Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 18

Porcine Vaccines

OUTLINE

The basic principles of vaccinating pigs are the same as in other species. Thus for diseases that are threats to growing piglets, injectable vaccines should be administered as soon as maternal antibody titers have waned. This is generally considered to be around three to six weeks of age. These piglets may then need to be boosted two to four weeks later depending on the manufacturer's recommendations. Because maternal antibodies do not interfere with mucosal immunity, oral or intranasal vaccines may be administered much earlier. There are many infections that pose a significant threat to newborn piglets. These are controlled by vaccinating pregnant sows and thus promoting the production of colostral antibodies. It is noticeable that many pig vaccines appear to take a long time to induce protective immunity. Examples include the vaccines against foot-and-mouth disease, *Lawsonia intracellularis*, and porcine respiratory and reproductive syndrome (PRRS) (Tables 18.1 and 18.2).

Vaccine Administration

INJECTION

As always, it is essential to follow the manufacturer's recommendations regarding administration route, dose, and any withdrawal period. Vaccines given in an inappropriate manner or in the wrong place can trigger injection site reactions and carcass blemishes. As a result, subcutaneous vaccines should be administered, preferably behind the ear, using a short 12-mm, 18-gauge needle. Pigs must be restrained firmly to prevent needle breakage. If an intramuscular injection is required, a 38-mm, 18-gauge needle will be required for sows and gilts. For suckling pigs, a short 12-mm needle is adequate for injecting into muscle. The neck is the preferred site for intramuscular injections. It is important to ensure that the intramuscular vaccine is injected into the muscle, not into the subcutaneous fat. Multiple vaccines may be given on the same day but the injections should be given at different sites. When using a bottled multidose vaccine, a sterile needle should be used to withdraw the vaccine into the syringe, whereas another needle is used to inject the pig. Only healthy pigs should be vaccinated.

NEEDLE-FREE INJECTION

Swine producers are increasingly using needle-free injection devices, such as high-pressure jet injectors to improve vaccination speed and safety, and to minimize carcass quality issues arising from injection site lesions (Fig. 18.1). Use of these transdermal devices has many advantages

TABLE 18.1 ■ **Vaccination of Piglets Under 6 Months of Age**

Vaccine	Vaccine Timing	Comments
Antibacterial Vaccines		
Swine erysipelas	Vaccinate with 2 doses, 3–4 weeks apart beginning at 6–8 weeks of age.	An oral vaccine can be given to piglets over 8 weeks of age. Withdrawal time 21 days.
Colibacillosis	An oral vaccine may be given in the drinking water before weaning to prevent postweaning scours. To prevent edema disease, vaccines are administered in drinking water to piglets over 18 days.	Most vaccines against colibacillosis are given to sows before farrowing. Withdrawal time 21 days.
Mycoplasmal pneumonia	Vaccinate healthy piglets over 3 weeks of age. Revaccinate 2–3 weeks later.	There is also a single dose vaccine available given at 3 weeks of age. Semiannual revaccination is recommended for some vaccines. Withdrawal time 21 days.
Atrophic rhinitis (Bordetella)	Vaccinate intranasally within 1–3 days of age. The precise timing depends on the vaccine.	Withdrawal time 21 days.
Pleuropneumonia *Actinobacillus pleuropneumoniae*	Vaccinate at weaning (4–5 weeks) and 3–4 weeks later.	A third dose may be administered in the case of an outbreak or an imminent threat. Withdrawal time 21 days.
Porcine proliferative enteritis	Vaccinate piglets over 3 weeks of age with a single intramuscular dose. Oral vaccines are administered in drinking water to piglets over 3 weeks of age.	Withdrawal time 21 days.
Glasser's disease *Haemophilus parasuis*	Vaccinate piglets over 5 weeks of age and boosted 2–3 weeks later.	Some vaccines may be given at 7–10 days. Withdrawal time 21 days.
Salmonellosis	Drinking water vaccine given to piglets over 2–3 weeks of age. Injectable, given to piglets over 3–5 weeks of age. Intranasal may be given to piglets over 1 day of age.	Withdrawal time 21 days.
Streptococcus suis	Vaccinate piglets at 3 and 5 weeks of age if the sow has not been vaccinated.	Withdrawal time 21 days.
Antiviral Vaccines		
Porcine parvovirus	Vaccinate with 2 doses, 3–5 weeks apart with the second dose 2–4 weeks before breeding.	Revaccinate annually before breeding. Revaccinate boars semiannually. Withdrawal time 21 days.
Pseudorabies	Vaccinate piglets 1–7 days old intranasally, followed by intramuscular vaccination of all the other pigs on the farm.	Revaccinate breeding animals semiannually. Withdrawal time 21 days.
Porcine circovirus	Vaccinate at 3 weeks of age, revaccinate at 6 weeks. Some producers prefer 1 and 3 weeks of age or even at 2 and 4 weeks.	Withdrawal time 21 days.

TABLE 18.1 ■ **Vaccination of Piglets Under 6 Months of Age** (Continued)

Vaccine	Vaccine Timing	Comments
Porcine respiratory and reproductive syndrome virus	Vaccinate piglets over 3 weeks of age with a single dose. Another such vaccine may be given at 1 day of age. The autogenous intranasal vaccine may be administered at 7–10 days and at weaning (3 weeks).	Boosted semiannually. Withdrawal time 21 days.
Porcine epidemic diarrhea	Vaccinate piglets over 3 weeks of age and revaccinate 3 weeks later.	Withdrawal time 21 days.
Influenza	Vaccinate piglets over 3–5 weeks intramuscularly, followed by a second dose 2–3 weeks later. Vaccinate piglets over 1 day of age. intranasally.	Revaccinate semiannually. Withdrawal time 21 days.
Rotavirus	Vaccinate with the oral or injectable vaccine at 7–10 days preweaning.	If using the oral vaccine do not return the piglet to the sow for at least 30 minutes. Withdrawal time 21 days.

These tables are examples of consensus vaccination programs. Individual programs are variable and will reflect animal health, local environmental and housing conditions, severity of challenge, and disease prevalence, in addition to professional judgment. Be sure to follow the manufacturer's recommendations on the label.

