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African swine fever

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ABSTRACT

The continuing spread of African swine fever (ASF) outside Africa in Europe, the Russian Federation, China and most recently to Mongolia and Vietnam, has heightened awareness of the threat posed by this devastating disease to the global pig industry and food security. In this review we summarise what we know about the African swine fever virus (ASFV), the disease it causes, how it spreads and the current global situation. We discuss current control methods in domestic and wild pigs and prospects for development of vaccines and other tools for control.

1. Introduction

Pigs provide an important source of high-quality protein and production is predicted to increase in future to meet growing global demands for meat. However, the supply of pork is threatened by infectious diseases, and amongst these African swine fever (ASF) is currently causing greatest concern. This is particularly true since its introduction to and dramatic spread in 2018 in China, which has half of the world's pig population. African swine fever virus (ASFV) infection of pigs and wild boar can result in the rapid death of almost all infected animals. The lack of a vaccine hinders control, which is further complicated by the presence of infected wild suids in some regions. As ASF is a notifiable disease to the World Organisation for Animal Health (OIE), introduction to a new country or region results in imposition of trade restrictions. Attempts to control the disease require international cooperation and the race is on to develop vaccines and other control strategies. Up-to-date information on ASF outbreaks in domestic pigs and cases in wild boar is available on the OIE World Animal Health Information System (https://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/diseasehome). This includes daily information on new disease outbreaks, follow-up reports and interactive disease distribution maps for specified time periods are also available. The Food and Agriculture Organisation (FAO) of the United Nations also publishes updates on the current ASF situation, (http://www.fao.org/ag/againfo/programmes/en/empres/ASF/situation_update.html).

2. African swine fever virus

ASF is caused by a large double-stranded DNA virus that replicates in the cell cytoplasm and is the only member of the *Asfarviridae* family (Fig. 1). There are no closely related viruses (Alonso et al., 2018). The main target cells for ASFV replication are macrophages. Modulation of macrophage function by the virus is important for the pathogenic and immune evasion mechanisms. The virus genome varies between about 170 and 193 kbp and codes for between 150 and 167 proteins, including those required for virus replication (Dixon et al., 2013; Redrejo-Rodriguez et al., 2006). Many genes are not essential for replication including inhibitors of host defence, such as inhibitors of the type I interferon response and apoptosis (Afonso et al., 2004; Reis et al., 2016; Brun et al., 1996; Dixon et al., 2017; Hernaez et al., 2013; Rodriguez et al., 2002; Zhang et al., 2010). The genome length variation mainly results from gain or loss of members of different multigene families (MGF) (Chapman et al., 2008; Dixon et al., 2013; Rodriguez et al., 1994). The large virus particle contains some 68 virus-encoded proteins present in multiple layers (Alejo et al., 2018).

3. Host range and pathogenesis

ASFV infects domestic and wild suids, including warthogs (*Phacochoerus africanus*) and bushpigs (*Potamochoerus larvatus*) in Africa and wild boar (*Sus scrofa*) in Eurasia. Soft ticks of the *Ornithodoros* species can be infected over long time periods and act as virus reservoirs. In East Africa the virus is maintained in an ancient sylvatic cycle involving warthogs and *O. moubata* soft ticks that inhabit their

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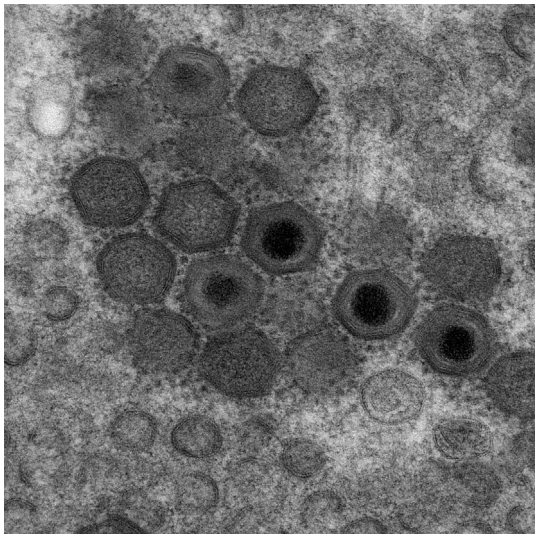

