appropriate in cases where the disease is widespread or contained in widely scattered foci, where the disease is difficult to identify, where there is a significant delay between infectivity and case confirmation, or where there is a significant delay between vaccine administration and the onset of protection.

In addition to stamping out infected herds and issuing a stop movement, immediate vaccination with the C-strain vaccine (or another LAV vaccine) may be conducted in a ring around an outbreak.[102] LAV vaccines induce a solid herd immunity 1–2 weeks earlier than E2 marker vaccines.[102] The program should include observation and surveillance of the vaccinated animals. If the vaccinated animals are not infected with the field CSFV strain, then the pigs can be slaughtered.[102] Whenever a LAV vaccine is used, export of pork and pork product restrictions must be considered.

12.3.7 Barrier Vaccination

Barrier vaccination is very similar in principle to ring vaccination; however, the vaccination zone is used to prevent the infection from spreading from a neighboring country or region into the uninfected area, rather than to keep it from spreading outward from infected premises. Geographic and political features usually have an important influence on the shape and location of the vaccination zone.

12.3.8 Blanket Vaccination

Blanket (mass) vaccination can be conducted throughout an entire country or throughout an OIE-defined zone with a separate status. Countries are most likely to consider blanket vaccination when a disease becomes widespread. This form of vaccination can be carried out indefinitely in countries or zones defined as "CSF free with vaccination"; however, this designation affects trade status.

12.4 Establishing a Vaccination Zone

A vaccination zone should be the smallest area possible as vaccinated pigs may need to be destroyed in order to more quickly prove freedom from CSF.[140] Restrictions may need to be instituted to control the use of vaccine as well as pig movement when establishing a vaccination zone.[141] The size of the vaccination zone may vary with the types of vaccines available, the density of domestic pigs in the area and if feral swine are present. In the U.S.:

- The **Containment Vaccination Zone** is an emergency vaccination zone within the CSF Control Area. Vaccination may be performed in the Infected Zone and/or the Buffer Zone.
- The **Protection Vaccination Zone** is an emergency vaccination zone outside the Control Area in the CSF-Free Area. Barrier vaccination is used in this zone to prevent CSFV from spreading into areas free of the virus.

More information on each of these strategies can be found in the APHIS Foreign Animal Disease Framework documents.

12.5 Advantages and Disadvantages of CSF Vaccination

All types of vaccination decrease the short-term resources required for carcass disposal, but require resources to implement, manage, and maintain a vaccination, movement, and permitting system for the vaccinates. Vaccination is also expected to suppress virus transmission. Vaccination-to-live could potentially decrease the number of animals that must be culled. All other factors being equal, vaccination-to-live would result in the most benefits for animal survival and domestic continuity of business. However, vaccination-to-live may have a detrimental effect on exports. More information on the effect of CSF vaccination on OIE status can be found in section 17.5.

13. FIELD EXPERIENCES WITH CSF VACCINATION

Summary

CSFV vaccines that meet standards for safety and efficacy and are administered correctly have the potential to decrease circulation of the virus, thereby reducing economic losses in different situations. Different countries have used a variety of approaches to control or eradicate CSFV.

CSFV LAV vaccines have been successfully used in domestic swine in Brazil, Bulgaria, Israel, the Republic of Korea, Mexico, Romania and the U.S. These vaccines have also been used for CSF control in wild boar in Bulgaria and Germany. The commercially available E2 marker vaccine Porcilis Pesti® (MSD Animal Health) has been used in Mexico.

Countries including Brazil and Mexico have used a zoned approach to CSF eradication, in which vaccination is practiced in some parts of the country but not others. In some countries where CSFV vaccine use was phased out after outbreaks diminished—such as Brazil and the Republic of Korea—the virus re-emerged within a few years. Great Britain and the Netherlands both successfully eradicated CSFV without the use of vaccination.

13.1 Brazil

From approximately 1980–1990, vaccination with the C-strain LAV vaccine was extensively used in Brazil.[142] The size of the country made CSF eradication challenging, so in 1992, Brazil implemented a plan to divide the country into three areas for CSF control.[142] Area I contained the three southern states. This area was free of CSFV and vaccination was prohibited. Area II included states with endemic CSFV. These states had a relatively large swine population and vaccination was made mandatory. The remainder of the country comprised Area III. In Area III, raising swine was not viewed as significant, so vaccination was not made mandatory.[61] Swine industry stakeholders from each of the states in Area I created a private fund to cover expenses if herd depopulation was needed during an outbreak.[61] This plan was very successful, and by 1998, the use of CSF vaccine was prohibited in all of Brazil except when directed by the Ministry of Agriculture.[143]

In 2001, regions in the south, southwest, central-west and the states of Bahia and Sergipe were declared CSFV free.[142] At that time, the country was divided into two regions—one region had been free of CSFV since 1998 and in the second region, CSFV remained endemic.[61] About 75% of Brazil's swine production occurred in the CSF free zone.[144] LAV vaccine use continued in the northeast region (considered an infected zone), where 12 CSF outbreaks occurred in 2001. No outbreaks were detected in 2002, and four known outbreaks occurred in 2003 in the CSF infected zone. No outbreaks occurred in 2004 [144]

From 2006–2008, CSF outbreaks continued to occur outside of the area free of CSF. Outbreaks were resolved utilizing disinfection, quarantine, and stamping-out.[46] In February 2009, Brazil notified the OIE of a CSF case in a modern swine facility outside of the CSF free area.[46] Vaccine use was prohibited at that time. However, following additional outbreaks in April and May 2009, the Animal Health Department approved the use of vaccine for pigs in the State of Rio Grande do Norte.[46] During 2009, Brazil used a LAV virus vaccine to control confirmed CSF outbreaks in areas considered CSF-endemic. Over 90,000 pigs received the vaccine.[46] Vaccine was not used in the area free of CSF, and remains prohibited in the rest of the country of Brazil. According to the OIE, CSF has not been reported in Brazil since 2009.[6]