TABLE 18.2 ■ **Vaccination of Adult Pigs**

Vaccine	Vaccine Timing	Comments
Antibacterial Vaccines		
Swine erysipelas	Vaccinate gilts and boars at 6.5 months or older and boosted 3–4 weeks later. Sows should be boosted on the day of weaning before rebreeding. Alternatively, pigs should receive 2 doses 3–5 weeks apart, with the second dose 2–4 weeks before breeding.	Withdrawal time 21 days.
Colibacillosis	Vaccinate gilts and sows 5 and 2 weeks before farrowing. Timing depends upon the brand of vaccine; two doses are given 4–8 weeks and 2–3 weeks before farrowing. In second or subsequent pregnancies a single dose may be given 2–3 weeks before farrowing.	Withdrawal time 21 days.
Leptospirosis	Vaccinate breeding pigs including boars, twice 4–6 weeks apart. Revaccinate every 6 months. Any new boars and gilts entering the breeding herd also need to be vaccinated. Do not vaccinate periparturient sows.	Withdrawal time 21 days.
Atrophic rhinitis (Bordetella)	Vaccinate sows about 2–5 weeks before farrowing.	Withdrawal time 21 days.

Continued on following page

TABLE 18.2 ■ **Vaccination of Adult Pigs** (Continued)

Vaccine	Vaccine Timing	Comments
Clostridial dysentery	Vaccinate sows 2–6 weeks before farrowing. Revaccinate sows before each subsequent farrowing.	Withdrawal time 21 days.
Pleuropneumonia	Revaccinate annually or semiannually.	Withdrawal time 21–60 days.
Glasser's disease	Vaccinate feeder pigs on arrival and boost 2 weeks later.	Withdrawal time 21 days.
Streptococcus suis	Vaccinate gilts and sows 5 and 2 weeks before farrowing.	Withdrawal time 21 days.
Antiviral Vaccines		
Porcine parvovirus	Vaccinate breeding sows and boars 3–4 weeks apart. Sows should be boosted at each weaning. Boars should receive 6 monthly boosting.	Withdrawal time 21 days.
Pseudorabies	Vaccinate sows and piglets intranasally when 1–7 days old, followed by intramuscular vaccination of all the other pigs on the farm.	Withdrawal time 21 days.
Porcine respiratory and reproductive syndrome virus	Vaccinate sows and gilts 3–4 weeks before breeding or during pregnancy to prevent the reproductive form of the disease.	Withdrawal time 21 days.
Porcine epidemic diarrhea	Vaccinate pregnant sows, 5 and 3 weeks before farrowing.	In subsequent pregnancies give a single dose 2 weeks before farrowing.
Influenza	Vaccinate healthy breeding pigs in 2 doses 3–5 weeks apart. Revaccinate 2–4 weeks before breeding.	Revaccinate boars semiannually and sows annually before breeding. Withdrawal time 21 days.
Transmissible gastroenteritis	Vaccinate sows and gilts orally with two doses 3–5 weeks before farrowing and boost with the intramuscular (IM) vaccine one week before farrowing. Otherwise give the IM vaccine 5 and 2 weeks before each farrowing.	Prime with the oral vaccine and boost with an intramuscular vaccine. Withdrawal time 21 days.
Rotavirus	Used with transmissible gastroenteritis. Vaccinate sows 2–5 weeks before farrowing.	Prime with the oral vaccine and boost with an intramuscular vaccine. Withdrawal time 21 days.

These tables are examples of consensus vaccination programs. Individual programs are variable and will reflect animal health, local environmental and housing conditions, severity of challenge and disease prevalence in addition to professional judgment. Be sure to follow the manufacturer's recommendations on the label.

Fig. 18.1 A high-pressure jet injector used to vaccinate pigs. This instrument is powered by either compressed air or liquid CO_2. It delivers a vaccine dose of 0.1ml to 0.5ml. (Courtesy of Pulse NeedleFree Systems, Inc.)

Fig. 18.2 The use of a high pressure jet injector in piglets is less traumatic, less painful, and reduces injection site lesions when compared with syringe and needle injections. (Courtesy of Pulse NeedleFree Systems, Inc.)

including improved safety as a result of the following: elimination of broken needles and accidental needle sticks; required needle disposal and consistent vaccine delivery; reduced vaccine volume, greater antigen dispersion, faster administration, and reduced pain and distress. As described in Chapter 8, these high-pressure jet injectors permit the vaccine antigen to penetrate the epidermis and dermis. They require one-half to one-tenth of a conventional dose of vaccine administered by syringe because of the widespread antigen dispersion and its subdermal location. Disadvantages include the start-up cost of equipment, its infrastructure (especially if using a high-pressure CO_2 gas supply), its maintenance, the required operator training, and some uncertainty as to the dose of antigen delivered. Newer devices have disposable nozzle faces that can be changed when necessary and when used in different farms. These devices therefore have the advantage of preventing the spread of infection that results from needle use. Transdermal jet injectors are best used at sites where the skin is thin, soft, and hairless. They should not be administered over bone or thick fat. In piglets the best site is the neck (Fig. 18.2).

PRRSV, porcine circovirus type 2 (PCV2), and *Mycoplasma hyopneumoniae* vaccines designed specifically for transdermal administration have been licensed in Europe.

ORAL VACCINATION

Although vaccines have traditionally been administered by subcutaneous or intramuscular injection, the growth of large pig growing enterprises has stimulated a switch to other methods of mass vaccination. Oral vaccination is increasingly used in swine operations. Individual animals may be drenched, but delivery through the watering system is preferred. The vaccine is added to the water delivery system to deliver the correct antigen dose to each pig. Generally, water is withheld from the pigs for one to two hours before vaccination depending on environmental conditions. All medications, sanitizers, and disinfectants must be removed from the drinking water first. Likewise, the system must be flushed with nonchlorinated water beforehand. Antibiotics or other antimicrobials should not be used from three days before to three days after vaccination (total seven days). However, a nonmedicated week is ideal after vaccination. The lines from the vaccine container to the furthest spigot or pen drinker must be precharged with vaccine solution. The amount should be such that the pigs receive the correct vaccine dose within four hours.