Fig. 1. Morphogenesis of ASFV particles in cytoplasmic factory areas. The multi-layered virus particle enters macrophages/monocytes by receptor-mediated endocytosis or macropinocytosis. The core particle is released into the cytoplasm from late endosomes following pH-dependent dissociation of the extracellular envelope and capsid and fusion of the internal envelope with the endosomal membrane. The core particle contains virus-encoded enzymes, including the RNA polymerase, that are required for early gene transcription, which begins in the cytoplasm in partially uncoated cores immediately following entry. Early transcripts code for enzymes and other proteins needed for virus replication and for inhibition of host defences. DNA replication begins in the cytoplasmic factory areas at about 4–6 h post-infection. The late stage of gene transcription is dependent on the onset of DNA replication; late transcripts code for proteins required for virion morphogenesis and enzymes to be packaged into virus particles for use during the next round of replication. Particles at different stages of assembly are shown in red. Those with a dense nucleoprotein core shown in black are the intracellular mature form. The nucleoprotein core is surrounded by a less dense core shell, an internal envelope on the structures on which the icosahedral capsid is assembled. Extracellular virions (not shown) have an additional external envelope gained as the virus buds through the plasma membrane.

burrows. Infection does not cause obvious clinical signs in these wildlife hosts in Africa, except in young animals, which develop a transient viremia (Jori et al., 2013).

In the early 1900s, ASFV emerged to cause a highly lethal haemorrhagic disease in domestic pigs (Montgomery, 1921; Arias and Sanchez-Vizcaino, 2002; Penrith, 2013; Wilkinson, 1989). Since that time, several disease forms have been observed in domestic pigs and wild boar, both in the field and in experimental infections. Highly virulent isolates cause peracute and acute disease that can result in case fatality close to 100% within 4–15 days post-infection. In the subacute form of disease, caused by moderately virulent isolates, mortality rates are lower (30–70%). The initial clinical signs of acute forms of ASF are associated with high fever, above 41 °C, and include loss of appetite and lethargy. The onset of clinical signs depends on the dose but typically are observed about 3 or 4 days post-infection.

As the disease progresses, animals may stop eating and become increasingly moribund; bloody diarrhoea, vomiting and abortion may be observed. Characteristic pathological changes associated with vasculitis include skin erythema, pulmonary oedema, hyperaemic splenomegaly, haemorrhagic lymphadenitis and petechial haemorrhages in the kidneys, lungs and urinary bladder. Infection is associated with very high levels of virus in the blood (up to 10^9 $TCID_{50}$/ml) and tissues, particularly the spleen and lymph nodes.

Infection is associated with lympho- and thrombocytopenia, destruction of vascular endothelial cells and induction of disseminated intravascular coagulation. A characteristic feature of acute ASF is the induction of massive apoptosis of bystander uninfected lymphocytes in infected tissues and blood. This is observed around infected macrophages in tissues, suggesting that factors on the surface or secreted by infected cells are involved in induction of apoptosis.

Low-virulence isolates can cause a chronic disease with low fatality rates and the absence of vascular lesions. However, signs including delayed growth, emaciation, joint swelling and skin ulcers may be observed. Wild boar show the same acute signs of disease as domestic pigs (Blome et al., 2013; Sanchez-Cordon et al., 2018; Sanchez-Vizcaino et al., 2015).

4. Modes of transmission

4.1. Transmission between domestic pigs

ASFV can be transmitted readily between infected pigs by direct contact involving infection by the oral-nasal route or through skin abrasions. The very high levels of virus, particularly in the blood, provide a large source of virus for direct or indirect infection of animals, and virus is also present in other excretions and secretions, including urine, faces and saliva. Aerosol transmission is thought to occur only over short distances (Olesen et al., 2017). Ingestion of infected material on contaminated surfaces, feed or water can result in infection of pigs. In East Africa, where the soft tick vector is present in some villages, these can play a role in maintaining a reservoir of virus for infection of pigs, but are currently not thought to be involved elsewhere.

Pigs which recover from infection with moderate or low virulence isolates may remain persistently infected and may spread infection to pigs in contact. However the frequency and duration of virus persistence and their potential role in virus spread is not known. Some studies indicate that virus is cleared from these animals within a few months and their potential role in transmission is therefore more limited (Petrov et al., 2018).