13.2 Bulgaria

In March 2000, four-month-old pigs were diagnosed with CSF in eastern Bulgaria.[55] In 2006, Bulgaria received approval to use emergency vaccination to eradicate CSFV.[12] Backyard pigs tested positive in May 2008. A control program, including vaccination in wild boar, was implemented for all of Bulgaria in an effort to eradicate CSFV in the wild boar population.[145] In spite of utilizing vaccine, in September 2009, CSF was diagnosed in wild boar in northern Bulgaria close to the Romania border. CSF has not been reported in Bulgaria since 2009, according to the OIE.[6]

13.3 Germany

From 1990–1998, 424 CSF outbreaks were reported in domestic pigs in Germany with additional cases diagnosed in wild boars.[53] Available information suggests direct or indirect contact with infected wild boars or swill feeding was responsible for a majority of outbreaks in domestic pigs.

In February 2002, the European Commission (2002/161/EC)[146] approved the use of CSF vaccine in feral pigs by oral immunization in specific areas of Germany. Those areas where vaccine was used were modified in October 2002[147] and February 2003.[148] Oral baits containing a LAV vaccine based on the C strain were used to immunize wild boar.[148] The last OIE-reported cases of CSF in domestic pigs occurred in 2007 and wild boar in 2009.[6]

13.4 Great Britain

The last CSF outbreak in Great Britain occurred in 2000. Sixteen farms were affected with about 75,000 pigs culled to control disease spread.[141] According to the Classical Swine Fever Disease Control Strategy for Great Britain, "the policy is not to vaccinate against CSF, although it is available should the disease

situation require it."[141] An emergency vaccination plan, if needed, must be submitted to and approved by the European Commission.[11] Vaccine could then be acquired from the European Union bank.[141]

13.5 Israel

According to the OIE,[6] CSF infection was confirmed in both domestic and wild animals in Israel in 2009. Domestic animals tested positive on a farm near the Lebanon border. Wild boars found dead in the area also tested positive for CSF antigen, therefore, wild boars were suspected as a possible source of infection for the domestic herd. Fomites were also a possible source of infection. Vaccination, modified stamping-out, and disinfection were listed as measures taken to eradicate CSFV.[46] Israel did not report using any CSF vaccine during 2009, but used 500 doses of CSF vaccine in 2010.[46] According to the OIE, CSF has not been reported in Israel since 2010.[6]

13.6 Mexico

In 1996, Mexico was divided into three zones for CSF control purposes: 1) the area free of CSF, 2) the eradication area, and 3) the control area. In the free and eradication areas, CSF vaccination was prohibited; in the control area, CSF vaccination was mandatory.[149] In 1998, a CSF outbreak occurred in the eradication area,[149] an area free of CSFV since 1996. CSF-infected pigs from the backyard pig population in the control area in Mexico were believed to be the source of the infection. Producers approached the government asking for approval to use the commercially available marker vaccine Porcilis® Pesti.[149,150] The vaccine was registered for use in 1998, and vaccination was allowed in the eradication area to prevent spread of CSFV.[150] Martens et al.[150] studied the use of this vaccine in the field during this time. They concluded that the vaccine was useful in reducing clinical signs and limiting the spread of new outbreaks.

In August 1999, a CSF outbreak was reported in San Carlos, along the U.S.-Mexico border.[151] San Carlos, in the State of Tamaulipas, was thought to be CSF-free. The CSF infected pigs originated from a family production unit, which commonly included a few head of free-ranging animals that may ingest swill.[151] The outbreak was eradicated using several control measures, including quarantine, stamping-out, and stop movement, but vaccination was not used.

However, by 2000, CSF outbreaks were occurring in both the eradication area and control areas in Mexico, and CSF LAV vaccine was being used regularly to control these outbreaks.[149] In 2001, Mexico was then divided into just two areas with the northern-most states remaining CSF free while in the rest of the country CSF had become endemic. Infection and movement of backyard pigs was thought to be the main reason for CSFV spread in Mexico and the only way to eradicate CSFV from Mexico would be to focus on this population.[149]

According to the OIE,[6] Mexico had 15 CSF outbreaks from 2002–2004 , two CSF outbreaks in 2005, no CSF outbreaks from 2006–2008, and four CSF outbreaks in 2009. Mexico has been free of CSF from 2010 until the time of this writing (July 2017).

13.7 Netherlands

The Netherlands had been free of CSFV for more than 10 years, until the virus was detected on February 4, 1997 in a pig dense area. By the time of detection, CSFV had likely been in the country for at least 5–7 weeks.[152] During the outbreak, which lasted for more than a year, at least 11 million pigs were destroyed and more than 13,000 farms were involved.[7]

Only the Ministry of Agriculture can decide if vaccines will be used, which vaccines would be used, and how they would be used within a program.[153] Only veterinarians can administer the CSF vaccine and only registered CSF vaccines may be used. At the time of the outbreak, vaccination for CSF was not allowed in

the Netherlands unless special approval was granted for its use in an emergency vaccination program[11] in conjunction with other control measures. Stamping-out and stop movement orders were the main tools used to eradicate CSFV from the Netherlands during this outbreak.[10]

13.8 Republic of Korea

CSF was first reported in the Republic of Korea in 1908, but by 1947, CSFV had become endemic with many outbreaks to follow over the next several years.[154] In 1967, a LAV vaccine, LOM-850 , was used in Korea and led to a large decrease in the number of CSF cases.[154] In 1996, the country launched a campaign to eradicate CSFV that consisted of three stages. The goal of the first stage was to decrease the number of outbreaks through vaccination and culling.[89] The second stage included mandatory vaccination and testing. In the third and final stage, vaccination would be prohibited as the country moved to CSF free status. The number of CSF outbreaks decreased until no cases were reported in 2000 and 2001. On December 1, 2001, CSF vaccination was prohibited and the OIE was notified of the Republic of Korea's CSF-free status.[89]

