Review Article

African Swine Fever: Research Gaps in Vaccine Development and Immune Evasion

Sumit Sharma[1,2], Md. Rimon Bhuiyan[1,2*], Syeda Shamapika Ahmed Shimi[1,2], Md. Raufur Rahman Akanda[3,4], Md. Abdul Mannan Bhuiyan[5] and Mst. Roksana Akter[6]

[1]Department of Veterinary & Animal Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh; [2]Faculty of Veterinary & Animal Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh; [3]Department of Physiology and Pharmacology, Gazipur Agricultural University, Gazipur-1706, Bangladesh; [4]Faculty of Veterinary Medicine and Animal Science, Gazipur Agricultural University, Gazipur-1706, Bangladesh; [5]Faculty of Social Sciences, Tejgaon College, University of Dhaka, Dhaka-1000, Bangladesh; [6]Faculty of Social Sciences, Government Bangla College, University of Dhaka, Dhaka-1000, Bangladesh.

Abstract | African swine fever (ASF), caused by African swine fever virus (ASFV), is a devastating transboundary disease of domestic pigs and wild boars. Despite extensive research, the lack of a safe and effective vaccine continues to hinder global disease control. This review summarizes current evidence on the major research gaps in ASFV vaccine development and immune evasion mechanisms that limit the development of effective vaccination strategies. A narrative review was conducted using peer-reviewed literature retrieved from PubMed, Scopus, Web of Science, and Google Scholar, together with reports from the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (WOAH). Current vaccine development is challenged by the complex biology of ASFV, incomplete characterization of viral proteins, macrophage tropism, and sophisticated immune evasion mechanisms that suppress host antiviral responses. Live attenuated vaccines provide the most promising protection but remain limited by safety concerns, genetic stability, and incomplete cross-genotype protection. Inactivated, subunit, nucleic acid, and viral-vectored vaccines have shown limited or inconsistent efficacy. Emerging evidence of antibody-dependent enhancement (ADE) further highlights the need for careful antigen selection and comprehensive vaccine safety evaluation. Progress toward an effective ASF vaccine requires improved understanding of ASFV biology, immune correlates of protection, and standardized vaccine evaluation strategies. Addressing these research gaps will support the development of safe, broadly protective, and field-applicable vaccines for long-term ASF control.

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***Correspondence** | Md. Rimon Bhuiyan, Department of Veterinary & Animal Sciences, University of Rajshahi, Rajshahi- 6205, Bangladesh;
Email: mdrimonbhuiyan1999@gmail.com, s1911168127@ru.ac.bd
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Introduction

African swine fever (ASF) is an acute, febrile, haemorrhagic viral disease of domestic pigs and wild boars caused by the African swine fever virus (ASFV), a large, enveloped, double-stranded DNA virus classified as the sole member of the family *Asfarviridae* (Dixon *et al*., 2013). First described in Kenya in 1921 (Costard *et al*., 2009), ASF has evolved from a localised African epizootic into a devastating global panzootic affecting pig populations across Africa, Europe, Asia, and- most recently- the Americas (Wu *et al*., 2021). The disease is characterised by high fever, widespread haemorrhagic lesions of multiple organs, and mortality rates approaching 100% in highly virulent strains, making it among the most lethal viral diseases of domestic livestock (Wang *et al*., 2022).

The epidemiological trajectory of ASFV underwent a decisive and catastrophic shift in 2007 when genotype II ASFV escaped Africa and was introduced into Georgia, subsequently spreading uncontrollably throughout Eastern Europe and the Caucasus region (Costard *et al*., 2009). Its introduction into China in 2018 triggered the largest livestock disease crisis in recorded history, resulting in the death or culling of approximately 225 million pigs- roughly one-quarter of the entire global pig population- and estimated economic losses of USD $119 billion in China alone (Texas A&M Natural Resources Institute, 2024). By January 2025, ASF had become endemic in more than 50 countries, with first occurrences confirmed in Sri Lanka (December 2024), Albania, and Montenegro in 2024 (WOAH, 2025).

The absence of an approved, universally available, safe, and efficacious vaccine means that ASF control remains entirely dependent on stamping-out policies, strict movement restrictions, and intensive biosecurity measures- strategies that are economically ruinous and socially disruptive, particularly for smallholder farmers in low- and middle-income countries (FAO, 2024). These measures have repeatedly failed to prevent the pandemic's spread, underscoring the irreplaceable necessity of a protective vaccine for long-term control (WOAH, 2025).

This review comprehensively identifies and discusses the persistent research gaps in ASF vaccine development and immune evasion mechanisms that continue to impede effective disease control. Specifically, it examines the genomic and structural complexity of ASFV, dissects its multi-layered immune evasion strategies, critically appraises current vaccine platforms and their limitations, highlights the newly recognised danger of antibody-dependent enhancement (ADE), and proposes priority research directions for the international scientific community.