Information on effective biosecurity measures to reduce the introduction of ASFV and to prevent its spread between farms is available on a number of websites, and is summarised in a recent review (Bellini et al., 2016).

4.2. Transmission between wild suids

Wild suids in Africa can be persistently infected and develop few if any clinical signs and little or no viremia. Young warthogs develop a transient viremia that is sufficient to infect *Ornithodoros moubata* ticks that feed on them. ASFV can be transmitted between these ticks transtadially, between different nymphal stages, transexually and transovarially. The *Ornithodoros* tick vector is thought to play an important role in virus transmission between warthog hosts.

In contrast, infected Eurasian wild boar, *Sus scrofa*, develop similar disease signs to domestic pigs including high levels of virus in blood, excretions and secretions. Thus transmission of ASFV between wild boar by direct or indirect contact with infected animals or contaminated surfaces, feed or water also occurs readily. An additional route of infection between wild boar is thought to be contact with infected carcasses (Berg et al., 2015; Probst et al., 2017). The physical stability of the virus means that these may remain infectious over long periods. In contrast, dead pigs are usually quickly removed from farms.

4.3. Transmission from wild suids to domestic pigs

In the sylvatic cycle in Africa, the soft ticks which reside in warthog burrows feed for only a short time on their mammalian host before dropping off, and their capacity to spread virus to other hosts is limited. For these reasons transmission from warthogs, *Ornithodoros moubata* ticks or bushpigs to domestic pigs is thought to be relatively infrequent and limited to village farms in areas close to the wildlife reservoirs (Jori and Bastos, 2009; Jori et al., 2013).

In Eurasia, by contrast, domestic pigs may be readily infected by wild boar, either by direct or indirect contact. In a number of countries (for example the Baltic States and Poland) ASF has spread dramatically in wild boar populations which can move in wildlife corridors across borders and constitute an important mechanism for virus spread and a reservoir for infection of domestic pigs. In some areas, there is a high density of wild boar, which makes contact with domestic pigs all the more likely, particularly those raised in establishments with insufficient biosecurity or where pigs are allowed outdoors to forage during the day.

4.4. Transmission brought about by various forms of human activity

Human activity can lead to transmission of ASFV over both short and long distances. The virus survives for periods of weeks or months in meat products, and their feeding to domestic pigs can result in infection. Heating meat products results in virus inactivation, thus well-cooked meat does not pose a risk to infection. Other types of meat processing, such as air drying, do not immediately inactivate virus, so that the meat may remain infectious over varying periods. Other materials contaminated by virus, including clothing, boots, transport vehicles and hunting knives, also act as a source of indirect transmission to pigs (Guinat et al., 2016; Sanchez-Vizcaino et al., 2015).

Longer-distance jumps of ASF have usually involved pigs or wild boar eating infected meat, as was suspected recently in China and Belgium. Movement of infected pigs over long distances can also result in disease spread. Stability of the virus in carcasses or excretions and secretions from infected wild boar also maintain a reservoir for infection of other wild boar or indirect transmission to pigs, particularly during the colder months. The virus can persist for several weeks, if not months, in very cold temperatures. Feeding of pigs on materials such as grass contaminated by infected wild boar can also result in infection.

The early clinical signs of ASF are unspecific and associated with fever, and can easily be confused with other diseases, making early diagnosis difficult, especially if introduced to a new region where ASF is not suspected. Significant spread can therefore occur before disease control measures are introduced.

5. Global distribution of African swine fever

5.1. Africa

In the early 1900s, African swine fever emerged from the ancient wildlife reservoir in East Africa (Fig. 2). It was first described in Kenya as an acute haemorrhagic fever in domestic pigs with case fatality approaching 100% (Montgomery, 1921). The warthog and tick cycle have been described in seven southern and eastern African countries. ASF subsequently spread through domestic pig populations in most sub-Saharan countries, reaching West Africa in the 1950s. The disease has remained endemic or causes sporadic outbreaks in most sub-Saharan African countries causing a high socio-economic impact amongst both rural poor and commercial farmers (Penrith, 2013).

