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Cowpox virus and cowpox-like diseases in cattle and buffalo: A comprehensive review

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Abstract Cowpox virus (CPXV) is a zoonotic orthopoxvirus of veterinary and public-health importance because of its broad host range, phylogenomic diversity, and diagnostic complexity. This comprehensive review summarizes current knowledge of CPXV taxonomy, genome organization, host range, transmission ecology, clinical disease, differential diagnosis, laboratory confirmation, molecular epidemiology, and One Health relevance, with particular attention to bovine hosts and the epidemiological context of Iraq and the Middle East. Although historically linked to cattle, current evidence supports a multi-host reservoir–spillover model in which wild rodents are considered the most plausible reservoirs, whereas domestic animals, captive species, livestock, and humans are generally regarded as incidental hosts. In cattle and buffalo, pox-like lesions may resemble those caused by vaccinia-like orthopoxviruses, buffalopox virus, parapoxviruses, lumpy skin disease virus, bovine herpes mammillitis, or non-infectious teat disorders. In water buffalo, published orthopoxvirus literature is dominated by buffalopox rather than confirmed classical CPXV, making etiological confirmation especially important. Clinical and histopathological findings are valuable for recognizing suspected cases but remain insufficient for definitive species-level identification. Molecular approaches, including PCR, sequencing, and whole-genome sequencing, are therefore essential for clarifying viral identity, resolving taxonomic complexity, supporting genomic tracing, and improving molecular epidemiology. In Iraq, published evidence has focused mainly on lumpy skin disease virus and parapoxviruses, while comparable genomic evidence for classical CPXV remains limited, representing an important knowledge gap. Pox-like disease may also impair animal welfare and milk production and create occupational exposure risks for milkers, animal handlers, veterinarians, and laboratory personnel. Overall, integrated field investigation, molecular confirmation, phylogenetic analysis, biosecurity, and One Health surveillance are needed to strengthen detection and interpretation of cowpox-like diseases in Iraq and the wider region.

Keywords: orthopoxvirus, pox-like lesions, molecular diagnosis, whole-genome sequencing, zoonoses, one health

1. Introduction

For this narrative review, relevant literature was identified through searches of PubMed, Scopus, Web of Science, and Google Scholar, with particular emphasis on publications from 2020 to 2026, while older landmark studies were retained when necessary for historical, taxonomic, or virological context. Search terms included combinations of “cowpox virus,” “Orthopoxvirus,” “cowpox-like disease,” “cattle,” “water buffalo,” “buffalopox,” “vaccinia-like virus,” “parapoxvirus,” “lumpy skin disease,” “molecular diagnosis,” “PCR,” “whole-genome sequencing,” “phylogenomics,” “Iraq,” and “Middle East.” Particular attention was given to studies addressing cattle, buffaloes, Iraq, the Middle East, molecular diagnosis, genomic characterization, differential diagnosis, and zoonotic relevance.

1.1. General characteristics of poxviruses

Members of the family *Poxviridae* are large, enveloped, brick-shaped to ovoid viruses with linear double-stranded DNA genomes and covalently closed hairpin termini. Their genomes are among the largest animal-virus genomes, ranging from approximately 128 to 375 kbp, and encode proteins required for replication, transcription, morphogenesis, and virus–host interactions (Moss, 2013; McInnes et al., 2023). Poxviruses replicate mainly in the cytoplasm within viral factories, a feature that distinguishes them from most DNA viruses. Veterinarily, they cause cutaneous and mucosal lesions that may overlap clinically and pathologically; therefore, laboratory confirmation is essential for accurate diagnosis, surveillance, and genomic characterization, particularly for genetically diverse and zoonotically important viruses such as CPXV (Moss, 2013; Bruneau et al., 2023; McInnes et al., 2023).