The global burden of ASF extends beyond livestock mortality to encompass profound ecological, economic, and food security implications. In endemic African regions, ASF causes recurrent population crashes in wild boar and domestic swine populations, creating ecological bottlenecks and disrupting established wildlife management protocols. The economic impact transcends direct production losses: trade restrictions imposed by ASF-free countries result in market barriers worth billions of dollars annually. This disproportionately affects smallholder farmers in low- and middle-income countries who lack resources for intensive biosecurity or herd replacement. ASF's pattern of emergent spread through multiple geographic routes (terrestrial, maritime transport contamination, wildlife corridors) demonstrates the inadequacy of current surveillance protocols and emphasizes the urgent necessity for vaccination-based strategies to complement existing biosecurity measures.

Literature search strategy and study selection

This narrative review was conducted through a comprehensive literature search to identify current evidence on African swine fever virus (ASFV) vaccine development, immune evasion mechanisms, and emerging research gaps. Peer-reviewed articles, reviews, and official reports published primarily between 2009 and 2026 were retrieved from major scientific databases including PubMed, Scopus, Web of Science, and Google Scholar (see supplementary search strategy). Additional epidemiological and policy-related data were obtained from authoritative international sources, including the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (WOAH).

The search strategy employed multiple keyword combinations including: 'African swine fever virus', 'ASFV vaccine', 'immune evasion', 'live attenuated vaccine', 'subunit vaccine', 'antibody-dependent enhancement', 'macrophage infection', 'cGAS-STING', and 'DIVA diagnostics'. Studies were

prioritised based on: (1) direct relevance to ASF vaccine development or immunological mechanisms; (2) methodological quality and experimental rigour; (3) novelty of findings; and (4) contribution to identifying unresolved research gaps. Experimental studies, mechanistic immunology papers, systematic and narrative review articles, and recent vaccine development reports were included where directly relevant to the review objectives. English-language publications were prioritised, though relevant non-English studies were considered when available.

Genomic and structural complexity of asfv: a foundational research gap

A principal and often underappreciated barrier to ASF vaccine development lies in the extraordinary genomic complexity of ASFV (Fan *et al*., 2024). The ASFV genome spans 170–193 kb of double-stranded DNA and encodes approximately 150–167 open reading frames (ORFs) and more than 200 proteins, the vast majority of which remain functionally uncharacterised (Fan *et al*., 2024). This extensive repertoire of unknown gene products severely constrains the rational identification of protective antigens suitable for subunit, vectored, or nucleic acid vaccine platforms.

A critical biological distinction further compounds this challenge: unlike conventional poxviruses, ASFV primarily infects monocytes and macrophages- the central effectors of innate immune surveillance and primary antigen-presenting cells linking innate and adaptive immunity (Orosco, 2023; Niu *et al*., 2023; Zhang *et al*., 2024). This exquisitely selective cell tropism explains in part why vaccine platforms effective against poxviruses have largely failed when applied to ASFV.

A critical research gap therefore persists in the systematic functional characterisation of the ASFV proteome. The roles and immunological significance of more than 100 poorly characterised ORFs- particularly those involved in immune modulation, virulence determinism, and host range specification- remain largely unknown (Fan *et al*., 2024). Reverse vaccinology approaches, defined as the systematic identification of vaccine antigens through computational prediction combined with functional validation, offer a promising but as yet incompletely realised strategy for addressing this fundamental knowledge deficit (Orosco, 2023; Niu *et al*., 2023).

Immune evasion mechanisms: complexity and knowledge gaps

ASFV has evolved extraordinarily sophisticated, multi-layered immune evasion strategies that systematically subvert both innate and adaptive immunity, creating profound and multifaceted challenges for vaccine-mediated protection (Lv *et al*., 2025). A comprehensive understanding of these mechanisms is indispensable not only for basic immunological knowledge but for the rational, mechanistically-informed design of vaccine antigens capable of eliciting protective immunity despite viral interference (Niu *et al*., 2023; Zhang *et al*., 2024) (Table 1).

Interferon pathway antagonism

The cGAS–STING pathway constitutes the primary cytoplasmic DNA-sensing axis responsible for initiating innate antiviral responses. ASFV encodes multiple proteins that potently suppress this pathway at distinct molecular nodes. Unbiased functional screening has identified at least four ASFV proteins- pI215L, pE301R, pD345R, and pS273R- that suppress cGAS-STING-induced interferon (IFN) production through distinct, non-redundant molecular mechanisms (He *et al*., 2022). The viral CD2v protein (EP402R) interacts directly with both STING and IRF3, inhibiting their nuclear translocation and consequent type I IFN production (He *et al*., 2022). The complete repertoire of ASFV IFN antagonists and their relative contributions in vivo remain incompletely characterised, representing a significant gap in understanding the innate immune suppression landscape (He *et al*., 2022).