5.2. Europe

5.2.1. Europe before 2007

The first introductions of ASF to Europe were to Portugal in 1957 and again in 1960, and were presumed to have been caused by feeding food waste from flights from Africa to pigs near Lisbon airport. The likely source of virus was considered to be infected pork from Angola. The disease then remained endemic in Spain and Portugal until the mid-1990s, spreading from there to other European countries (France, Sardinia, Malta, Belgium, the Netherlands) the Caribbean and South America (Cuba, Dominican Republic, Haiti, Brazil). All of these outbreaks were eradicated, except for Sardinia, where ASF remains endemic.

5.2.2. Europe since 2007

In 2007 the disease was first reported in Georgia, most likely introduced by infected pork carried on ships from East Africa. The consequent scavenging by wild boar or feral pigs of the poorly disposed waste and delays in diagnosis meant that the disease became established in the wild boar population, leading to outbreaks in domestic pigs. ASF then continued to spread across the Caucasus region and into southern Russia in 2007, then further north and east through large geographic jumps. A number of factors led to further spread, including high levels of movement of people around conflict regions, the lack of good farming practice and biosecurity, to prevent the spread of infection onto farms, poor compensation to farmers and lack of traceability of pigs. This is contributed to by farmers selling pigs quickly to avoid being caught up in movement restrictions, resulting in the establishment of disease and large geographic jumps.

ASF was reported from many regions of Western Russia as well as Ukraine and Belarus in the intervening period and, in January 2014, the first cases in wild boar were reported from the European Union, in Lithuania on the border with Belarus. Infection has been reported in Estonia, Latvia, Lithuania and Poland since 2014; in the Czech Republic, Hungary, Romania and Bulgaria in 2018; and outside the EU, in both European and Asian Russia (including the exclave region, Kaliningrad), Ukraine, Moldova. Belgium also reported cases in wild boar in 2018, with some 245 animals testing positive in a limited area on the borders with France and Luxembourg. The exact source of infection is not known, but movements of vehicles and contaminated products are the most likely primary sources.

Romania has faced a very different type of epizootic this year, in which the majority of cases have been reported in backyard or domestic pigs and only a few in wild boar; this contrasts with other affected EU member states, where most cases are in wild boar, with only occasional spill-overs into the domestic pig population. The reasons for this unusual situation in Romania are not fully understood, but are most likely related to human factors, including failure to implement effective biosecurity procedures to avoid infection entering farms.

5.3. China and other Asian countries

The first ASF outbreak in China (Shenyang City, Liaoning region) was reported to the OIE on August 3, 2018. However, this may not have been the original case, since a similar disease had been found in the suburban district of Shenyang City almost two months previously (Wei et al., 2018). For example, some piglets illegally purchased from a village of neighbouring Jilin Province started to show ASF-like symptoms, and 28 out of 100 piglets died from March 24. On July 6, the farmer sold the 45 remaining pigs to a nearby farm and all of them died very quickly. The main clinical and pathological signs observed were consistent with acute ASF (Wei S., 2018). Electron microscopy revealed ASFV-like virus particles in the spleen samples of two dead pigs, and PCR analysis showed that spleen, liver and kidney samples were positive for ASFV. Sequence analysis showed that the sequences of B646L (p72), E183L (p54) and B602L were identical to that of Georgia 2007/1 and related strains (Chen et al., 2018; Zhou et al., 2018). The tissue samples of two dead pigs were confirmed as positive for ASFV by the China Animal Health and Epidemiology Center (Ge et al., 2018).

The Ministry of Agriculture and Rural Affairs of China immediately initiated an emergency response. Although the measures were implemented properly, the disease spread very quickly with 4 outbreaks in August, 20 in September, 27 in October and 22 in November. More than 100 outbreaks in domestic pigs had been reported from 23 provinces by December 31 (Fig. 2). The main transmission routes between August and November were estimated by the Chinese Government to include trans-regional transportation of live pigs and pork products (19%), swill feeding (34%), and movement of people and vehicles (46%) (ProMED-mail Archive Number: 20181130.6173813).