In April 2002, two CSF outbreaks were reported with several more cases to follow later in the year.[89] In December 2002, the use of emergency CSF vaccination was used in areas surrounding the outbreaks, while stamping-out was also conducted in the infected areas. Although the outbreaks appeared to be contained, 65 new outbreaks occurred in March and May 2003.[89] A majority of these were connected to the purchase of young breeding animals from a farm involved in the December 2002 outbreaks. The Republic of Korea decided at that time to resume a national vaccination policy.[89] Outbreaks have continued to occur since then, with the most recent cases being reported to the OIE in early 2014.[6]

13.9 Romania

From 1974 to 2001, CSF vaccination with LAV vaccines was mandatory in Romania. During this time, only one CSF outbreak occurred (in 2001).[155] In January 2002, vaccination against CSF was discontinued in western Romania. Soon after, a CSF outbreak occurred in March. During 2002, 38 cases were diagnosed.[155] Over the next two years, the number of CSF cases remained largely unchanged, with 155 in 2003 and 182 in 2004. However, more than 1000 cases were diagnosed in 2005, and nearly 1400 were detected in 2006.[155]

In December 2006, Romania received approval to reinstate emergency vaccination against CSF.[12] During 2007 and 2008, domestic pigs in noncommercial holdings were vaccinated with LAV vaccine by injection, wild boar were vaccinated using baits, and a marker vaccine was used by commercial pig herds.[156] Following the vaccination campaign, virus spread and clinical signs were reduced. Romania reported no CSF outbreaks during 2008.[157]

Commission Decision 2008/897/EC placed financial limits to the amount of funding provided for vaccines for 2009.[156] This led to changes in the 2009 emergency vaccination protocol. Pigs in commercial holdings were no longer vaccinated, but domestic pigs in noncommercial holdings continued to receive LAV vaccine injections and the wild boar population continued to receive LAV vaccine in baits. More than 4,000,000 pigs were vaccinated for CSF in nonprofessional holdings in 2009. More than 250,000 baits were distributed to feral swine; nearly 7000 were recovered unconsumed.[158] No CSF cases have been reported to the OIE from Romania since 2008.[6] In 2010, Romania stopped vaccination of domestic pigs, but continued to vaccinate wild boars within 20 km of other countries.[157] Because of this, Romania could not declare CSF-free status.

13.10 United States

Beginning in the late 1800s, swine producers throughout the U.S. used a variety of serums and vaccines in their attempts to control CSF.[1] However, as safer vaccines became available in the 1950s, States began to prohibit the use of virulent hog cholera virus vaccine.[1]

Eradication of CSFV was authorized on September 6, 1961.[1] Federal funds began to support the program in the summer of 1962, although funding was not always available at the level needed to support the program over time. During the early years of the eradication program, improvements were made to diagnostic procedures, reporting systems were established, and communications were coordinated between all States. Progress phases were established, and each State was required to report their status. The phases were : Phase I–Preparation, Phase II–Reduction of Incidence, Phase III–Elimination of Outbreaks, and Phase IV–Protection Against Reinfection.[1] By January 1, 1975, all States reported their status to be Phase IV.

Hog cholera vaccines were extensively used before the eradication program and during its early stages.[1] By 1969, eight states had prohibited the use of all CSF vaccines while 33 states reported prohibiting only modified live virus CSF vaccine usage.[1] Vaccine usage was addressed on the national level on May 24, 1969, when the USDA prohibited the interstate movement of CSF modified live virus vaccine after July 1, 1969 with the goal of eliminating the usage of all CSF vaccines by January 1, 1970.

Feral swine infected with CSFV were identified in Florida in 1968 and 1969. Trapping, testing, and removal of infected swine was successful, and vaccine was not used in these instances.[1]

After CSF vaccination was prohibited, other eradication measures were more aggressively used including quarantine and euthanasia of infected animals. Finally, in 1978, the U.S. was declared free of CSF.[68] At that time, the cost to eradicate CSF had been more than $140 million dollars (more than $525 million in 2017 dollars).

14. MODELING STUDIES AND VACCINATION

Models, while imperfect, can be used to evaluate control strategies implemented in a previous CSF outbreak or predict the outcome of a future CSF outbreak. Differences in size and density between swine operations in the U.S. and other countries could affect the applicability of modeling results.

Backer et al.[159] evaluated vaccination strategies utilizing data from the 1997–98 CSF outbreak in the Netherlands. The four control strategies implemented included 1 km ring culling, and 1 km, 2 km, and 3 km ring vaccination with marker vaccine. Analysis of the outbreak size and duration showed that 1 km ring culling was more effective than 1 km vaccination, while the 2 km and 3 km ring vaccination were more effective than culling, 1 km vaccination, or both.[159]

In 2009, Backer et al.[160] compared the ability of different control strategies, including vaccination, to control CSF transmission. Using the 2006 Dutch pig farming structure, five control strategies were evaluated including: EU-required implementation of restriction zones and transport regulations, culling of detected infected herds, and contact tracing; one preemptive ring culling strategy (in rings of 1 km radius around detected outbreaks); and three ring vaccination strategies (in rings of 1, 2 and 5 km radius).[160] Findings indicated that ring vaccination with a 2 km radius around an infected premises is as effective as ring culling in a 1 km radius.[160]

The results of the Backer et al. 2009[160] study were later used to evaluate the economic impact of CSF control strategies. Bergevoet et al.[161] developed a mathematical model describing the effects of marker vaccination and transmission of CSF virus between individual animals, pens, and farms in the

Netherlands.[161] It was concluded that emergency vaccination can be an effective strategy when compared to pre-emptive culling to control CSF epidemics when a larger vaccination radius is used, however, small outbreaks may occur more frequently on vaccinated farms. Therefore, the frequency and methods of diagnostic testing used must be determined with this in mind.