Antigen presentation disruption

ASFV inhibits MHC class II antigen processing and presentation in infected macrophages, impairing CD4+ T helper cell activation and the downstream cascade of adaptive immune responses essential for durable protection (Zhu *et al*., 2019; Lv *et al*., 2025). A recent systematic analysis identified that dendritic cell (DC)–ASFV interactions have been extensively understudied, with very few studies rigorously analysing how ASFV modulates DC maturation, cytokine production, and antigen-presenting function (Lv *et al*., 2025). This represents a major knowledge gap, since dendritic cells bridge innate and adaptive immunity and are critical for T-cell priming in vivo (Figure 1). ASFV infection appears to impair DC maturation and migration, potentially abrogating the immunological synapse formation required for effective T-cell

Table 1: *ASFV Immune evasion mechanisms & knowledge gaps*

Immune Evasion Mechanism	Viral Proteins & Impact	Knowledge Gaps (Highlighted)
Type I Interferon Suppression	• Proteins: pI215L, pE301R, pD345R, pS273R, CD2v • Effect: Blocks cGAS-STING pathway • Inhibits IFN-β production	• Complete repertoire of IFN antagonists? • Interaction mechanisms with pattern receptors?
MHC II & Antigen Presentation	• Target: Dendritic cell maturation • Known: MHC II inhibition • Effect: Impairs CD4+ T-cell priming	• DC-ASFV interaction mechanisms? • DC maturation & cytokine production pathways? • Antigen presentation efficiency?
Apoptosis & Inflammation Modulation	• Proteins: pA224L (anti-apoptotic) • TNF superfamily modulators • Effect: Prolonged viral replication	• Individual TNF ligand contributions? • Inflammation dysregulation mechanisms?
Antibody-Dependent Enhancement (ADE) NEWLY EMPHASIZED	• Protein: pA137R (proven ADE inducer) • Target: FcγRII/FcγRIII on macrophages • Effect: Paradoxical worsening on vaccination	•CRITICAL: • Which other antigens induce ADE? • Screening pipeline needed

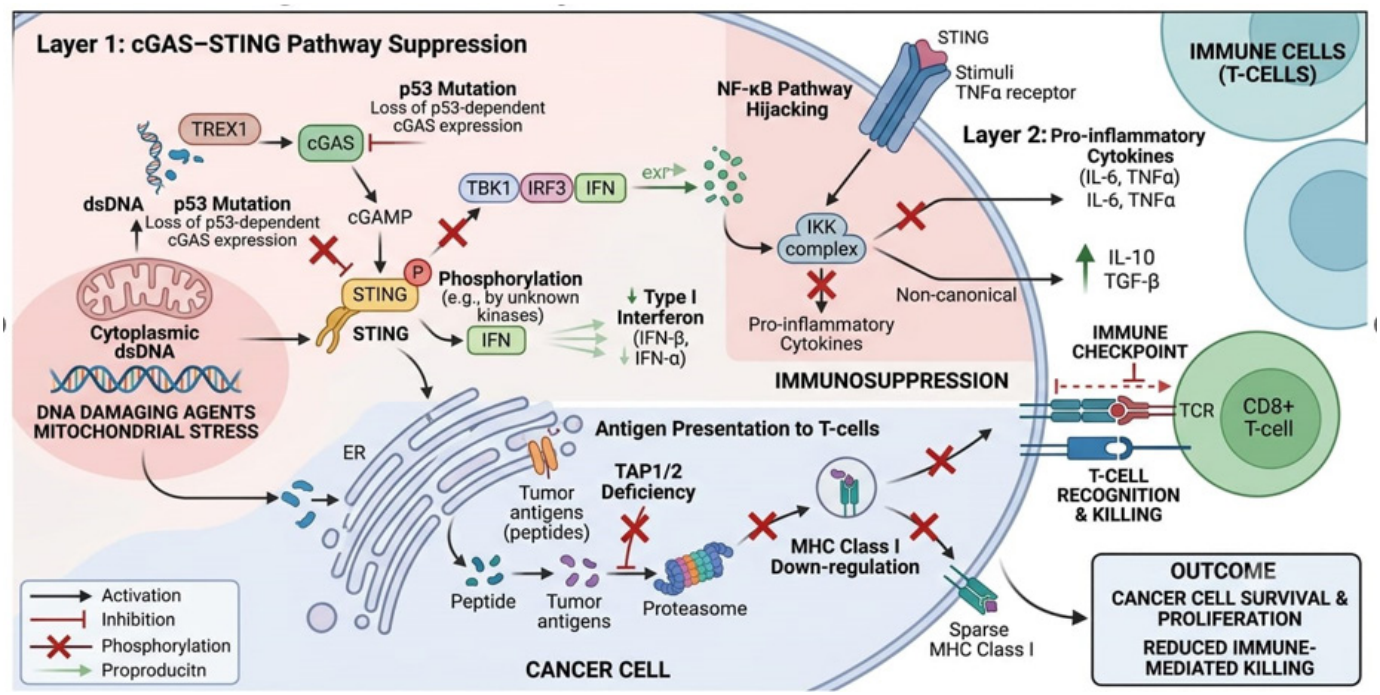

Figure 1: *Multi-layered immune evasion cascade*

priming (Lv *et al.*, 2025).