To accurately add the correct dose of vaccine to the water supply, a proportioner is used. This is a device that accurately feeds a measured amount of vaccine solution into the water supply. Before administering the vaccine, it is essential to calibrate the proportioner by measuring the flow-rate of water through the device for the same period and with the same pigs to be vaccinated to ensure that each pig receives an appropriate dose of vaccine. Alternatively, the vaccine solution can be added to the water line using a peristaltic pump, which will also require calibration. If these are not available, the vaccine may be added to a measured amount of water in a trough.

To ensure that the vaccine remains stable in the drinking water, it is common to add a stabilizer. In most cases thiosulfate blue is used to neutralize any chlorine. Skimmed milk may be used if thiosulfate blue is not available. The blue dye or the milk also indicates the presence of the vaccine in the water.

Antibacterial Vaccines

SWINE ERYSIPELAS

Erysipelothrix rhusiopathiae causes diamond skin disease in addition to arthritis, heart disease, and abortion. Vaccines available include both bacterins and attenuated live products. The immunity produced by these bacterins is relatively short lived, usually lasting no longer than one year and sometimes considerably less. For instance, a formalin-inactivated erysipelas bacterin protects for only four to five months, and breeding stock should therefore be revaccinated every six months. Modified live vaccines are available for use in breeding herds. Some brands may be given orally. However, the modified live strains may spread to other, unvaccinated pigs and reversion to virulence is a concern. It is also essential that piglets not be vaccinated before maternal antibody titers have waned. This is generally assumed to be around three to six weeks. Any earlier and maternal antibodies may block their responses. Vaccination failures are multifactorial and may occur in response to improper handling of vaccine, management stress, and occasionally as a result of strain specific antigenic differences. There is usually good cross-protection between different bacterial serotypes.

COLIBACILLOSIS

Escherichia coli is probably the commonest cause of severe scouring in newborn, suckling, and weaned piglets. The currently available vaccines in the United States are either bacterins or bacterin-toxoids (inactivated *E. coli* enterotoxins). The vaccines are given to gilts and sows before farrowing to ensure that newborn piglets receive high-titered colostral antibodies. Timing depends upon the specific vaccine used. Because this type of procedure depends upon the piglets receiving colostrum, it will not work if a piglet does not suckle or the sow lactates poorly. Failure of passive transfer is always a risk in these situations.

ATROPHIC RHINITIS

Atrophic rhinitis is characterized by nasal discharge, shortening and twisting of the snout, and atrophy of the turbinate bones. Two forms of the disease are recognized. A severe form is caused by toxigenic strains of *Pasteurella multocida,* either alone or in combination with *Bordetella bronchiseptica*. A milder form is caused by *B. bronchiseptica* alone. Several adjuvanted whole cell *B. bronchiseptica* bacterins together with toxigenic or nontoxigenic strains of killed *P. multocida* or a *P. multocida* toxoid are available. The *P. multocida* bacterins are usually of capsular type D, but some also contain capsular type A. Live attenuated vaccines containing *B. bronchiseptica* are also available. Bacterins containing *B. bronchiseptica* alone are not effective in preventing the severe form of the disease but may be of use in controlling the milder form. These vaccines do not

prevent nasal colonization by these bacteria. The most important *P. multocida* antigen is a toxin. As a result, *P. multocida* toxoids are highly protective. However, the level of toxoid present in some bacterins may be insufficient to produce an effective antitoxin response. Unfortunately, toxoid purification also adds to the cost of product. Recombinant toxoids have been shown to be very effective and a DNA-plasmid vaccine containing the toxoid gene also works well.

LEPTOSPIROSIS

Leptospira infections in pigs give rise to a chronic carrier state and pigs then shed the organisms in their urine. The predominant species include *Leptospira interrogans* serovars Pomona, Icterohemorrhagiae, Canicola, Hardjo, and Bratislava; *L. borgpetersenii* serovar Hardjo-bovis and *L. kirschneri* serovar Grippotyphosa. The two most common serovars in swine leptospirosis are Pomona and Bratislava. Pigs are also the maintenance hosts for serovar Bratislava. Leptospirosis rarely causes acute disease but results in infertility, sporadic abortions, stillbirths, weak piglets, and increased piglet mortality. All available Leptospira vaccines are therefore combined bacterins containing multiple serovars. These bacterins may be combined with erysipelas in a single dose vaccine (Farrowsure B, Zoetis). Vaccination will not eliminate the carrier state. As discussed in other species, immunity to Leptospira is short lasting and requires frequent re-boosting.

CLOSTRIDIAL DYSENTERY

Clostridium perfringens type C causes fatal necrohemorrhagic enteritis in piglets under three weeks of age. A type C specific toxoid may therefore be given to sows three to six weeks before farrowing to provide maternal immunity to piglets. An antitoxin is effective if given to piglets within two hours of birth.

MYCOPLASMAL DISEASES

Mycoplasma hyopneumoniae causes porcine enzootic pneumonia, a highly contagious chronic respiratory disease that causes enormous economic losses worldwide. It damages the respiratory tract so that animals develop secondary bacterial and viral infections such as porcine pleuropneumonia. This infection is especially harmful when it occurs in association with immunosuppressive viruses such as porcine respiratory and reproductive system virus or porcine circovirus-2. The control of enzootic pneumonia is mainly based on management and vaccine-induced protection. Inactivated whole bacterial vaccines are most widely employed. These bacterins may be given to piglets and to introduced growers and breeders. They prevent or reduce the severity of lung lesions while improving daily weight gain. A modified live vaccine (*Mhp*-168 strain) attenuated by more than 300 serial passages *in vitro* is used in China and may provide superior protection. A bacterin is also available against *Mycoplasma hyorhinis* a cause of arthritis, pericarditis, and peritonitis in pigs.