Information from the Bergevoet et al.[161] and Backer et al.[160] studies suggests that utilizing vaccination in a large radius may minimize the duration of the epidemic. Vaccination would address animal welfare concerns—which arise when culling larger numbers of animals—and would benefit the swine industry economically by reducing the duration of the outbreak. However, depending on the number of animals within the proposed area of ring vaccination, the number of vaccine doses available may be a limiting factor.

Paarlberg et al.[9] devised a model of a U.S. CSF outbreak in which 11 million pigs were destroyed, export of live animals and pork was halted, and domestic pork consumption fell by 1%. Two scenarios were examined in which different swine populations were primarily affected; one primarily involved breeding pigs, while the second focused on market swine. Estimated losses range from $2.6 to $4.1 billion. This model did not include the use of vaccine as a tool to control the CSF outbreak.

In 2008, CSFCWG used the quantitative Kemper-Trego (KT) decision model to evaluate available CSF vaccines and diagnostics.[68] They concluded that the ideal CSF vaccine must prevent transmission, be efficacious in all ages of animals, provide immunity for one year, prove safe in all pigs to be vaccinated, be capable of one dose administration, be able to be manufactured quickly, possess an expiration date of at least 24 months, protect pigs in 7 days or less, have an accompanying DIVA test, have a short withdrawal period, and have a reasonable price.[68] Through their analysis, CSFCWG determined that while commercially available CSF vaccines are safe and efficacious, they need to be improved. In particular, better DIVA vaccines are needed.

15. MOVEMENT RESTRICTIONS AND VACCINATION

Movement restrictions may be used with or without vaccination to limit the spread of CSFV. During the 1997–98 CSF outbreak in the Netherlands, animal transport was prohibited within a 10 km radius of the infected farm.[10] Even empty animal transporters were not allowed movement within this zone. After a testing period of 7 days, to determine the extent of CSF infection within the zone, the transport ban was limited to the movement of pigs and pig manure.[10] Vaccination was not used during this outbreak.

During a 1990s CSF outbreak in Mexico, pigs and pork products were not allowed movement from the endemic control area (where CSF vaccine was mandatory) into either the eradication area (where CSF had been eliminated and vaccine use was prohibited) or CSF-free areas.[149] However, this was difficult to enforce as low market prices in the control areas encouraged smuggling live animals into the eradication area. Vaccine was used in the control areas in Mexico, but if administered incorrectly, vaccinated pigs could have served as a source of infection in the eradication area. Biosecurity remains an important component to any CSF vaccine program. Even with CSF vaccine usage, the virus has spread when good biosecurity practices were not followed.[149]

16. PERMANENT IDENTIFICATION OF VACCINATED ANIMALS

Vaccinated animals must be permanently identified. In the Netherlands, when use of the CSF vaccine was mandatory, animals were identified by ear tags.[102] In Australia, vaccinated animals are to be permanently identified in case a vaccination-to-kill policy is adopted (in which all vaccinated animals would be destroyed).[140] In the U.S., many forms of identification such as ear tattoos, ear notches, and semi-

permanent ear tags are used to identify livestock under normal circumstances. In the event of a CSF outbreak, no method to identify CSF vaccinates has been pre-determined.

17. LOGISTIC AND ECONOMIC CONSIDERATIONS

Summary

The decision to vaccinate must include an assessment of technical feasibility and funding. This includes evaluation of vaccine supply and DIVA tests (if applicable); logistics of vaccine administration; and resources needed for associated activities including individual animal identification, traceability, movement permitting, and serosurveillance to prove freedom from disease.

Many factors can influence CSF transmission and disease response efforts. Cold weather can interfere with proper cleaning and disinfection of vehicles and fomites. Long transport distances could facilitate disease spread. With more than one million swine in trucks on the road every day, CSFV could be easily transmitted over multiple production sites. Swine density in the area of an outbreak can also influence vaccination plans. For example, a large number of vaccine doses would be needed if ring vaccination were to occur in a swine dense area. Feral swine are increasing in numbers across the U.S. The potential contact between feral and domestic swine endangers the health of the domestic herd. If feral swine became infected with CSFV, oral vaccination with a LAV vaccine may be beneficial.

The advantages and disadvantages of vaccination must be weighed against those of depopulation. Considerations include the effect of vaccination on trade and exports, market shocks, potential restrictions on marketing products from vaccinated animals, the types of stakeholders affected (e.g., small-scale operators with limited safety nets vs. large-scale operators), the extent of the outbreak, disruption of tourism, and impacts on local economies.

Consideration should be given to whether genetically irreplaceable stock, endangered species or other unusually valuable animals can be successfully protected with biosecurity measures, and whether vaccination would be beneficial. Their degree of isolation from livestock should be part of this analysis.

According to the OIE, as described in Article 15.2.3, a country or zone may not be considered CSF-free if vaccination against CSF has been carried out in domestic and/or captive wild pigs during the past 12 months (unless there are means of distinguishing between vaccinated and infected pigs).

As stated in Article 15.2.6, the OIE will restore CSF free status to a previously affected country or zone according to the following criteria:

- *When stamping-out without vaccination is practiced:* free status can be restored three months after the last case.
- *When stamping-out with emergency vaccination is practiced:* free status can be restored three months after the last case and the slaughter of all vaccinated animals, OR three months after the last case without the slaughter of vaccinated animals where there are means of distinguishing between vaccinated and infected pigs.