Apoptosis and inflammatory modulation

Transcriptomic analyses of ASFV-infected porcine alveolar macrophages (PAMs) have demonstrated that TNF superfamily cytokines- including FASLG, LTA, LTB, and TNFSF10- are major contributors to ASF pathogenesis through apoptosis induction (Zhu *et al.*, 2019). ASFV simultaneously encodes anti-apoptotic proteins (notably pA224L, an inhibitor of apoptosis) protecting the infected macrophage from premature death, thereby maximising viral replication time (Wang *et al.*, 2022). Simultaneously, ASFV suppresses anti-inflammatory signalling while amplifying pro-inflammatory responses and reactive oxygen species production, creating a dysregulated inflammatory environment contributing directly to haemorrhagic pathology and tissue damage (Zhu *et al.*, 2019; Wang *et al.*, 2022).

Vaccine development: Current status and critical gaps

The development of an effective ASF vaccine is widely acknowledged as the single most important objective in veterinary infectious disease research (WOAH, 2025; FAO, 2024). Four main vaccine platform categories have been pursued: inactivated vaccines, subunit and nucleic acid vaccines, live attenuated vaccines (LAVs), and experimental viral-vectored vaccines. None has yet achieved the combination of complete protective efficacy, acceptable safety profile,

and regulatory approval needed for global deployment (Fan *et al.*, 2024; Orosco, 2023; Niu *et al.*, 2023; Zhang *et al.*, 2024) (Table 2).

Inactivated vaccines

Traditional inactivated ASFV vaccines have been consistently shown to fail in conferring protective immunity against challenge with virulent strains, even when evaluated with diverse adjuvant formulations and delivery routes (Fan *et al.*, 2024; Wang *et al.*, 2022). This failure is predominantly attributed to the inability of killed virus preparations to stimulate adequate cell-mediated immune responses- particularly cytotoxic CD8+ T lymphocyte (CTL) responses- which appear essential for effective protection against ASFV (Orosco, 2023; Zhang *et al.*, 2024). Moreover, inactivated vaccines may paradoxically have potential to induce ADE in some circumstances, a possibility that has not been adequately systematically investigated but represents a concerning knowledge gap for future development efforts.

Table 2: *ASFV Vaccine platform categories*

Vaccine platform	Mechanism	Efficacy & Status	Key gaps & Concerns
Inactivated Virus	Killed virus ± adjuvant	No protection (Pre-clinical only)	• Insufficient cell-mediated immunity • May paradoxically worsen via ADE •ADE screening required
Subunit & Nucleic Acid	Recombinant protein, DNA, or mRNA	Incomplete protection (Pre-clinical → clinical)	• Humoral-only response (poor CTL) • No field efficacy data •Which antigens cause ADE? • Protective correlates unknown
Live Attenuated (LAV) ✓	Attenuated whole virus (replicating) ✓ BEST AVAILABLE	✓ Best available (Genotype II) • Variable cross-genotype (Commercial: NAVET-ASFAVAC, Vietnam, 2023)	• Reversion-to-virulence risk • Adverse reproductive effects •Field stability & safety in breeding animals?
Viral Vector	ASFV antigens in heterologous vectors	Variable/incomplete (Pre-clinical only)	• Few efficacy studies in target species • Lack of controlled challenge trials •ADE assessment needed