PORCINE PLEUROPNEUMONIA

Actinobacillus pleuropneumoniae is a major pig pathogen that causes a highly contagious severe necrotizing hemorrhagic pneumonia with high mortality. Animals that survive, fail to thrive and become asymptomatic carriers. It causes significant losses to the pig industry. Effective vaccination is difficult because of the existence of two different biotypes and 16 different serotypes based on their capsular antigen structure. The predominant serotypes vary internationally. Killed, whole cell bacterins have been widely employed, but the protection afforded is inconsistent and is generally serotype specific. These bacterins, at best, reduce mortality but do not prevent infection or even the development of lesions.

Studies on the pathogenesis of porcine pleuropneumonia show that the organism releases soluble exotoxins called Apx toxins that play a central role in disease pathogenesis. Bacterins do not contain these Apx toxins, a factor that might partially explain their lack of efficacy. Vaccines are available in some countries that incorporate three inactivated exotoxins, Apx I, II, and III. These vaccines reduce pleuritis, mortality, and lung lesions while improving daily weight gain. They do not prevent clinical disease. Other important antigens include the outer membrane proteins and pilus proteins. A 42 kDa outer membrane protein is used in combination with the Apx toxins in some vaccines (Porcilis APP, Merck and Pleurostar APP, Novartis).

Currently only bacterins containing serotypes 1, 5, and 7 are available in the United States. Because of strain specificity, the serotype present on a farm should first be identified by culture and serology before deciding on vaccination. This situation is thus one in which the use of autogenous vaccines should be considered.

SALMONELLOSIS

Salmonellae are facultative intracellular bacteria. As a result, cell-mediated immunity is more important than humoral immunity. Nevertheless, many Salmonella bacterins have been developed. Some may contain more than one serovar. The organisms are killed with formaldehyde and then adjuvanted with aluminum hydroxide or mineral oil. Attenuated live vaccines are available in some countries. A live attenuated strain of *Salmonella choleraesuis* is available that can be administered intranasally or in drinking water.

LAWSONIA ENTEROPATHY

Lawsonia intracellularis is an obligate intracellular bacterium that causes either acute disease (proliferative hemorrhagic enteritis) or a chronic disease (porcine proliferative enteropathy). It occurs in grower and finisher pigs 3 to 12 months of age and can cause significant losses. The organism causes an increase in the thickness of the intestinal wall because of hyperplasia of infected enterocytes. The acute disease results in "ileitis" that results in enterocyte necrosis, bloody diarrhea, and sudden death. In the chronic form, disease symptoms such as lethargy, chronic enteritis, and weight loss develop progressively in weaner and grower pigs. Natural infection with *L. intracellularis* stimulates effective immunity.

Two types of vaccines are currently available. An inactivated intramuscular vaccine may be given to piglets over three weeks of age. Alternatively, modified-live oral vaccines may be administered in drinking water, drenched, or in liquid feed. These should not be administered before three weeks of age because of maternal antibodies. As with all live bacterial vaccines, antibiotics should be withheld before and after vaccination. These vaccines are reconstituted in an appropriate volume of drinking water. They should be consumed within four to six hours of thawing the vaccine. There is little or no fecal shedding of the vaccine strain. This live vaccine does not appear to induce strong immunity, nevertheless antibodies to the *Lawsonia* autotransporter A (LatA) protein in addition to the flagellae and the bacterial hemolysin have been found in the serum of vaccinated pigs. It is believed that immunoglobulin A (IgA) mediates most protection, but cell-mediated responses also contribute. It takes three to four weeks before immunity develops. The vaccine does not prevent infection and additional management interventions need to be employed to control the infection on a farm. Fecal shedding and clinical disease severity are reduced, although weight gain is improved in vaccinated pigs.

GLASSER'S DISEASE

Haemophilus parasuis causes systemic disease characterized by polyserositis, polyarthritis, and meningitis. Infection is controlled by a bacterin directed against serovars 4, 5, and 13. Thus the

serovar present on a farm should be identified before using the vaccine. This vaccine may be combined with *Mycoplasma pneumoniae* vaccine.

STREPTOCOCCUS SUIS

Streptococcus suis is a zoonotic pathogen that causes septicemia, pneumonia, meningitis, arthritis, and acute death. There are multiple serotypes of this organism, but serotype 2 is the most virulent and significant. Bacterins are available but do not induce protection against heterologous strains. Subunit vaccines may also contain a virulence factor, suilysin, plus a muramidase-released protein and an extracellular protein factor. They are effective against most homologous and heterologous strains. However, these antigens are not conserved in all strains. Reverse vaccinology analysis has identified other conserved extracellular proteins that may serve as protective antigens.

Antiviral Vaccines

PORCINE PARVOVIRUS

Porcine parvovirus is common in pigs and is a major cause of reproductive failure in sows resulting in early death, mummified piglets, and infertility. It was initially called SMEDI (Swine Mummification, Embryonic Death, and Infertility). Because the infection is so common the main method of control is early vaccination. An inactivated vaccine may be given to breeding pigs before first breeding. Parvovirus vaccine is also available in combination with erysipelas and leptospirosis bacterins.

PSEUDORABIES

Also called Aujesky's disease, pseudorabies is a severe neurologic disease of pigs caused by Suid herpesvirus-1 (SuHV-1). Pigs are its natural hosts, and the virus can survive latently in them. It can also cause lethal disease in ruminants, carnivores, and rodents. Vaccination must be used as part of a comprehensive disease control program. The use of continuous large-scale vaccination using DIVA vaccines has permitted the detection and removal of pigs infected with a wild-type virus. As a result, the disease has been eradicated from Canada, the United States, Mexico, many countries in Western Europe, and New Zealand. This remarkable success can serve as a model for the eradication of other diseases through the use of genetically engineered marker vaccines employing a DIVA diagnostic strategy.

The earliest pseudorabies vaccines consisted of inactivated or modified live products. As expected, the attenuated live vaccines were more effective than the killed products and they were well attenuated. Hence, they were considered very safe for application but were not DIVA compatible making eradication challenging. They protected pigs from clinical disease and decreased viral shedding, but they did not induce sterile immunity nor prevent latent infections.