17.1 Technical Feasibility of Vaccination

To conduct a successful vaccination campaign, an effective and safe vaccine must be available, and the vaccine supply (and DIVA test supply, if used) must be sufficient to carry out vaccination in a timely manner to stop or reduce virus transmission.[14] The vaccine administration requirements (e.g., 1 or 2 doses, oral or parenteral, etc.) must be considered, along with the duration of immunity. Vaccination teams must be available to administer the vaccine, and biosecurity guidelines must be followed to prevent

virus transmission. Laboratories must have the diagnostic capacity to identify CSF cases.[14] Slaughter and disposal capacity must be considered if a vaccination-slaughter program is implemented. Additional issues that must be addressed during a vaccination campaign include individual animal identification, traceability, and movement permitting.

17.2 Epidemiological Considerations

17.2.1 Weather

Extreme weather conditions may play a role both in disease transmission and disease response efforts. During the 1997–1998 CSF outbreak in the Netherlands, transportation vehicles were believed to play a role in virus transmission, as approximately 39 farms were infected before measures were taken to eliminate CSFV.[48] The outbreak occurred during the winter months, when extreme cold may have prevented proper vehicle cleaning and disinfection.[48] Cold weather conditions could similarly affect a U.S. CSF response.

17.2.2 Distance

Animal transport distance can play a role in disease spread. In Europe, the introduction of a single common market has led to an increase in the distance pigs are transported.[42] In the U.S., approximately one million pigs are transported daily, some for long distances. Transportation could easily facilitate disease spread within the U.S. The distance animals are transported may influence the numbers of animals to receive the CSF vaccine.

17.2.3 Swine Density

The U.S. has many swine dense areas. If a herd (or herds) in a swine-dense area become infected with CSFV, the vaccination zone may include a large number of animals. The number of vaccine doses required to vaccinate all animals within the zone may itself be a limiting factor. Density of pig herds may also be an important predictor of local transmission. When analyzing the 1997–98 outbreak in the Netherlands, Benard et al.[162] determined a positive association between higher pig densities and local spread of CSFV. Preemptive slaughter can be used to decrease pig density and therefore, local spread.

17.2.4 Feral Swine

The increasing number of feral swine in many parts of the U.S. presents a disease threat to domestic swine. Contact between domestic and feral swine must be prevented. Feral swine have infected domestic swine with CSFV in Germany[53] and Italy.[163] Feral swine can be immunized with oral baits; the practice has been carried out during spring, summer and autumn.[164] During each season, baits are distributed twice at four-week intervals.[164] Appropriate bait location and feral swine hunting bans must be addressed if a feral swine vaccination program is to be successful.[164]

17.2.5 Infection with Other Pathogens

Other pathogens circulating in a swine herd may influence the success of a CSF vaccination program. Suradhat[130] demonstrated that when CSFV vaccinated pigs are co-infected with PRV, and then challenged with CSFV, fatal CSFV infection can result. Suradhat et al.[130] also investigated the possible interference of PRRSV with CSF vaccination and demonstrated when pigs are infected with PRRSV prior to vaccination with C-Strain vaccine, CSF vaccine failure may result.

17.3 Costs Associated with Vaccination

Economic viability plays an important role in the decision to vaccinate. Vaccination results in both direct and indirect costs. The direct costs of vaccination include:

- Investment costs—e.g., vaccine development, vaccine availability, and vaccine delivery infrastructure;[165]
- Variable or recurrent costs including the cost of vaccines and delivery;[165] and
- Costs to identify vaccinated animals, permit their movement, and conduct serosurveillance to prove freedom from disease (in a vaccinate-to-live strategy).

There may also be indirect costs that result from vaccination such as lost productivity (caused by stress to animals), disruptions of agricultural routines, and adverse reactions to the vaccine.[165]

The advantages and disadvantages of vaccination must be weighed against those of depopulation. Blanket vaccination, or inappropriately targeted vaccination, is expensive and there is an increased risk that infected animals will not be detected because clinical signs may be suppressed.[166]

17.4 Vaccination and Market Effects

The overall impact of vaccination on international trade in livestock products, including long term impacts on trade, is an important consideration for CSF. Vaccination is expected to be most beneficial when the outbreak ends sooner, or when vaccination allows the most stringent disease control measures to be carried out in a limited area.[165] It is also expected to be beneficial if it impacts a livestock sector in an area where there will be a limited effect on exports (i.e., zoning will be possible/practical). If the outbreak can be stopped with rapid culling, there is likely to be short-term distress but little long-term effect on livelihoods, especially if indemnity can be provided.[165] However, if culling is more widespread or the disease is out of control, vaccination may save livelihoods.[165]

Vaccination is likely to be most beneficial to livelihoods when it can:

- Provide effective disease control with little depopulation, especially if indemnity is not available for culled animals;[165]
- Prevent national markets from being disrupted or rapidly restore them;[165]
- Minimize other economically important factors such as the disruption of tourism or impacts on local economies;[165] and
- Reduce the time export markets are lost.

Vaccination may be particularly beneficial to small-scale operators whose safety nets are limited.[165] If stamping-out is used, culling may have a minimal effect on the national economy but a significant effect on smallholders and small-scale traders who depend on regular cash flow from agriculture. Although indemnity may be available for depopulated animals, it rarely covers the cost of lost production, time, and cash flow.[165]

Market shocks can result from loss of consumer confidence (decreased demand), very severe culling, or the closing of markets.[165] Unless consumers can be persuaded that products from vaccinated animals are safe, consumer fear can cause market shocks, even when the disease is controlled by vaccination. If export markets are affected by vaccination, domestic markets can also be affected, because animal products that were once exported may be sold within the country, lowering prices.[165] Producers for domestic markets can also be affected by quarantines. If animals are larger than normal weight and/or are released into the market in a short period after quarantine is lifted, prices may be lower.[165] The cost of keeping and feeding animals through the quarantine period should also be taken into consideration.