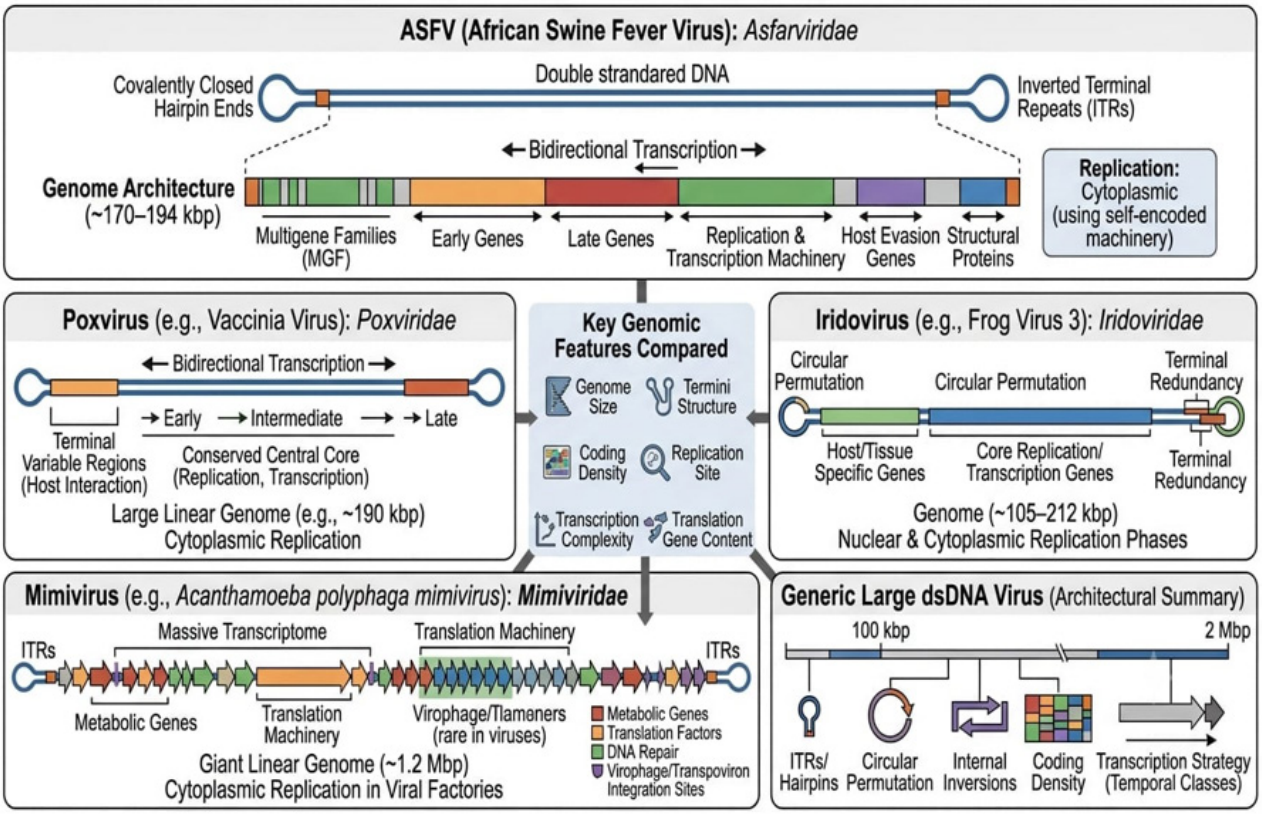

Figure 2: *Comparative genomic organization of african swine fever virus (ASFV) and other large dsDNA viruses.*

Table 3: *Priority research gaps & proposed solutions*

Priority category	Specific gap	Proposed approach	Expected outcome / timeline
Functional Proteomics	>100 ORFs with unknown: • Immune function • Viral virulence role	• CRISPR-based screening • Reverse vaccinology • Structural analysis	Identify novel immune-evasion targets Timeline: 3–5 years
ADE Risk Assessment (URGENT PRIORITY)	Absence of: • Standardized ADE screening • Safety evaluation pipeline	• Mandatory FcγR-dependent ADE assays (in vitro) • In vivo challenge studies • Antigen screening panel	Safe antigen identification; prevent ADE-worsened infection Timeline: 1–2 years
Cell-Mediated Immunity Correlates	Lack of standardized: • CD8+ CTL correlates • NK & γδ T-cell markers	• Standardized ELISPOT & flow cytometry • Harmonized assays across labs • Cross-platform validation	Enable rational vaccine design Timeline: 2–3 years
Cross-Genotype Protection	Protection against non-Genotype II ASFV: • Unknown efficacy • Global gap	• Systematic vaccine testing against all genotypes • Head-to-head comparisons • Field studies	Globally deployable vaccine platforms Timeline: 2–4 years
DIVA-Compatible Diagnostics	Cannot discriminate: • Vaccine response vs. • Natural infection	• Develop infection-specific serological markers • Molecular diagnostic tools	Enable vaccination in control programs Timeline: 2–3 years
NEW: ASFV–Dendritic Cell Interactions	Effects on: • DC maturation & migration • Antigen presentation	• Ex vivo DC infection models • Single-cell transcriptomics • Adjuvant screening	Optimize vaccine formulation & adjuvants Timeline: 2–3 years