These early attenuated strains, designated the Bartha or K-61 strain and the BUK (Norden) strain were used in many vaccines. Genetic sequencing revealed that both were missing a large gene segment the gene for viral glycoprotein (g)E and the Bartha strain was also missing an additional gene encoding gI. Passage of a field strain in cell culture in the presence of the mutagen bromodeoxyuridine, also resulted in loss of virulence as a result of a deletion in the virus's thymidine kinase (TK) gene.

With this knowledge, a genetically engineered TK-negative mutant became the first licensed genetically modified vaccine. Other deletion mutants soon followed. These deletions usually involved gE and gI, but gG- and gC-deleted strains have also been produced. Because these major antigens are missing, it was soon recognized that these could form the basis of a DIVA strategy.

Antibodies to gE present in wild viral strains are relatively easy to detect. Countries seeking to eradicate pseudorabies employ gE-deleted vaccines. Commercial ELISA kits are available to test for antibodies to gE. Currently in the United States there is a single modified live vaccine available with gI and gX deletions. It can be given intramuscularly or intranasally. The modified live vaccine (MLV) multiplies at the site of inoculation and in regional lymph nodes. The lack of thymidine kinase ensures that the virus will not survive in nervous tissue. It is administered after maternal immunity has waned followed by semiannual revaccination. Breeding herds should be vaccinated quarterly. Some current vaccines appear to be ineffective against variant SuHV-1 viruses that have recently emerged in China.

PORCINE RESPIRATORY AND REPRODUCTIVE SYNDROME

Porcine respiratory and reproductive syndrome (PRRS) is the most significant cause of pig infectious disease losses worldwide and the most economically significant disease affecting US pig production. It has been estimated that it causes economic losses in the United States alone of about US$664 million per year or up to US$156 per litter. It has been especially devastating in China and Southeast Asia.

PRRS viruses (PRRSV) are small, enveloped, single-stranded, positive-sense RNA viruses belonging to the family *Arteriviridae*. There are two distinct genotypes, the European (type 1), and the North American (type 2) with about 60% genetic identity between them. These two genotypes have been classified as two different species in the genus *Porartevirus,* PRRSV-1, and PRRSV-2. They cause clinically identical diseases. However, because these RNA viruses do not replicate faithfully, they generate a "mutant swarm" of diverse variants within each genotype. As a result, it has proven very difficult to produce effective broad-spectrum vaccines. For example, four distinct lineages are associated with PRRSV-1, and ten lineages have been identified within PRRSV-2. Recombination can occur between these lineages. Most isolates from North and South America, and Asia belong to PRRSV-2.

PRRSV infection is restricted to cells of the monocyte-macrophage lineage including dendritic cells. As their name implies, the PRRSVs cause a syndrome characterized by reproductive failure, infertility, abortions, anorexia, and secondary pneumonia. When they invade the respiratory tract, they kill alveolar macrophages, and as a result are immunosuppressive. This suppression of the immune defenses within the lungs results in an increase in secondary bacterial pneumonia. It takes about 32 weeks for T cells to produce interferon in PRRSV-infected pigs. This is exceedingly slow and is attributed to virus-mediated immunosuppression and excessive regulatory T cell activity. T cell memory is also very poor after revaccination. Conversely, when PRRSVs infect neonatal piglets, they develop polyclonal B cell activation, autoimmunity, enlarged lymph nodes, and hypergammaglobulinemia (a 100- to 1000-fold increase in immunoglobin G). Cell-mediated responses and virus-neutralizing antibodies to PRRSV do not develop for several weeks after challenge as a result of loss of $CD4^+$ helper T cells. Because of this, PRRSV can cause persistent infections lasting for up to six months. The ongoing mutations and constant emergence of new PRRSV variants as they adapt to existing immunity ensures that vaccines are of limited usefulness.

Inactivated PRRS vaccines have been licensed worldwide. They do not induce detectable antibodies and stimulate a very weak cell-mediated responses. When used in growing pigs and boars, these vaccines fail to reduce the duration of viremia, virus shedding in semen, and respiratory signs after virulent challenge. The benefits of inactivated vaccines are more obvious when given to infected animals where they improved reproductive performance, for example, increased farrowing rate, number of weaned pigs, and the health status of piglets born to vaccinated sows. Thus they act as therapeutic vaccines rather than preventative ones. More recently, an intranasal vaccine (Barricade PRRSV, Aptimmune), containing poly (lactic)-co-glycolic acid nanoparticle-entrapped inactivated autogenous PRRSV vaccine, together with a whole cell *Mycobacterium*

tuberculosis lysate as the adjuvant, has been shown to induce cross-protective immunity against heterogeneous strains.

Modified live PRRSV vaccines have been licensed in several countries. Those in the USA have been developed from the North American, PRRSV-2, whereas the European vaccines contain PRRSV-1. These MLV-PRRSV vaccines elicit relatively weak innate, humoral, and cell-mediated responses. PRRSV-specific antibodies appear at about two weeks, and peak around four weeks after vaccination. Most of these antibodies, however, are directed against the viral N (nucleocapsid) proteins and have no neutralizing activity. Neutralizing antibodies appear about four weeks after vaccination and demonstrate relatively low titers.

The MLV-PRRS vaccines reduce deaths, and piglets born to vaccinated gilts had a higher body weight and improved survival at weaning than those born to nonvaccinated gilts. In PRRSV-infected sows, MLV vaccines reduce abortions and hasten the rate of return to estrus and increase the farrowing rate and the number of weaned pigs. In growing pigs, the MLV-PRRSV vaccines reduce viremia, respiratory signs, and improve growth performance.

Protection conferred by PRRSV-1 vaccine does not protect against PRRSV-2 challenge and vice versa.

One major concern regarding the use of MLV-PRRSV vaccines is their potential for shedding and the development of persistent infections. Vaccinated pigs may develop a viremia for up to four weeks after immunization. As a result, reversion to virulence may possibly occur. This may occur through mutations of the vaccine virus and/or recombination with wild-type virulent PRRSV strains. The reverted vaccine virus may cause both reproductive and respiratory disease and affect growth performance. Piglets born to these infected sows may become carriers and shed the virus. In addition, MLV-PRRS vaccinated boars can spread the virus in semen to naïve animals.