Modeling of the 1997–1998 CSF outbreak in the Netherlands showed that if vaccination is chosen, vaccination within a radius of 2 to 5 km is preferred to vaccination within a radius of 1 km.[161]

17.5 Effect of Vaccination on OIE Status

According to the OIE, as described in Article 15.2.3, a country or zone may not be considered CSF-free if vaccination against CSF has been carried out in domestic and/or captive wild pigs during the past 12 months (unless there are means of distinguishing between vaccinated and infected pigs). [46]

As stated in Article 15.2.6, the OIE will restore CSF free status to a previously affected country or zone according to the following criteria:

- *When stamping-out without vaccination is practiced:* free status can be restored three months after the last case.
- *When stamping-out with emergency vaccination is practiced:* free status can be restored three months after the last case and the slaughter of all vaccinated animals, OR three months after the last case without the slaughter of vaccinated animals where there are means of distinguishing between vaccinated and infected pigs.[46]

Examples of recent CSF outbreaks and effect of vaccination on OIE status can be found in section 13.

17.6 Vaccination of Special Populations

Consideration should be given to whether genetically irreplaceable stock, endangered species, or other unusually valuable animals can be successfully protected with biosecurity measures, and whether vaccination would be beneficial. Their degree of isolation from livestock should be part of this analysis.

According to Article 5 of European Directive 2001/89/EC,[11] in the EU, if a CSF outbreak affects pigs kept for scientific purposes or if they are a rare breed in a laboratory, zoo, wildlife park, or fenced area, officials may be exempt from killing infected animals. Officials could also include these animals in an emergency vaccination plan request to the European Commission asking that these animals be vaccinated during an outbreak.

18. PUBLIC ACCEPTABILITY OF VACCINATION AS A COMPONENT OF CSF ERADICATION

Summary

Vaccines improve animal health and welfare. Vaccines also improve animal productivity, for the benefit of the producer, as well as food safety and food security for the consumer. Attitudes toward CSF vaccination among the public may be influenced by attitudes toward mass culling, animal welfare concerns, and the acceptability of meat from CSF-vaccinated animals in markets. The public may be less likely to accept withholding CSF vaccine over concern of trade implications.

CSFV poses no known risk of human infection for personnel handling the agent, handling infected animals, eating pork, or carrying out diagnostic tests. CSFV is highly species-specific and under natural conditions, it is capable of infecting only domestic pigs and wild boar.

Procedures have been established by the OIE to inactivate CSFV in pork and pork products. Measures have been recommended to help minimize consumer concerns regarding food from animals vaccinated during an emergency.

In general, the use of vaccines improves animal health and human health by preventing or controlling disease outbreaks. Vaccination also improves animal welfare, increases animal productivity for the benefit of the producer, and reduces food safety and food security concerns for the consumer.[167]

Attitudes toward CSF vaccination among the public may be influenced by attitudes on mass culling and animal welfare concerns, as well as the acceptability of meat from CSF-vaccinated animals in markets. The public may be less likely to accept withholding CSF vaccine over concern of trade implications.[168] There has been intense public criticism when large numbers of apparently healthy animals were culled during some outbreaks, including the 2001 epizootics in the U.K. and the Netherlands. In the 1997–1998 CSF outbreak in the Netherlands, over 7 million head of weaned and slaughter weight pigs were killed for welfare reasons, while over 2 million young pigs between 3 to 17 days of age were euthanized by lethal injection to ease the stress on the rendering system.[10]

An EU survey was conducted in 2004[169] to better understand the view of those involved in the control strategies in countries having experienced outbreaks from FMD, CSF, and avian influenza. During the outbreaks, EU Directive 2001/89/EC was followed, in which vaccination is prohibited unless an emergency vaccination plan is submitted to and approved by the European Commission. The control strategies used were mainly quarantine of infected herds, stop movement of animals in the area, and culling of infected and suspect herds. According to Cohen et al.,[169] stamping-out greatly affected the people directly involved. Owners and workers described clinical signs relating to post-traumatic stress syndrome such as severe stress, loss of self-esteem, and loss of self-confidence. Significant economic losses also occurred.

A Dutch survey was conducted to determine how the meat from vaccinated animals would be viewed by the consumer. Product labeling played a large role in the perception of the consumer. For example, even when meat was identified as coming from vaccinated animals, it was favored when described as "exclusive," "animal-friendly," and "environmentally-friendly." However, meat from vaccinated animals did not perform as well due to concerns of flavor, convenience, and quality. It was concluded that consumers may continue to purchase meat from vaccinated animals, although this can be affected by product presentation.[161]

18.1 Classical Swine Fever Disease as a Zoonosis

CSFV poses no known risk of human infection for personnel handling the agent, handling infected animals, eating pork, or carrying out diagnostic tests.[62] Accordingly, it has a low categorization in health and safety regulations.[62]

18.2 The Use of Meat from Vaccinated and/or Potentially Infected Animals

Consideration should be given to whether meat and other products from vaccinated animals can be used, and whether they will need to be treated (because vaccination might mask the presence of virus) before they are allowed into markets.

Vaccines are used regularly in livestock without adverse effects on human health. CSFV is species-specific and under natural conditions, it is capable of infecting only domestic pigs and wild boar.[170] During the CSF outbreak in the U.K. in 2000, the U.K. Food Standards Agency stated that there were not any food safety implications in their current outbreak. CSF vaccines were used extensively in the U.S. for decades before CSF was eradicated in the 1970s.