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1.2. Taxonomic classification of the family Poxviridae

According to the current ICTV taxonomy, the family *Poxviridae* belongs to the realm *Varidnaviria*, kingdom *Bamfordvirae*, phylum *Nucleocytoviricota*, class *Pokkesviricetes*, and order *Chitovirales*. It includes two major subfamilies: *Chordopoxvirinae*, which infect vertebrates, and *Entomopoxvirinae*, which infect insects. This classification reflects evolutionary separation while preserving the shared structural and genomic features of poxviruses. Because poxviruses differ in host range, genome organization, gene content, phylogeny, and zoonotic potential, comparative genomics and phylogenetic analysis are essential for distinguishing clinically similar pox-like diseases (Gubser et al., 2004; Yu et al., 2021; McInnes et al., 2023).

1.3. Veterinary and zoonotic importance of poxviruses

Poxviruses are important veterinary pathogens of domestic, wild, and companion animals, with variable host range, virulence, tissue tropism, and clinical outcomes. In livestock, they commonly cause papular, pustular, nodular, crusted, or proliferative lesions that may reduce welfare and productivity by decreasing milk or meat production, causing weight loss, increasing treatment costs, leading to secondary complications, and reducing market value. The genus *Orthopoxvirus* is also important zoonotically, as several members can infect humans through contact with infected animals, lesions, body fluids, or contaminated environments. Reduced cross-protective immunity after cessation of smallpox vaccination further supports the need for One Health surveillance that integrates animal reservoirs, host ecology, human exposure, genomic monitoring, and public health preparedness (Haller et al., 2014; Limon et al., 2020; Gieryńska et al., 2023; De Pascali et al., 2024).

1.4. Defining features, major species, and serological cross-reactivity of the genus Orthopoxvirus

The genus *Orthopoxvirus* includes large double-stranded DNA viruses of major medical, zoonotic, and veterinary importance. These viruses differ in host range, ecology, genome content, and pathogenicity, ranging from host-specialized to broad-host-range viruses. Host specialization is often associated with genome reduction, whereas broad-host-range orthopoxviruses usually retain larger genomes and diverse immune-modulating genes (Reynolds et al., 2018; Tseng et al., 2025). Major orthopoxviruses include variola virus, vaccinia virus, cowpox virus, mpox virus, camelpox virus, and ectromelia virus, which differ in host association and disease relevance (McInnes et al., 2023; Reynolds et al., 2018). A defining feature of this genus is strong serological cross-reactivity due to shared antigens, which supports cross-protection after vaccinia-based vaccination but limits species-level diagnosis by conventional serology. Definitive identification generally requires PCR, sequencing, or genomic analysis (Grossegesse et al., 2023; Byrne et al., 2025; McInnes et al., 2023).

2. Cowpox Virus: Historical Background and Current Scientific Understanding

2.1. Historical background of Cowpox virus

Cowpox has a central place in infectious disease history because the disease historically known as “cowpox” contributed to the development of vaccination against smallpox. Rural observations in England linked cow-pox exposure among milkmaids to protection against smallpox, and Edward Jenner later transformed this observation into an experimental preventive method by inoculating James Phipps in 1796 with material from cow-pox lesions. This work established vaccination as a safer alternative to variolation and marked a milestone in the history of immunization (Riedel, 2005). However, the historical term “cow-pox” should not be equated directly with modern CPXV classification. Genomic studies show that viruses historically labeled as CPXV are not genetically uniform but belong to divergent phylogenetic groups. Historical overlap among cowpox, vaccinia, and horsepox further complicates interpretation, making genomic characterization, phylogenetic placement, and comparative analysis essential for modern CPXV identification (Carroll et al., 2011; Schrick et al., 2017; Molteni et al., 2022).