Wild boar are widely distributed in China, including both natural

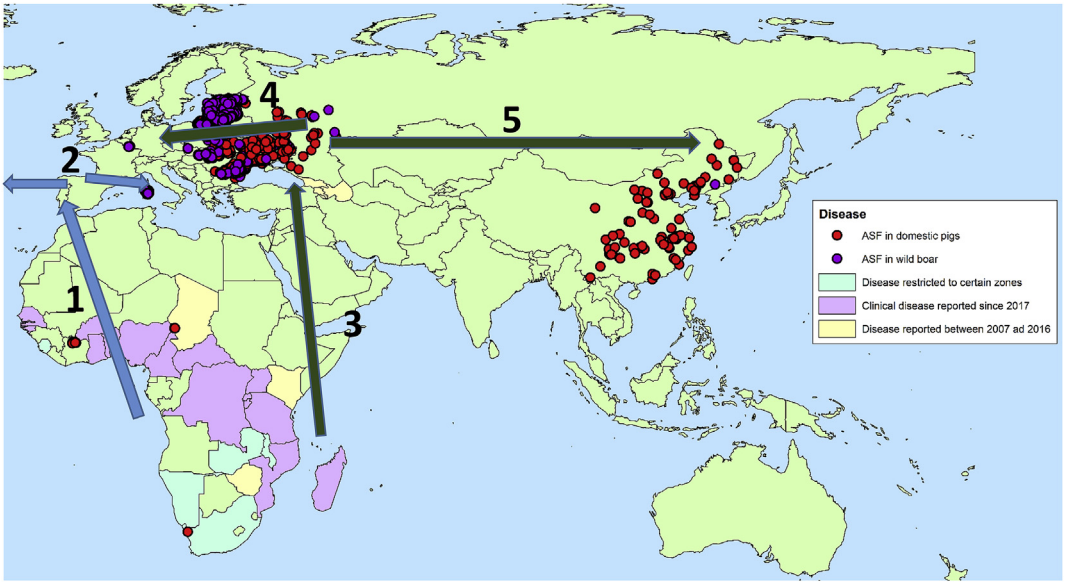

Fig. 2. Chronology of the transcontinental spread of ASFV and outbreaks in domestic pigs and detection in wild boar during 2018. Transcontinental spread is indicated by arrows and numbers. 1. In blue, the spread of genotype I virus from West Africa to Portugal in 1957 and 1960 is shown; this was thought to involve the feeding to pigs of infected meat introduced from aircraft. 2. From the Iberian peninsula, the virus spread to other European countries and to South America and the Caribbean. These outbreaks were eradicated by the mid-1990s, except from Sardinia, where the disease remains endemic. 3. In 2007, ASFV genotype II spread from the east coast of Africa to Georgia in the Transcaucasus region, thought to be introduced through infected meat eaten by pigs from shipping near the Black Sea port of Poti. 4. From Georgia, the virus spread to neighbouring countries, including the Russian Federation and to eastern European countries, including a number in the EU. In 2018 there was further westward spread in Poland and to Belgium. 5. In 2018, ASFV genotype II spread from Russia or Europe to China, rapidly spreading to many provinces and threatening further spread in the region. In 2019, the first outbreaks in Mongolia and Vietnam were reported. Outbreaks of ASF in domestic pigs reported to the OIE during 2018 are shown as red dots, and detections in wild boar as purple dots. African countries that reported the disease from 2007 to 2016 are shown in yellow, and those that have reported ASF since 2017 are shown in purple. Countries where the disease is restricted to certain zones are shown in turquoise. Source of information: OIE WAHIS https://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/Diseasedistributionmap. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and farmed animals. Two ASF outbreaks in wild boar have been reported. On November 16, 2018, a dead wild boar was found in the Huijiang district of Jilin Province, close to the border with North Korea, and PCR analysis showed that tissue samples were positive for ASFV. Comprehensive epidemiological investigation suggested that the case had no direct connection with domestic pig infection, and the source of infection remains unknown (ProMED-mail Archive Number: 20181210.6203157).

In January, 2019 ASF was reported in Mongolia, and it has since been confirmed in 7 different provinces. Spread to other countries in Asia is considered likely by the FAO (http://www.fao.org/news/story/en/item/1150618/icode/). This is further highlighted since there have been several examples of ASFV-positive pork products being carried to other Asian countries by airline passengers (ProMED-mail Archive Number: 20190126.6279425). In February 2019 Vietnam authorities reported three outbreaks and by the end of the month had reported 33 separate outbreaks in 6 different provinces. This is unsurprising given trade and movements between China and Vietnam but indicative of the risk of further spread in the region.