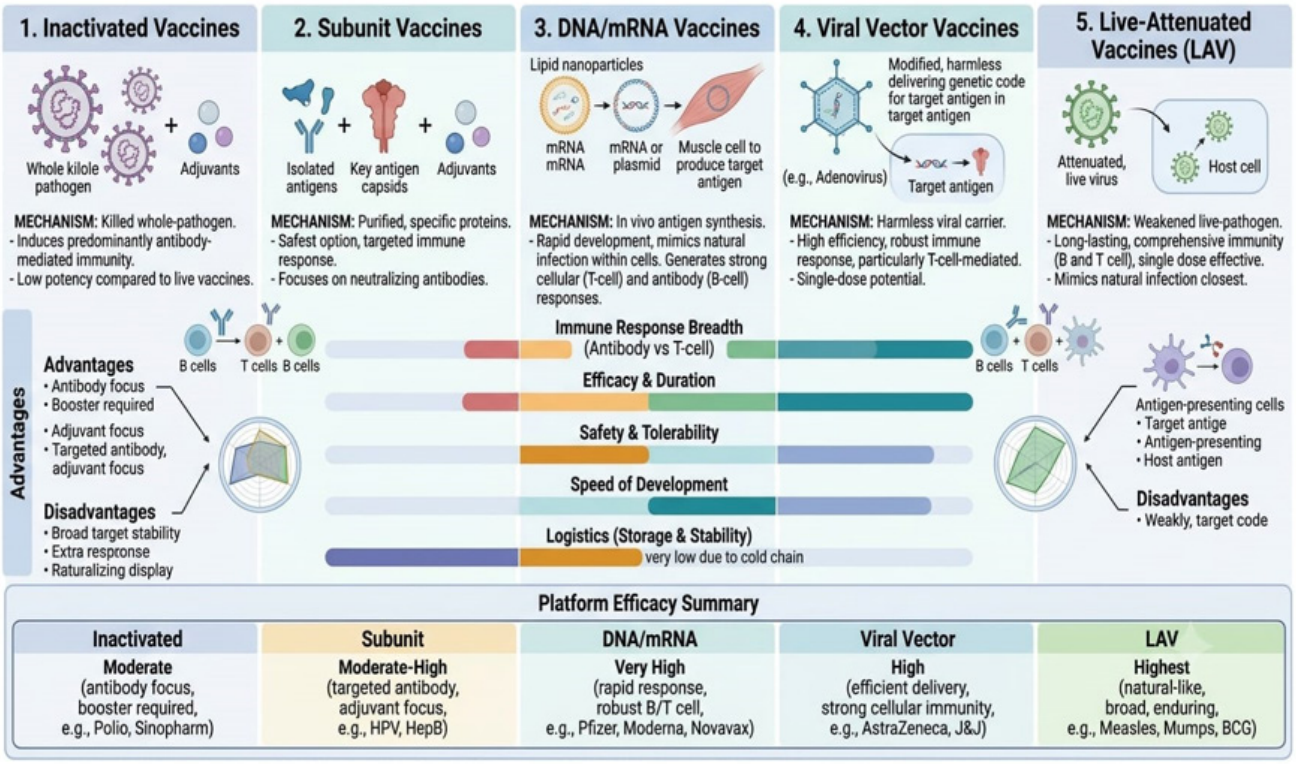

Figure 3: *Comparative vaccine platform efficacy and immunological performance model.*

Subunit and nucleic acid vaccines

All ASFV subunit vaccine candidates evaluated to date have failed to confer complete sterilising protection against challenge with highly virulent homologous strains (Orosco, 2023; Niu *et al.*, 2023; Zhang *et al.*, 2024). This failure persists despite the evaluation of multiple structural proteins and antigen combinations across various delivery platforms, including viral vectors, DNA plasmid vaccines, and mRNA vaccines. Emerging mRNA-based platforms incorporating multiple ASFV antigens represent a scientifically promising but still largely pre-clinical

avenue, with no published data from controlled virulent challenge trials in target species as of April 2025 (Wang and Shi, 2026; Hu *et al*., 2025). The absence of protective efficacy data from rigorously controlled in vivo studies on these newer platforms represents a critical evidence gap (Figure 2).

Live attenuated vaccines (LAVs)

LAVs currently represent the most efficacious ASF vaccine strategy. The regulatory approval of ASFV-G-ΔI177L (marketed as NAVET-ASFAVAC; Navetco, Vietnam) as the world's first commercial ASF LAV in 2022 marked a landmark milestone in the decades-long effort to control this disease (Wang *et al*., 2021). However, LAV development faces critical unresolved challenges. Recent evidence demonstrates that ASFV-G-ΔI177L can revert to virulence after serial passaging in pigs (Urbano *et al*., 2025), and its administration to sows has been associated with adverse reproductive effects including increased abortion rates, raising significant concerns for field deployment (Urbano *et al*., 2025). Cross-protection against the diverse panel of ASFV genotypes circulating globally remains inadequately evaluated, with most studies focussing on genotype II; protection against other genotypes (particularly genotypes I, VIII, and IX) remains largely undefined (Orosco, 2023; Niu *et al*., 2023; Zhang *et al*., 2024) (Figure 3).

Antibody-Dependent enhancement (ADE): A critical and emerging research gap

A particularly alarming and only recently characterised research gap is the phenomenon of ADE in ASFV infection. A pivotal 2024 study demonstrated that antibodies against the ASFV structural protein pA137R-induced in both naturally infected pigs and those immunised with pA137R- paradoxically enhanced viral replication in PAMs through FcγRII- and FcγRIII-mediated mechanisms, increasing viral attachment and cellular internalisation rather than neutralising the virus (Yang *et al*., 2024; Zhai *et al*., 2025). Critically, subsequent research confirmed that pigs immunised with recombinant pA137R exhibited significantly more severe clinical signs and earlier mortality upon virulent ASFV challenge compared with unimmunised control animals (Yang *et al*., 2024; Zhai *et al*., 2025). These findings establish a proof-of-principle that ADE is not merely a theoretical concern but a real and demonstrable hazard for ASFV vaccine candidates.

The implications are profound: current ADE-screening protocols for ASFV vaccines are inadequate, and a comprehensive, standardised, and mandatory ADE-evaluation framework for all vaccine candidates must be established prior to their advancement to field trials (Yang *et al*., 2024; Fuchs *et al*., 2025). Whether other ASFV antigens similarly induce ADE- beyond pA137R- remains entirely unknown and represents a critical knowledge gap that could affect all vaccine platform development efforts.