2.2. Evolution of scientific understanding of Cowpox virus

Scientific understanding of CPXV has shifted from a host- and lesion-based concept to a genome-informed evolutionary and ecological framework. Modern CPXV research relies on comparative genomics, phylogenetics, host-range assessment, and ecological context, demonstrating that CPXV is not merely a bovine-associated poxvirus but rather part of a broader zoonotic orthopoxvirus complex with diverse hosts and marked evolutionary heterogeneity (Bruneau et al., 2023; Diaz-Cánova et al., 2022). Ecologically, CPXV is recognized as a Eurasian orthopoxvirus with a broad host range involving domestic animals, captive wildlife, zoo animals, rodents, and humans. Wild rodents are the most plausible reservoirs, while cattle, cats, zoo animals, and humans are generally spillover hosts (Chantrey et al., 1999; Silva et al., 2021; Bruneau et al., 2023). Whole-genome sequencing has further shown that CPXV-related viruses form multiple divergent clusters, requiring genomic and molecular epidemiological approaches for accurate interpretation (Diaz-Cánova et al., 2022).

2.3. Taxonomic complexity and phylogenomic diversity of Cowpox virus

Genome-based studies show that the designation "cowpox virus" does not represent a single, uniform, or evolutionarily coherent lineage. Earlier classifications relied on host association, lesion morphology, or classical phenotypes. However, comparative genomics has demonstrated that viruses traditionally labeled CPXV are genetically heterogeneous and may comprise several distinct lineages rather than a single monophyletic group (Carroll et al., 2011; Mauldin et al., 2017). Whole-genome studies confirmed this complexity: Carroll et al. (2011) questioned the notion of CPXV as a single species, Mauldin et al. (2017) highlighted problems with host-based naming, and Dabrowski et al. (2013) and Franke et al. (2017) showed that CPXV isolates cluster into multiple clades. Therefore, suspected CPXV isolates should not be classified by host species, lesion appearance, or historical terminology alone, but by whole-genome sequencing, comparative genomics, and phylogenomic analysis (Carroll et al., 2011; Dabrowski et al., 2013; Mauldin et al., 2017; Franke et al., 2017).

3. Morphology, Genome Organization, and Molecular Biology of Cowpox Virus

3.1. Virion morphology and ultrastructure

Cowpox virus shares the typical poxvirus morphology: large, enveloped, brick-shaped to ovoid virions with linear double-stranded DNA genomes. Poxvirus particles are approximately 220–450 nm long and possess a complex lipoprotein membrane with tubular or globular surface structures, features characteristic of *Poxviridae* rather than CPXV alone (McInnes et al., 2023). This structural complexity supports cytoplasmic replication and viral autonomy, including virus-encoded RNA polymerase activity, as shown in studies of vaccinia virus transcription (McInnes et al., 2023; Grimm et al., 2019; Walsh, 2017). Electron microscopy can detect poxvirus-like particles but cannot distinguish CPXV from other orthopoxviruses; species-level identification requires PCR, sequencing, or whole-genome phylogenetics. Nevertheless, virion size, membrane organization, and surface proteins remain important for attachment, entry, morphogenesis, and spread (McInnes et al., 2023; Hyun, 2022; Yu et al., 2025).

3.2. Genome type, size, and organization

CPXV, like other poxviruses, has a large linear double-stranded DNA genome with covalently closed terminal hairpins. Across *Poxviridae*, genome sizes range from approximately 128 to 375 kbp, while CPXV is among the larger orthopoxviruses. Fennoscandian CPXV genomes are approximately 220–222 kbp with 215–219 predicted open reading frames, reflecting extensive coding capacity and supporting its broad host range, biological diversity, and taxonomic complexity (McInnes et al., 2023; Díaz-Cánova et al., 2022; Bruneau et al., 2023). The CPXV genome follows the typical orthopoxvirus pattern, with conserved central genes involved in replication, transcription, and virion formation, and more variable terminal regions encoding host-range, immunomodulatory, pathogenicity, and virus–host interaction proteins (Hendrickson et al., 2010; Gruber et al., 2018; Bruneau et al., 2023).