Another cause for concern is the potential for antibody-mediated enhancement. Nonneutralizing antibodies can enhance macrophage uptake of either the vaccine virus or a circulating heterogeneous virus. This probably accounts for the polyclonal B cell activation.

In an effort to control PRRS in Denmark in late 1996, pigs were vaccinated against PRRSV-2. Unfortunately, the virus in this introduced vaccine reverted and as a result both PRRSV species now circulate within Danish pigs. Because of the immunosuppressive effects of the vaccine virus, it may also reduce the efficacy of other pig vaccines.

DNA, subunit, and virus-vectored PRRSV vaccines are under development. All appear to suffer from the problem of the great antigenic heterogeneity of PRRSV so it will be important to identify broad neutralizing epitopes. Alternatively, chimeric vaccines containing multiple epitopes may broaden cross-protection.

PORCINE EPIDEMIC DIARRHEA

Porcine epidemic diarrhea virus (PEDV) is a positive sense single-stranded RNA alphacoronavirus that causes acute watery diarrhea, vomiting, anorexia, dehydration, and death in neonatal piglets. It first appeared in the United States in 2013. It has since spread to Canada. Mortality may reach as high as 80% to 100%, and it has been estimated that it has caused a 10% loss in the US pig population. PEDV can also cause diarrhea, agalactia, and infertility in sows. Multiple mutant strains are continuing to emerge, a feature that is causing problems with currently available vaccines in addition to creating a constant demand for new vaccines. Because of the early onset of this disease, maternal immunity is critically important. Vaccination of sows is the most widely employed protective procedure. The virus spike (S) protein is required for the virus to bind to host cell receptors. This highly variable virus protein is the most antigenic and the target of neutralizing antibodies. Variations in the S gene and thus the epitopes on the S protein have significant effects on its virulence and antigenicity. PEDV is a type I enteropathogenic virus that infects villous enterocytes and can be suppressed by local mucosal immune responses.

Multiple commercial PED vaccines have been developed, especially in Asia. They include inactivated and modified live products. They may be combined with transmissible gastroenteritis virus (TGE) and rotavirus vaccines. Two inactivated PED vaccines are available in the United States. One is an adjuvanted inactivated whole virus vaccine containing both the S- and M-proteins for prefarrowing vaccination of pregnant gilts and sows. The other inactivated vaccine contains the S-protein only and is not adjuvanted. It is also given to sows before farrowing. Studies have shown that administering the vaccine to sows in the early stages of pregnancy works equally well.

Modified live PED vaccines that have been attenuated in tissue culture have been widely used in Asia. For example, a trivalent, PEDV, TGEV and porcine rotavirus vaccine is used in China. They may reduce mortality but the most highly attenuated vaccines do not appear to prevent virus shedding after challenge. In an effort to improve vaccine efficacy multiple different vaccines may be used. Both live and killed vaccines can be administered in series such as live-killed-killed or live-live-killed-killed. The difficulty is compounded by the continual emergence of new virus strains. Oral attenuated vaccines are available in South Korea and the Philippines for use in sows. This makes good sense because one is seeking to induce high colostral and milk antibody levels. The MLV-PED vaccines reduce mortality in piglets born to orally vaccinated sows, but do not prevent infection or viral shedding.

An alphavirus replicon RNA vaccine against PED has been provisionally licensed by US Department of Agriculture (USDA) (Chapter 6). It is derived from a Venezuelan equine encephalitis replicon expressing the PEDV spike gene.

TRANSMISSIBLE GASTROENTERITIS

Transmissible gastroenteritis (TGE) is an enteric disease of pigs caused by an alphacoronavirus related to PEDV. A respiratory variant, porcine respiratory coronavirus is not a primary pathogen but is associated with the pig respiratory disease complex. TGEV multiplies in the intestinal enterocytes and causes villous atrophy and enteritis. Unlike PEDV, the prevalence of TGE is declining, as is the market for TGE vaccines. Both modified live and inactivated vaccines have been licensed in the United States. The inactivated vaccines are given to nursing or weaned piglets by intramuscular injection. They do not induce a strong protective response against acute disease but are useful in controlling low-level enzootic infections.

Modified live vaccines may be used in pregnant sows to induce maternal immunity or in nursing or weaned piglets to induce active immunity. Unfortunately, these vaccines do not stimulate a strong IgA response because they do not replicate sufficiently within enterocytes.

Other Important Vaccines

SWINE INFLUENZA

Influenza in pigs is a highly contagious disease characterized by fever, coughing, sneezing, nasal discharge, lethargy, and depressed appetite—just like humans. It is caused by an influenza A virus of the *Orthomyxoviridae* family (IAV-S). Morbidity is very high but mortality is low. It causes a significant reduction in the growth rate of affected pigs and contributes to the porcine respiratory disease complex. It is potentially zoonotic. Currently H1 and H3 subtypes are circulating associating with N1 and N2 neuraminidases (H1N1, H1N2, and H3N2). However, within each virus strain are diverse antigenic subtypes. The hemagglutinin (HA) is the major target of neutralizing antibodies and hence a key vaccine component. Only inactivated adjuvanted IAV-S vaccines are currently available in North America. Some may contain a single viral strain whereas others

may contain two or three strains. An intranasal nanoparticle adjuvanted autologous vaccine is now available in some US states. There is also an alphavirus replicon RNA vaccine available (Chapter 6). Many of these vaccines are available in combination with other antigens. They generally prevent clinical disease but may not be able to prevent viral shedding.

A complicating factor to be considered in influenza vaccination is vaccine-associated enhanced respiratory disease. Thus when pigs are vaccinated using an oil-adjuvanted whole inactivated virus vaccine, and subsequently challenged with a homotypic but antigenically mismatched influenza virus, they may develop greater lung damage. In these cases, the vaccine induced antibody binds to, but fails to neutralize, the challenge virus. Thus immune-complex mediated damage occurs in addition to the virus-induced damage.

CLASSICAL SWINE FEVER (HOG CHOLERA)

Classical swine fever (CSF) is a highly contagious disease caused by a pestivirus in the family *Flaviviridae,* which is closely related to the bovine diarrhea viruses and sheep border disease virus. In acute outbreaks clinical signs are nonspecific with high fever and depression, diarrhea, or constipation, ataxia, paralysis, or convulsions. Most affected pigs die within 3 weeks.