6. Control strategies

6.1. Africa

ASF is endemic in pigs in sub-Saharan Africa. In East Africa the virus also circulates in a wildlife cycle involving wild suid hosts, warthogs, and soft-bodied ticks of Ornithodoros spp. Nevertheless, to preserve their ability to trade, countries such as South Africa have been able to implement ASF-free zones, where movement restrictions and biosecurity measures protect the domestic pig population from disease incursions. The South Africa ASF zone encompasses most of Limpopo region, part of Mpumalanga, the north area of North West region and a small area of Kwa Zulu Natal (https://www.nda.agric.za/vetweb/epidemiology/Disease%20Maps/ASFcopy.pdf).

In these areas, domestic pigs must be kept in pig-proof pens, kraals or camps to prevent contact with wild suids, and movement restrictions are in place. Prevention focuses on these and other biosecurity measures, such as cooking of any meat or other kitchen waste fed to pigs, disinfection of boots and vehicles entering farms, and education about the disease and measures to avoid it. Disease control strategies focus on the immediate culling of infected pigs on a farm and surrounding farms to prevent spread, supported by legislative frameworks and compensation. The FAO has been at the forefront in promoting an Africa Strategy for ASF which focuses on a framework for partners and regional cooperation (http://www.fao.org/3/a-i6053e.pdf).

6.2. Europe

ASF is a notifiable disease in the EU, and as such any suspicion of disease must be reported to and investigated by the competent authority. Disease control legislation (Council Directive 2002/60/EC and Commission Implementing Decisions 2014/709/EU and 2018/2015/EU) sets out disease control zones (3 km and 10 km zones), as well as a series of additional animal movement restrictions and control measures applicable to the movement and trade of live pigs, feral pigs and wild boar and meat and products of such origin. These restrictions are based on whether infection has been detected in wild animals only (Parts II and IV), in pig holdings as well as wild animals (Part III) or if there is a risk due only to proximity to the cases (Part I). The areas are defined in the Annex of 2014/709/EU.

Further explanation is available from the EU working document SANTE/7112/2015/Rev.2, which describes the regions of affected EU member states based on their epidemiological status and level of risk (https://ec.europa.eu/food/sites/food/files/animals/docs/ad_control-

measures_asf_wrk-doc-sante-2015-7112.pdf). The European disease control legislation is aimed at avoiding unnecessary disturbance to trade within the EU and avoiding unjustified barriers to trade by third countries, and is aligned with standards approved by the OIE. Mitigating measures to reduce spread in wild boar have been considered in recent scientific opinions published by the European Food Safety Authority (Berg et al., 2015; More et al., 2018). Constant changes to the status of different control zones can introduce the risk of spread of disease through meat products.

6.3. China and Asia

As noted above, after the first ASF outbreak reported on August 3, 2018, the Ministry of Agriculture and Rural Affairs of China initiated an immediate emergency response (PRO/AH/EDR > African swine fever - Asia: China (LN) domestic swine, 1st report, OIE Archive Number: 20180803.5945484). The control strategies have included zoning/compartmentalization, culling of all pigs in the affected area, safe disposal of dead animals, products and contaminated materials, restriction of pig movement, and stringent disease surveillance. Classic sanitary measures are also employed, including restriction of swill (waste food from kitchens) feeding, early virus detection by clinical signs and laboratory diagnosis, thorough cleansing and disinfection, comprehensive epidemiological investigation and strict biosecurity measures on pig farms. Finally, appropriate import policies are implemented to ensure that neither infected live pigs nor pork products are introduced, including proper disposal of waste food from aircraft, ships or vehicles coming from affected countries, and policing illegal imports of live pigs and pork products.