3.3. Conserved and variable genomic regions

The orthopoxvirus genome is organized into a conserved central region and more variable terminal regions. The central region encodes essential functions such as DNA replication, transcription, mRNA biosynthesis, virion assembly, and other core life-cycle steps. These genes are functionally constrained and mainly shaped by purifying selection, making them useful for deep evolutionary comparison (Esteban & Hutchinson, 2011; Molteni et al., 2023). In contrast, terminal regions vary in sequence and gene content and encode proteins involved in host range, virulence, immune evasion, and virus–host interactions. In CPXV, variation in terminal and accessory genes is especially important because phylogenomic studies show that CPXV-related viruses are highly heterogeneous and form multiple lineages; therefore, genome-wide comparisons are needed for lineage assignment and biological interpretation (Esteban & Hutchinson, 2011; Bruneau et al., 2023; Díaz-Cánova et al., 2022).

3.4. Host-range, virulence, and immune evasion genes

CPXV is notable for its broad host range, partly linked to its large repertoire of accessory and host-interaction genes. However, host range also depends on host restriction factors, cell type, immune environment, ecological exposure, and virus–host interactions. Many poxvirus host-range factors act after entry by antagonizing antiviral restriction pathways, including SAMD9/SAMD9L, IFIT proteins, FAM111A, and ZAP (Bruneau et al., 2023; Oliveira et al., 2017; Xiang, 2025). CPXV virulence is closely linked to immune evasion through interference with antigen presentation, cytokine and chemokine signaling, NK-cell activation, apoptosis, and complement. Examples include CPXV14, which engages Fcγ receptors, and p28/N1R, which supports replication in human and murine macrophages. Variation in terminal host-interaction genes likely contributes to CPXV host range, zoonotic potential, virulence, and evolutionary diversity (Alzhanova & Früh, 2010; Esteban & Hutchinson, 2011; Bourquain et al., 2021; Iyer et al., 2022; Bruneau et al., 2023; Xiang, 2025).

3.5. Replication cycle and molecular biology of Cowpox virus

CPXV follows the conserved orthopoxvirus replication strategy, with gene expression, DNA replication, and virion assembly occurring predominantly in the cytoplasm. After entry and core release, early transcription begins within the viral core via the virion-associated RNA polymerase and transcription factors. Gene expression then proceeds through early, intermediate, and late phases; late genes mainly encode structural proteins, morphogenesis factors, and enzymes packaged into progeny virions. Although many mechanistic details come from vaccinia and mpox studies, they are relevant to CPXV because core replication and transcription machinery is conserved (Moss, 2013; Broyles, 2003; Grimm et al., 2019; Yang et al., 2010; Deng et al., 2025). Viral DNA replication occurs in cytoplasmic factories that concentrate viral genomes, replication proteins, transcriptional components, and selected host factors. Virion assembly proceeds from immature virions to mature infectious virions and extracellularly wrapped forms that enhance spread. Recent vaccinia work suggests viral factories may function as biomolecular condensates, with H5 contributing to factory formation, DNA replication, and progeny production (Condit et al., 2006; Roberts & Smith, 2008; Liu et al., 2014; Moss, 2015; Greseth & Traktman, 2022; Zhu et al., 2025).

4. Host Range, Transmission Ecology, and Global Epidemiology of Cowpox Virus

CPXV is a zoonotic Eurasian orthopoxvirus with a broad host range and an ecology based on maintenance in wildlife and spillover into incidental hosts. Modern evidence does not support a cattle-centered view; instead, CPXV is best interpreted within a multi-host reservoir–spillover system, where wild rodents are the most plausible reservoirs, while cattle, buffaloes, cats, pet rodents, zoo animals, captive mammals, and humans are usually spillover hosts. Field studies in Great Britain identified bank voles, wood mice, and short-tailed field voles as important reservoirs, and human cases are commonly linked to contact with infected animals or lesion material, including pet rodents. Thus, CPXV detection in cattle or buffalo indicates exposure within a broader ecological network, not primary reservoir status (Chantrey et al., 1999; Campe et al., 2009; Ninove et al., 2009; Bruneau et al., 2023; Silva et al., 2021).