CSF was eradicated from the United States in 1976. It currently exists in Central and South America, Asia, and sporadic outbreaks continue to occur in Eastern Europe. Vaccination is not permitted in CSF-free countries. Conversely, it may be mandatory in countries where the disease is endemic. Normal practice is to vaccinate all pigs over two weeks of age except for piglets born to vaccinated sows. These piglets should be vaccinated at eight weeks.

The immunodominant protective antigen is the envelope glycoprotein, E2. Inactivated vaccines have largely been replaced by safe and effective modified live attenuated vaccines. These vaccine viruses have been attenuated either by passage in rabbits (C strain), or in tissue culture passage at low temperatures (ALD-strain and the Thiverval strain). Although very effective, these vaccines do not yet have DIVA capability. As a result, there are severe movement restrictions placed on vaccinated animals and their products. Oral C-strain CSF vaccines are used in Europe and Japan to control the infection in wild boars (Chapter 20).

Subunit vaccines based on the expression of the E2 protein, and generated in a baculovirus system have also been developed. These permit a DIVA strategy but they are not as effective as the modified live products. Pigs develop immunity within 10 days and it lasts for 2 to 3 years. Maternal immunity lasts for six to eight weeks.

A pestivirus chimera vaccine, CP7_E2alf, (Suvaxyn CSF Marker, Zoetis), using BVDV as its scaffold has been licensed by the European Medicines Agency. The BVDV E2 gene has been replaced by the CSF E2 gene. This vaccine combines DIVA capability with efficacy and protects against multiple CSF genotypes.

In 1936, a vaccine was developed against CSF that involved adding the dye crystal violet to pooled blood from viremic pigs. It was then incubated at 37° C for 14 days to kill the virus. It appeared to work well. However, because it contained pig blood, it sensitized recipients to other pig blood group antigens. As a result, vaccinated sows produced antibodies against these blood groups. If these sows were mated to boars of a different blood group, their piglets were at risk of developing hemolytic disease of the newborn. The sensitized sows concentrated these antibodies in their colostrum. Piglets suckling this colostrum ingested antibodies against their red blood cells. Affected piglets did not necessarily show clinical disease, although their red cells were sensitized by antibody. Other piglets showed rapidly progressive weakness and pallor of mucous membranes preceding death, and those animals that survived longest developed hemoglobinuria and jaundice. The disease ceased to be a problem when the crystal violet vaccine was withdrawn.

AFRICAN SWINE FEVER

Caused by the only member of the *Asfarviridae* family, a very large and complex DNA virus, African swine fever virus (ASFV) causes an acute viral hemorrhagic fever with very high mortality in domestic pigs. It is a robust virus that persists in the environment and is also spread by some soft ticks as well as by contaminated pork products. Endemic in much of sub-Saharan Africa, since 2007, ASF has spread through Georgia and Russia to reach China, Vietnam, Mongolia, North Korea, Cambodia, and Laos. The virus has also spread to Eastern Europe and is making inroads into Western Europe transported by contraband pork products and spread by wild boar. It is an enormous threat to the swine industry worldwide especially because there are no effective vaccines against ASF. Animals that recover from the disease, although apparently healthy, are persistent carriers and shedders of the virus.

Attempts to make a vaccine against ASFV have so far yielded disappointing results. The double-stranded viral genome varies in length, ranging from 170 to 190 kilobases depending on the isolate. It encodes 68 structural proteins and more than 100 infection-related proteins. Few of these proteins have known functions and many are immunosuppressive. The current pandemic is caused by the highly pathogenic, genotype II strain.

Conventional inactivated vaccines have been totally ineffective even when modern adjuvants are used. Subunit, DNA-plasmid, and virus-vectored vaccines have been developed but have also had very limited success. One cause of this is the difficulty in determining which of the numerous viral proteins to use in the vaccine. Several different ASFV proteins appear to be immunogenic and associated with protection but none are sufficient to induce solid protective immunity in pigs. Likewise, the major protective immunity mechanisms are not well understood. Neutralizing antibodies are important but not sufficient and cell-mediated responses are also required for protective immunity.

Modified live vaccines using traditionally attenuated virus may induce long-term immunity to homologous strains with the same genotype but not against heterologous strains. Studies on ASFV strain diversity suggest that this is caused, in part, by variations in capsid genes. Some 24 distinct genotypes of the major capsid protein have been described. Variations occur in multiple other viral proteins as well and their role in immunity needs to be resolved.

The vaccine problem is exacerbated by the observation that, under some circumstances, the immune response may enhance the disease. Attempts in Spain and Portugal in the 1960s to vaccinate pigs with a live attenuated vaccine resulted in both high antibody levels and the development of persistent viral infection and a chronic debilitating disease, with joint swelling, skin lesions, fever, viremia, and hypergammaglobulinemia. The control of ASF is an urgent necessity if the global swine industry is to survive and prosper.

FOOT-AND-MOUTH DISEASE

Commercially available foot-and-mouth disease virus (FMDV) vaccines have traditionally contained inactivated virus either in an aqueous suspension with aluminum hydroxide, saponin, or oil emulsion adjuvants. The conventional aqueous vaccines, however, stimulate low titer, short-lived immunity in pigs. As a result, the pig vaccines must be adjuvanted with oil based emulsion adjuvants. Double oil emulsion (Water/Oil/Water) adjuvants have significantly improved vaccine performance. They are generally created using Montanide ISA206 (Seppic, Paris, France). They have a longer duration of immunity although a slower onset of protection than aqueous vaccines in pigs. It can take as long as six weeks before a satisfactory level of immunity is reached. Pigs require a priming dose, then a boosting dose at 10 to 14 days to achieve the same level of protection that cattle acquire after a single dose of high potency foot-and-mouth disease vaccine. These vaccines decrease viral shedding by pigs, an important consideration for such a contagious

infection. They may also cause significant local injection site reactions. The duration of immunity is generally six months, but in areas where there is high virus challenge, the re-vaccination interval may need to be reduced.