If an individual animal tests negative following real-time RT-PCR, it can be excluded as source of infectious fresh meat for a short period of time. Animals may register negative in the very early stages of infection or they may contract infection right after testing. When an animal is vaccinated with a LAV

vaccine, then infected at least 4 days post vaccination, the risk of that carcass carrying infectious CSFV is very low.[124] Animals that are correctly vaccinated and test negative using real-time RT-PCR (after time has passed for an immune response to develop) are unlikely to test positive for CSFV at slaughter.[124]

Modeling indicates an eradication strategy applying correct vaccine usage and compliance may lower the risk of infectious CSFV in fresh meat, compared to the conventional strategy of pre-emptive culling.[124]

18.3 Procedures to Inactivate CSFV in Animal Products

In pork and pork products, CSFV survival varies depending how the product is stored and on the treatments used on processed meat.[62] In frozen pork, CSFV survival times of more than 4 years have been recorded.[59,62] In chilled fresh pork, CSFV has survived up to 85 days.[56-58,62] While little information is available on the survival of CSFV in pork stored at room temperature, artificially contaminated factory-processed abattoir waste held at 20°C (68°F) for 3 weeks was inactivated within 4 days.[62,171]

According to Article 15.2.23 of the OIE Terrestrial Animal Health Code,[46] inactivation of CSFV in meat should be accomplished by one of the following methods:

- *Heat treatment:* in a hermetically sealed container with a Fo value of 3.00 or more (where F is the time needed to inactivate the organism, expressed as thermal death time), OR heat treatment at a minimum temperature of 70°C (158°F), reached throughout the meat;
- *Natural fermentation and maturation:* using an available water (aw) value of not more than 0.93OR or a pH value of not more than 6.0. Natural fermentation and maturation for hams should last at least 190 days and for loins at least 140 days; or
- *Dry curing with salt:* for bone-in Italian style hams, at least 313 days. For bone-in Spanish style pork meat—Iberian hams, at least 252 days; Iberian shoulders, at least 140 days, Iberian loin, at least 126 days; and Serrano ham, at least 140 days.[46]

Procedures have also been established for the inactivation of the CSF virus in skins and trophies (see OIE Terrestrial Animal Health Code Article 15.2.25).[46]

Garbage fed to swine in the U.S. must be cooked. The regulations in 9 CFR §166.7 require that garbage be heated throughout at boiling (100°C or 212°F at sea level) for 30 minutes before being fed to swine. That time and temperature will inactivate CSF virus, FMD virus, and other pathogens.

18.4 Procedures for Marketing Animal Products After Emergency Vaccination

In general, there are increasing concerns among consumers about food safety and purity, and the understanding of the real risks in specific situations may be weak.[172] As reviewed by Scudamore[172], in 2005, the EU Directorate-General for Health and Consumer Protection and the European Food Safety Authority (EFSA) commissioned a survey[173] on the public perception of risk and particularly on food safety. This study, conducted in all EU countries, found that people were most concerned about factors such as pesticide residues, new viruses, bacterial contamination, and unhygienic conditions outside the home. There were also concerns about animal welfare, genetically modified organisms, environmental pollutants, food additives, and other issues. The report did not specifically address vaccination, but it suggests that consumers have a wide variety of concerns about food, with most directed toward issues that are not under the person's control.

Measures that could be taken to minimize consumer concerns, and limit the rejection of food from animals vaccinated during an emergency,[172] include the following:

- Develop a vaccination policy before an outbreak, and determine the conditions under which it would be used;
- Discuss the vaccination policy with all stakeholders. Remind stakeholders that vaccines are used routinely in livestock and poultry for endemic diseases;
- Obtain the support of the public for vaccination and other control policies;
- License vaccines before they will be needed. If a conditional license must be given to an emergency vaccine, consider its effect on consumer concerns. Provide safety information to all stakeholders about the use of such vaccines;
- Do not separately label products from animals vaccinated for CSFV;
- Give unequivocal and authoritative assurance that vaccinated products are safe to eat. This should include statements from national and international independent bodies that consumers respect; and
- Begin communication about CSF vaccines before an outbreak and continue to communicate during the outbreak.

18.5 Public Acceptability of Other CSF Control Strategies

The emotional impact of the destruction of apparently healthy animals should also be taken into consideration.[165] In the U.S., diseases have been controlled effectively in the past by culling infected and exposed animals, but there have been changes in agricultural practices, such as increased herd sizes, which may make the impact greater.[119]

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20. ACKNOWLEDGEMENTS

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Glossary

Adjuvant
A substance added to vaccines to enhance the capacity to stimulate the production of antibodies or cell-mediated immune responses.

Animal Product
Blood or any of its components, bones, bristles, feathers, flesh, offal, skins, and any by product containing any of those components that originated from an animal or bird.

Biosecurity
A series of management practices designed to prevent the introduction of disease agents onto or prevents the spread from an animal production facility.

Buffer Zone
Zone that immediately surrounds an Infected Zone or a Contact Premises.

Cerebellar Hypoplasia
Underdevelopment of cerebellum, the region of the brain that has an important role in motor control.

Cold Chain
The system used to ensure that vaccines stay within an appropriate temperature range from manufacturer to the point of administration.

Containment Vaccination Zone
Emergency Vaccination Zone within the Control Area. This may be a secondary zone designation.

Control Area
Consists of an Infected Zone and a Buffer Zone.

Cull
To voluntarily remove from the herd and sell to a slaughter facility.

Detection of Infection in Vaccinated Animals (DIVA)
A type of vaccine that is marketed with a companion diagnostic kit to detect infection of a natural pathogen in animals vaccinated against that disease.

Ear Tags
Tags, usually plastic, put in animals' ears to identify them. Every producer uses their own numbering system. They can easily be removed.

Efficacy
Specific ability or capacity of the biological product to effect the result for which it is offered when used under the conditions recommended by the manufacturer.

Endemic
Present in a population or geographical area at all times.