4.1. Natural reservoirs and incidental hosts

Wild rodents are the most likely natural reservoirs of CPXV, while most other infected species are incidental or spillover hosts. Bank voles, wood mice, and short-tailed field voles have been identified as important reservoirs in Great Britain, although these data should not be generalized outside Europe without local evidence. Despite the name “cowpox,” cattle are not considered the principal natural host. CPXV infections are more commonly recognized in domestic cats, pet rodents, zoo animals, captive exotic mammals, and humans. Therefore, detection in domestic or captive animals indicates spillover and exposure risk rather than long-term reservoir competence (Chantrey et al., 1999; Hazel et al., 2000; Silva et al., 2021; Bruneau et al., 2023; Costa et al., 2023).

4.2. Routes of transmission and the rodent–livestock–human interface

CPXV transmission occurs mainly through direct contact with infected animals, lesion material, or contaminated animal-associated materials, or through entry via damaged skin and mucocutaneous surfaces. Epidemiologically, CPXV is best understood within a reservoir–spillover framework: wild rodents are plausible reservoirs, whereas cats, pet rodents, zoo animals, livestock, and humans are usually incidental hosts. Human infections are often linked to infected cats or pet rodents, especially rats. Thus, transmission should be viewed as a broad rodent–domestic/captive animal–human interface rather than a simple rodent–livestock–human chain. In cattle and buffalo, suspected infection should be interpreted as possible spillover rather than proof of bovine reservoir status (Bruneau et al., 2023; Silva et al., 2021; Campe et al., 2009; Ninove et al., 2009; Möstl et al., 2013).

4.3. Geographic distribution and epidemiological patterns

Current evidence places CPXV mainly in Europe and parts of Eurasia, where most clinical and genomic reports involve domestic animals, companion animals, zoo animals, captive wildlife, and humans. Although CPXV taxonomy remains complex, its best-supported distribution is Eurasian rather than globally endemic. Epidemiologically, CPXV usually appears as sporadic cases, small clusters, or localized outbreaks, consistent with reservoir–spillover transmission rather than sustained transmission in cattle or humans (Bruneau et al., 2023; Silva et al., 2021; Kaysser et al., 2010; Costa et al., 2023).

4.4. Reported animal and human outbreaks

CPXV can cause clinically significant infections and localized outbreaks in diverse animal hosts, especially captive and zoological species. Recurrent cheetah outbreaks in Denmark, including fatal cases, suggested repeated introductions from wild rodent reservoirs. Genome-wide studies also documented CPXV in humans and several animal species, including rats, cats, jaguarundis, beavers, elephants, maras, and mongooses, confirming broad host range and phylogenetic diversity (Dabrowski et al., 2013; Stagegaard et al., 2017). Human cases are usually zoonotic rather than sustained human-to-human events. Pet-

rat-associated outbreaks, rat-to-elephant-to-human transmission, and severe fetal infection after maternal CPXV infection emphasize the zoonotic relevance of CPXV and support a reservoir–spillover interpretation (Kurth et al., 2008; Vogel et al., 2012; Ferrier-Rembert et al., 2021; Stagegaard et al., 2017).

4.5. Ecological determinants and gaps in global surveillance

CPXV occurrence is shaped by ecological contact between wildlife reservoirs and susceptible incidental hosts. Field studies in Great Britain show that CPXV circulates in wild rodents, especially bank voles and wood mice, and that transmission varies with host species, contact structure, and local conditions (Hazel et al., 2000; Carslake et al., 2006). At the wildlife–domestic animal interface, recognized infections often reflect exposure opportunities: cats, pet rodents, zoo animals, and captive species may acquire infection from infected rodents or contaminated environments and can reveal local viral diversity (Kaysser et al., 2010; Stagegaard et al., 2017; Ninove et al., 2009). However, global surveillance remains incomplete and biased toward clinically apparent cases, while systematic wildlife surveillance is limited. Broader molecular surveillance integrating field ecology, pathology, PCR, sequencing, and phylogenomics is needed to clarify CPXV distribution, host range, lineage diversity, and spillover pathways (Tseng et al., 2025).