PORCINE CIRCOVIRUS DISEASE

Several genotypes of porcine circovirus 2 (PCV2), a small DNA virus, are associated with multiple swine diseases such a postweaning multisystemic wasting syndrome, porcine respiratory disease complex, reproductive failure, granulomatous enteritis, necrotizing lymphadenitis, exudative epidermitis, and congenital tremors. Porcine circovirus (PCV) usually causes disease in pigs 6 to 12 weeks of age. These diseases may be classified as either systemic disease (PCV2-SD), or as reproductive disease (PCV2-RD). There are four genotypes of PCV2 circulating in the United States: PCV2a, 2b, 2d, and 2e, but the prevalence of these is shifting. Until 2005, 2a was the only known PCV genotype, but shortly thereafter 2b became predominant. In 2012, a mutant 2b was discovered. It differed from the nominate 2b by only one additional amino acid in the open reading frame 2 (ORF2). This mutant PCV2b with high virulence spread rapidly. It quickly displaced the nominate 2b as the predominant genotype and is estimated to be present in a third of US herds. It has now been reclassified as PCV2d. Especially severe disease occurs when PCV is combined with PRRSV, swine influenza, or *Mycoplasma hyopneumoniae*.

Twelve commercial vaccines are currently available in the United States. These include inactivated whole virus vaccines licensed for use in sows and gilts. Other vaccines have been developed for use in piglets. Two subunit vaccines contain the PCV2 capsid protein expressed in a baculovirus system. Also available is an inactivated chimeric vaccine in which the capsid gene from nonpathogenic PCV1 has replaced the same gene in PCV2. Another chimeric vaccine contains both PCV 2a and 2b antigens. All these vaccines stimulate both neutralizing antibodies and cell-mediated immunity against PCV2a and offer cross-protection against PCV2b and -d. PCV2 vaccines are also available in combination with *Mycoplasma* and PRRS vaccines. These vaccines reduce viremia and disease pathology and increase average daily weight gain.

AUTOGENOUS VACCINES

Autogenous vaccines are killed vaccines made from a specific bacterium or virus isolated from infected farms. They are usually made by a veterinarian or by a licensed producer under a special USDA license for use only in a client's flock or herd. In order for a producer to acquire and use an autogenous vaccine, there must be a valid veterinarian-client relationship. The selected organism is cultured, killed, usually with formalin and standardized for bacterial content. They are not usually tested for safety or efficacy. One example is that against *Actinobacillus pleuropneumoniae* where there are multiple different strains, few of which are present in commercial vaccines. These can be very effective if carefully prepared because the vaccine will contain all the bacterial antigens required for protection in that specific location. Another example is the use of autogenous bacterins against exudative epidermitis caused by *Staphylococcus hyicus*. Studies have shown that its use significantly reduced antibiotic use as well as morbidity and mortality in weaned pigs. Autogenous bacterins can be made against many pathogens including, *E. coli*, *Haemophilus parasuis, S. suis,* Pasteurella, and Salmonella. Autogenous swine influenza vaccines are also widely employed.

BOAR TAINT VACCINE

Adult boars accumulate androstenone and skatole in their adipose tissues that are responsible for the offensive odor in boar pork. The development of this odor is mediated by gonadotropin-releasing hormone (GnRH), which stimulates the production of follicle stimulating hormone

(FSH) and luteinizing hormone (LH). These stimulate testosterone production that induces the boar taint. Blocking of GnRH will effectively castrate the animals and consequently prevent the development of these odors. One way this can be done is to immunize boars with a vaccine consisting of an adjuvanted GnRH-protein conjugate. This induces short-lived antiGnRH antibodies that decline seven to eight weeks after the second injection. These antibodies neutralize endogenous GnRH and block its biological activity so that boar taint drops to undetectable levels. Vaccinated boars also show altered behavior that may improve weight gain, feed conversion, and carcass quality. It is obviously much less stressful for the pigs than physical castration. The vaccine, available in Europe, is administered in two doses subcutaneously with a four-week interval and four to five weeks before slaughter. It is potentially hazardous to the vaccinator should they inadvertently inoculate themselves.

Vaccination Timing and Protocols

Piglets should be vaccinated at weaning with circovirus and *Mycoplasma* and maybe with PRRSV vaccines (see Table 18.1). Weaning generally occurs at three to six weeks. Maternal immunity lasts for six weeks. Swine influenza vaccine should be administered at seven to eight weeks.

Prebreeding vaccines are given to sows to protect from reproductive failure. These may include Leptospirosis, Erysipelothrix, and parvovirus vaccines. Gilts should get two doses of lepto/parvo/erysipelas vaccine before breeding and perhaps also a PED vaccine. Many farms vaccinate pregnant sows against enterotoxigenic *E. coli* to provide colostral immunity against scours in piglets. Other vaccines that may be considered include those directed against PRRSV, swine influenza, and *Lawsonia intracellularis*.

Adverse Events

Allergic reactions are always a possibility. In pigs, anaphylaxis is largely the result of systemic and pulmonary hypertension, leading to dyspnea, and death. In some pigs the intestine is involved, whereas in others no gross intestinal lesions are observed. The most significant mediator identified in this species is histamine. Leptospira bacterins may induce a significant febrile response.

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Abstract: The growth of large, intensive pig operations has made effective vaccination imperative in the swine industry. This growth in size has been accompanied by outbreaks of disease such as porcine respiratory and reproductive syndrome (PRRS) and porcine epidemic diarrhea. These have caused massive losses, and effective vaccines are not yet available. Older diseases such as pleuropneumonia, erysipelas, enzootic pneumonia, proliferative enteritis, pseudorabies, and colibacillosis still persist, and classical swine fever and influenza remain as ongoing threats. The large size of many operations has required the introduction of mass vaccination procedures such as vaccination through drinking water. The current African swine fever pandemic makes the development of an effective vaccine against this virus, a matter of urgent necessity.

Keywords: porcine respiratory and reproductive syndrome, porcine epidemic diarrhea, pleuropneumonia, pseudorabies, influenza, oral vaccination, enteropathy.