Overall, these measures are effective to reduce disease spread. Epidemiological studies of 68 outbreaks revealed 3 major causes for spread of ASF virus. These were 46% by vehicles and workers, 34% by swill feeding, and 19% by transport of live pigs and their products across regions. Other measures introduced are summarised in regular reports from FAO http://www.fao.org/ag/againfo/programmes/en/empres/ASF/situation_update.html. However, new outbreaks are still ongoing due to complex factors, including difficult control of long borders, frequent exchanges of personnel and products with affected countries, rampant smuggling of pork products, large populations and high densities of domestic pigs and wild boars, high numbers of backyard and small pig farms with poor biosecurity, difficult control of long-distance, trans-region transportation of live pigs and pork products, and the difficulty of early detection of ASF, due to confusion of early clinical signs with other diseases. The relatively low rate of spread from infected animals may also result in a delay in suspecting disease outbreaks.

7. Prospects for development of vaccines

It was first reported in the 1950s that pigs that recover from ASF are protected against a second challenge with related virulent viruses (Detray, 1957). Prospects for vaccine development are considered good, since high levels of protection were achieved in these studies. However, progress has been slow and a vaccine licensed for use in the field is still a number of years away. Evidence indicates that antibodies have a role in protection, since passive transfer of antibodies from protected to naïve animals was shown to partially protect pigs against challenge (Onisk et al., 1994; Wardley et al., 1985). $CD8^+$ cells were also shown to be essential, since antibody-mediated depletion of this cell subset abrogated protection induced by a live, attenuated strain (Oura et al., 2005). Effective vaccines should therefore induce both protective antibody and cellular responses. The prospects for developing effective vaccines have recently been reviewed by an expert group, and a summary review has been published (Arias et al., 2017a).

7.1. Inactivated virus vaccines

The complexity of ASFV has been a major factor in the delay in vaccine development. Inactivation of virus, commonly used to produce vaccines against simpler viruses, has not succeeded (Blome et al., 2014; Stone and Hess, 1967), because inactivated vaccines usually work by inducing antibodies that inhibit virus infection of cells. These neutralising antibodies do not completely inhibit ASFV infection, probably because the virus particle has two infectious forms, extracellular and intracellular mature. Moreover, two mechanisms have been demonstrated for ASFV entry into macrophages, clathrin-mediated endocytosis and macropinocytosis (Andres, 2017; Hernaez et al., 2016). The multi-layered virus particle contains more than 80 proteins (Alejo et al., 2018), and different proteins are present on the surface of the extra-cellular enveloped and intracellular mature infectious virions, so that neutralising antibodies would have to be directed against several proteins. Earlier research identified virus proteins p72/B646L, p54/E183L and p30/CP204L as targets for neutralisation (Gomez-Puertas et al., 1996; 1998).

7.2. Live, attenuated virus vaccines

Live, attenuated vaccines can induce up to 100% protection (King et al., 2011; Leitao et al., 2001; O'Donnell et al., 2017; Reis et al., 2016, 2017), but safety issues, including adverse effects caused by the vaccine strain and potential for its persistence and transmission in the field have been obstacles for this strategy. Candidate live, attenuated vaccine strains have been generated by passage in cell culture or through the rational deletion of genes from more virulent strains. In addition, some low-virulence isolates have been shown to have potential as vaccine candidates (Boinas et al., 2004; Leitao et al., 2001).

Advances in knowledge of ASFV gene functions have identified target genes to delete to produce candidate live, attenuated vaccine strains; those showing promise include inhibitors of the type I interferon response, such as members of MGFs 360 and 505/530 or DP148R (O'Donnell et al., 2015; Reis et al., 2016; Reis et al., 2017). Deletion of other genes which directly facilitate virus replication, including B119L/9 GL, a protein involved in a redox pathway required for virus assembly, has also been successful (Lewis et al., 2000). Deletion of genes encoding some proteins of unknown function, such as DP96R/UK, has also resulted in attenuation (O'Donnell et al., 2017).

Lessons learned from studies with attenuated ASFV strains include the demonstration that deletion of genes from different strains does not always have the same outcome. For example, deletion of EP402R, which codes for the protein CD2v, which causes binding of red blood cells to infected cells and virus particles, from the BA71 strain resulted in virus attenuation and induction of protection, but when the same gene was deleted from a different virulent strain, no attenuation was observed (Borca et al., 1998; Monteagudo et al., 2017).