Epidemic
An (often sudden) increased number of cases over a broad geographic area.

Euthanasia
Deliberate ending of an animal's life in a manner that causes minimal pain and distress.

Fomite
An inanimate object or material on which disease-producing agents may be conveyed (e.g. feces, bedding, or clothes).

Free Area
Area not included in any Control Area.

Incubation Period
The period of time between infection and the development of clinical signs.

Infected Premises
Premises where a presumptive positive case or confirmed positive case exists based on laboratory results, compatible clinical signs, case definition, and international standards.

Infected Zone
Zone that immediately surrounds an Infected Premises.

Live Attenuated Vaccines (Modified Live Vaccines)
Vaccines that replicate themselves in the host but should produce no or only very mild clinical signs. They induce the animal to mount an immune response that will provide protection from severe disease by the natural pathogen.

Mortality
Death of an animal; dead animals can be referred to as mortalities.

National Veterinary Stockpile (NVS)
Established by Homeland Security Presidential Directive 9 and operational in 2006. Able to deploy large quantities of veterinary resources anywhere in the continental U.S. within 24 hours.

Outbreak
An increased number of cases (above what is expected) from a limited geographic area.

Potency
Relative strength of a biological product as determined by test methods or procedures as established by APHIS in Standard Requirements or in the approved Outline of Production for such product.
Prophylactic Vaccination
Taking measures to prevent disease via administration of vaccination.

Protection Vaccination Zone
Emergency Vaccination Zone outside the Control Area. This may be a secondary zone designation.

Purity
Quality of a biological product prepared to a final form relatively free of extraneous microorganisms and extraneous material (organic or inorganic) as determined by test methods or procedures established by APHIS in Standard Requirements or in the approved Outline of Production for such product, but free of extraneous microorganisms or material which in the opinion of the Administrator adversely affects the safety, potency, or efficacy of such product.

Quarantine
To place animals in strict isolation to prevent the spread of disease.

Rendering
A process of converting animal carcasses into a stable product that can be used for other purposes.

Reservoir
The environment in which a pathogen lives, grows, and multiplies. Can include humans, animals, and the physical environment. The reservoir is often, but not always, the source of infection.

Risk (Risk Pertaining to Infection)
The probability of becoming infected given that exposure to an infectious agent has occurred.

Sensitivity
The proportion of true positives that are detected by a diagnostic test.

Sentinel
A susceptible population, farm, or animal that is repeatedly sampled in order to assess health status over time; the "sentinel" must be representative of the at-risk populations, farms, or animals.

Stamping-out
The killing of the animals which are affected and those suspected of being affected in the herd and, where appropriate, those in other herds which have been exposed to infection by direct animal to animal contact, or by indirect contact of a kind likely to cause the transmission of the causal pathogen.

Suppressive Vaccination
Emergency vaccination conducted both within and around infected zones. Suppressive vaccination can take place throughout a country or compartment; however, this strategy may require large quantities of vaccine and sufficient human resources.

Susceptible Animal
Any animal that can be infected with and replicate the disease pathogen of concern.

Targeted Vaccination
Vaccination of selected animals or populations (e.g., uninfected animals of high value including livestock with valuable or unusual genetic backgrounds, long-lived production animals, zoo animals, or endangered species). Can also be directed at uninfected areas where there is a high density of susceptible animals.

Tracing
Information gathering on recent movements (during a defined time period) of animals, personnel, vehicles, and fomites (both to and from affected farms) to identify potential spread of disease to other livestock premises and to detect a putative source of infection for the affected farm.

World Organization for Animal Health (OIE)
The intergovernmental organization created by the International Agreement of 25 January 1924, signed by 28 countries. As of July 2017, the OIE totaled 181 Member Countries. OIE standards are recognized by the World Trade Organization as reference international sanitary rules. The purpose of the OIE is to guarantee the transparency of animal disease status world-wide.

Zoning
The practice of defining subpopulations of animals on a geographical basis, using natural, artificial, or legal boundaries, for the purpose of disease control (OIE).

Acronyms

Artificial insemination

APHIS
Animal and Plant Health Inspection Service; an agency of USDA

BVDV
Bovine viral diarrhea virus

CFR
Code of Federal Regulations

CSFCWG
Classical Swine Fever Countermeasures Working Group

CSFV
Classical swine fever virus

CVB
Center for Veterinary Biologics; a division of APHIS

DIVA
Detection of infection in vaccinated animals

DOI
Duration of immunity

EFSA
European Food Safety Authority

ELISA
Enzyme-linked immunosorbent assay

EU
European Union

FAT or FATST
Fluorescent antibody test

FAVN

FMD
Foot and mouth disease

GPE
Guinea pig cell-culture-adapted

IBC
Institutional Biosafety Committee

KT
Kemper-Trego

LAV Vaccine
Live attenuated virus vaccine

MAbs
Monoclonal antibodies

MLV
Modified live vaccine

NEPA
National Environmental Policy Act

NPLA
Neutralizing peroxidase-linked assay

NVS
National Veterinary Stockpile

OIE
Office International des Epizooties', currently referred to as the World Organization for Animal Health

PCR
Polymerase chain reaction

PD_{50}
Protective dose fifty

PK
Pig kidney

PRRS
Porcine Reproductive and Respiratory Syndrome

PRV
Pseudorabies virus

qRT-PCR
Quantitative reverse transcription polymerase chain reaction (also known as rRT-PCR, real-time reverse transcription polymerase chain reaction)

rRT-PCR
Real-time reverse transcription polymerase chain reaction (also known as qRT-PCR, quantitative reverse transcription polymerase chain reaction)

RT-PCR
Reverse transcription polymerase chain reaction

USAHA
United States Animal Health Association

USDA
United States Department of Agriculture

VNTs
Virus neutralizing tests