Priority research directions

Addressing the identified research gaps requires coordinated, multi-disciplinary, and adequately resourced research investments integrated within a comprehensive strategic framework (WOAH, 2025; FAO, 2024). The following priority areas are identified as most urgently requiring attention to accelerate vaccine development and improve global ASF control prospects (Table 3):

Functional proteomics and reverse vaccinology

Systematic functional characterisation of the more than 100 poorly understood ASFV ORFs is essential for identifying novel immune evasion targets and protective antigens (Fan *et al*.,2024). High-throughput functional screening approaches- including CRISPR-based gene editing, transient expression systems, and structural proteomics- integrated with reverse vaccinology computational pipelines represent the most promising route to accelerating this characterisation (Orosco, 2023). These approaches should prioritise identification of viral proteins that suppress dendritic cell maturation, as this remains an understudied area with high translational potential for vaccine adjuvant development.

ADE-Safe Antigen identification and mandatory screening pipeline

A structured, mandatory screening pipeline for evaluating all ASFV vaccine antigen candidates for ADE potential- prior to their inclusion in clinical trial formulations- is urgently needed (Yang *et al*., 2024; Fuchs *et al*., 2025). This pipeline should incorporate: (1) standardised in vitro assays in PAMs with FcγR expression profiling to identify ADE-inducing antigens; (2) analysis of antibody binding kinetics and neutralising capacity across FcγR subtypes; and (3) controlled in vivo challenge studies using both homologous and heterologous ASFV strains in small animal models prior to large-animal trials. Until this

framework is established and implemented, the risk of developing an ADE-inducing vaccine that worsens disease upon natural infection remains unacceptably high (Yang *et al*., 2024).

Correlates of protective cell-mediated immunity

Given compelling evidence that humoral immunity alone is insufficient for ASFV protection, rigorously defining the correlates of cell-mediated protective immunity- particularly CD8+ cytotoxic T lymphocyte (CTL) responses, natural killer (NK) cell activity, and γδ T-cell function- is a fundamental research priority (Orosco, 2023; Niu *et al*., 2023; Zhang *et al*., 2024). Standardised assays for measuring CTL responses in swine are urgently needed, analogous to ELISPOT (enzyme-linked immunosorbent spot)–based approaches used in human vaccine trials. Such standardised approaches would enable meaningful cross-study comparisons, meta-analyses, and harmonisation of immune response measurement across different research groups working on ASFV vaccines globally.

Cross-Genotype vaccine platforms

With multiple ASFV genotypes- including recombinant strains with complex mosaic genomes- circulating simultaneously across different global regions, the development of broadly protective vaccines through conserved antigen targeting or multi-genotype LAV platforms is critical for long-term and globally applicable pandemic control (Wang *et al*., 2021). Current vaccine development efforts have disproportionately focused on genotype II, which dominates Europe and Asia, while protection against African genotypes (I, VIII, IX, etc.) remains largely undefined despite their continued circulation. A systematic evaluation of vaccine candidates against the full spectrum of circulating ASFV genetic diversity is essential before any vaccine can be considered suitable for global deployment.

Advanced diagnostic and DIVA-Compatible tools

The development and rigorous field validation of DIVA (Differentiation of Infected from Vaccinated Animals)- compatible diagnostic assays are a practical prerequisite for any future vaccination-based control programme, as they enable epidemiological surveillance to continue alongside vaccination campaigns (Fan *et al*., 2024). Current LAV candidates, including ASFV-G-ΔI177L, do not allow clear DIVA distinction, significantly limiting their utility in national control programmes seeking to maintain disease-free status. The development of serological and molecular assays that specifically discriminate between ASFV-infection-induced and vaccine-induced antibodies and cellular responses is essential for post-vaccination surveillance in endemic regions.

ASFV- Dendritic cell interactions and immunosuppression mechanisms

ASFV effects on dendritic cell maturation, migration, cytokine production, and antigen-presenting capacity remain largely unexplored. Research utilising ex vivo dendritic cell infection models, single-cell transcriptomics, and mechanistic assays of antigen presentation is needed to reveal key immunosuppressive mechanisms and to inform rational adjuvant and vaccine formulation design strategies.

Limitations of this review

Despite the broad synthesis of current evidence on ASFV immune evasion and vaccine development, this review has several important limitations that should be acknowledged:

Rapidly evolving research landscape

The rapidly evolving nature of ASFV research means that newly emerging studies- particularly those related to live attenuated vaccine safety, mRNA-based vaccine platforms, and antibody-dependent enhancement mechanisms- may not have been fully captured beyond the final literature inclusion period. As this field advances at an accelerated pace, readers should regularly consult primary literature databases for the most current evidence.