An additional requirement for a live, attenuated ASFV vaccine is the development of companion diagnostic tests to differentiate infected from vaccinated animals. This requires the introduction of a negative marker for serological diagnosis, through the deletion or modification of a gene for an immunogenic protein from the vaccine strain. A recent Roadmap and Blueprint for vaccine development concluded that live, attenuated vaccines provide the fastest route forward, but having a vaccine licensed for use in the field will take a number of years (Arias et al., 2017b).

7.3. Subunit vaccines

Vaccines based on the delivery of individual or small groups of ASFV genes or proteins may ultimately be safer than live, attenuated vaccines. Combinations of recombinant proteins p72/B646L, p54/E183L and p30/CP204L induced partial protection in one study, but not in another, despite the induction of neutralising antibodies

(GomezPuertas et al., 1996; Neilan et al., 2004). Delivery of a CD2v/EP402R recombinant protein also induced partial protection (RuizGonzalvo et al., 1996). DNA vaccination with a gene fusion of CD2v/EP402R extracellular domain, p30/CP204L and p54/E183L and a ubiquitin gene induced partial protection, as did a library of small ASFV DNA fragments fused to ubiquitin. DNA vaccination induced strong cytotoxic T cell responses, in the absence of a specific antibody response (Argilaguet et al., 2012; Lacasta et al., 2014).

In the search for more potentially protective antigens, pools of ASFV genes have been delivered to pigs using non-replicating virus vectors, for example adenovirus and vaccinia virus (Jancovich et al., 2018; Lokhandwala et al., 2017). Good antibody and cellular responses were induced, and ranking of the immunogenicity of different antigens was achieved (Jancovich et al., 2018). Although these results are promising, much further work will be required to define a small pool of antigens and a delivery method that could be used in commercial vaccines.

8. Antiviral drugs and other control measures

8.1. Antiviral drugs

In the current absence of a vaccine, alternative control strategies can be considered. Proof of concept has been achieved for the use of small-molecule antivirals to limit virus replication and thus prevent the spread of another pig disease, classical swine fever (CSF) (Vrancken et al., 2009). An antiviral drug administered to CSF virus-infected pigs reduced the viral titre in the blood by 1000-fold, shortened the viremia period by 74% and reduced transmission from infected pigs to untreated sentinel pigs by 85%. Epidemiological modelling indicated that CSF outbreaks might be controlled as effectively with antiviral drugs as with more conventional strategies, such as pre-emptive culling and emergency vaccination (Backer et al., 2013; Vrancken et al., 2009).

ASFV has a number of virus-specific enzymes required for replication, including the RNA and DNA polymerases, which should be good specific targets for antiviral drug development. Several compounds have been shown to inhibit ASFV replication in cell culture (Frouco et al., 2017; Galindo et al., 2011; Hakobyan et al., 2018), but as yet none has been tested in pigs.

8.2. Other control strategies

Other control strategies have been suggested including the breeding or engineering of ASFV-resistant pigs. A successful strategy would first have to be developed to inhibit virus replication. This strategy might be successful in some scenarios with a structured pig breeding programme, but would not be effective in control of disease in wild suids.

9. Future research

Current ASF control strategies largely rely on rapid detection and implementation of quarantine and slaughter policies, which are often not effective, and can result in the culling of large numbers of animals. Alternatives such as a safe and effective vaccine would provide an additional tool that could help to control the disease in countries where ASF is endemic and to eradicate the virus from wild and domestic pigs. Although promising candidates are available, further work is needed before these could be used in the field. Underpinning research will be required to develop the next generation of vaccines, including information on how the virus modulates host responses to infection and the role of virus-encoded proteins in evading host defences *in vitro* and *in vivo*. This could lead to development of improved live attenuated vaccines.

More information is also required on the mechanisms and correlates of protection and the viral antigens that can induce that protection, which would help to progress the development of subunit vaccines. Further basic research on virus interaction with macrophages, including cellular and virus proteins involved in entry, replication and morphogenesis, would facilitate the development of improved cell lines for virus replication and vaccine production, and identify novel targets for vaccine development. Targets for antivirals would also be defined.

Further understanding of the mechanisms by which ASFV spreads in domestic pigs and wild boar will help with control efforts, since measures can be taken to avoid those routes. The Global Alliance for Research on African swine fever virus (https://www.ars.usda.gov/GARA/) has recently published a more complete report on research needs.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.antiviral.2019.02.018.

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