Laboratory-Based Evidence vs. Field reality

Much of the currently available evidence is derived from experimental studies conducted under controlled laboratory settings, which may not fully reflect field-level vaccine performance, epidemiological variability across diverse pig production systems, or vaccine efficacy in naturally infected populations. The translation of laboratory-optimised vaccine candidates to field effectiveness remains a critical and often unaddressed challenge.

Limited mechanistic understanding

Several conclusions regarding immune correlates of protection, ADE mechanisms, and dendritic cell suppression remain based on a relatively limited

number of mechanistic studies, particularly in porcine models. This restricts broader generalisability and extrapolation to field conditions where virus-host interactions differ significantly from controlled laboratory settings.

Heterogeneity in study design and methodologies

Heterogeneity in study design, viral genotypes investigated, host conditions (age, immunocompetence status), and immunological outcome measures across published studies limit direct comparison between vaccine candidates and immune response findings. Standardised outcome reporting and harmonised methodologies across research groups are needed to improve evidence synthesis.

Publication bias and language restrictions

While English-language publications were prioritised in this review, studies published in other languages or in non-English-indexed databases may have been underrepresented. Additionally, publication bias toward positive vaccine efficacy results may lead to overestimation of current vaccine platform success, while negative or null findings (vaccine failures) from unpublished sources or grey literature are not captured. This bias could distort the overall assessment of vaccine development progress.

Narrative rather than systematic methodology:

This review employs a narrative synthesis approach rather than formal systematic review methodology (PRISMA guidelines), meaning that study selection, quality assessment, and data extraction were not conducted using pre-specified protocols independently verified by multiple reviewers. While the narrative approach allows broader conceptual synthesis, it is more susceptible to reviewer bias in study selection and interpretation.

Priority research framework

Accelerating the development of safe and broadly protective African swine fever (ASF) vaccines requires a coordinated, multidisciplinary research strategy. Based on the evidence synthesized in this review, the following priorities should guide future investigations:

Functional characterization of ASFV proteins to identify virulence factors, immune evasion mechanisms, and novel vaccine targets using genomics, proteomics, and reverse vaccinology.

Identification of immune correlates of protection, particularly cell-mediated immune responses, to support rational vaccine design and standardized immunological evaluation.

Development of safe and broadly protective vaccine platforms with demonstrated cross-genotype efficacy, genetic stability, and compatibility with DIVA-based surveillance programs.

Establishment of standardized vaccine safety assessment pipelines, including routine evaluation for antibody-dependent enhancement (ADE) and long-term safety under experimental and field conditions.

Investigation of host–virus interactions, especially ASFV modulation of macrophages and dendritic cells, to improve understanding of immune evasion and identify new immunotherapeutic targets.

Strengthening international collaboration and surveillance through harmonized research protocols, data sharing, and coordinated efforts among research institutions, regulatory agencies, and international organizations to accelerate vaccine development and global ASF control.

Conclusions and Recommendations

African swine fever remains one of the most significant threats to global swine health and food security, largely because an effective, safe, and broadly protective vaccine is still unavailable. This review highlights that the major barriers to successful vaccine development arise from the complex biology of ASFV, including its poorly characterized genome, sophisticated immune evasion mechanisms, incomplete understanding of protective cell-mediated immunity, and concerns regarding the safety and cross-genotype efficacy of current vaccine candidates. Emerging evidence of antibody-dependent enhancement further emphasizes the importance of careful antigen selection and comprehensive vaccine safety assessment.

Future research should focus on functional characterization of ASFV proteins, identification of immune correlates of protection, development of cross-genotype and DIVA-compatible vaccine platforms, and establishment of standardized frameworks for vaccine efficacy and safety evaluation. Coordinated multidisciplinary research integrating

virology, immunology, genomics, and vaccinology will be essential to accelerate the development of safe and effective vaccines and to support sustainable global control of African swine fever.

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Novelty Statement

This review provides an updated and research gap–oriented synthesis of African swine fever virus (ASFV) vaccine development by integrating recent advances in viral immune evasion, vaccine platform limitations, and emerging safety concerns. Unlike previous reviews that primarily summarize vaccine candidates, this article systematically identifies the critical knowledge gaps hindering the development of safe and broadly protective ASF vaccines. Particular emphasis is placed on antibody-dependent enhancement (ADE) as an emerging challenge, dendritic cell–mediated immunosuppression, incomplete characterization of ASFV proteins, immune correlates of protection, cross-genotype vaccine development, and DIVA-compatible vaccine strategies. The review concludes with a structured research framework that prioritizes future investigations and provides practical directions for accelerating rational ASF vaccine development and global disease control.

Author Contributions

Md. Rimon Bhuiyan: Conceptualization, Methodology, Writing- Original Draft, Writing-Review & Editing, Supervision.
Syeda Shamapika Ahmed Shimi, Sumit Sharma, Md. Raufur Rahman Akanda, Md. Abdul Mannan Bhuiyan, and Mst. Roksana Akter: Writing-Original Draft, Data Curation, Critical Revision.

Generative AI and AI-assisted technology statement

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

Conflict of interest

The authors declare no conflicts of interest relevant to this work.

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