5. Clinical Disease, Pathogenesis, and Immune Response in Cattle and Buffalo

Interpretation of cowpox-associated disease in bovids requires diagnostic caution. In cattle, confirmed classical CPXV infection is uncommon, and contemporary descriptions of bovine CPXV disease remain limited compared with broader orthopoxvirus literature. Therefore, pox-like lesions in cattle should not be attributed to CPXV without laboratory confirmation (Bruneau et al., 2023; MacNeill et al., 2025). In water buffalo, the literature more commonly concerns buffalopox virus, a vaccinia-related orthopoxvirus, rather than confirmed classical CPXV. Buffalopox is a zoonotic disease primarily reported in Asian buffaloes, with occasional cases in cattle and humans (Martínez-Burnes et al., 2024; Pattanaik et al., 2024; Eltom et al., 2020). Thus, confirmed CPXV disease in cattle should be distinguished from CPXV-like or orthopoxvirus-like disease in buffalo, where buffalopox and vaccinia-like agents dominate; definitive attribution requires PCR, sequencing, or whole-genome analysis (MacNeill et al., 2025; Martínez-Burnes et al., 2024; Eltom et al., 2020).

5.1. Clinical manifestations in cattle

In cattle, orthopoxvirus-associated disease is most commonly reported in lactating animals, primarily affecting the teats and udder. Because confirmed classical CPXV in cattle is uncommon, many clinical descriptions are based on bovine vaccinia and vaccinia-like infections, which produce cowpox-like mammary lesions and require molecular confirmation. Lesions may be exanthematous, painful, ulcerative, necrotic, or crusting, often progressing from maculopapular rash to papules, vesicles, pustules, and scabs (Matos et al., 2018; MacNeill, 2022). Mammary lesions may interfere with milking, impair milk removal, predispose to secondary mastitis, and reduce milk production, creating welfare and economic concerns (Matos et al., 2018; MacNeill, 2022). Calves may develop oral or muzzle lesions after suckling infected teats. Because similar mammary lesions may result from CPXV, vaccinia-like orthopoxviruses, pseudocowpox virus, or bovine herpes mammillitis virus, diagnosis should rely on laboratory confirmation (Matos et al., 2018; MacNeill, 2022; MacNeill et al., 2025).

5.2. Clinical manifestations in buffalo

In water buffalo, direct evidence of classical CPXV disease is scarce, whereas the orthopoxvirus literature primarily concerns buffalopox virus. This distinction is important because pox-like disease in buffaloes cannot be confidently attributed to classical CPXV without laboratory confirmation. Nevertheless, buffalopox literature is useful for understanding orthopoxvirus-like disease and differential diagnosis in buffaloes (Eltom et al., 2020; Martínez-Burnes et al., 2024; Pattanaik et al., 2024). Reported buffalopox lesions commonly involve the muzzle, udder, teats or nipples, inner thighs, scrotum, ears, and periocular regions. Mild cases may show focal pustular lesions with central necrosis, while severe cases may become diffuse or systemic. Mortality is usually low, but morbidity and production losses can be substantial because udder and teat involvement may reduce milk yield by approximately 40–70% and predispose to mastitis (Eltom et al., 2020; Martínez-Burnes et al., 2024; Pattanaik et al., 2024).

5.3. Lesion development, pathogenesis, and tissue tropism

Orthopoxvirus-associated disease in cattle and buffalo is mainly epitheliotropic, affecting cutaneous and mucocutaneous sites. In cattle, lesions often involve the teats and udder and may progress through papules, vesicles, pustules, ulceration, crusting, and scab formation. In milking animals, teat trauma may rupture lesions and produce painful ulcerative or crusted mammary lesions, reflecting epidermal viral replication, epithelial injury, and inflammation rather than primary deep-tissue disease (MacNeill, 2022; MacNeill et al., 2025; Matos et al., 2018). Lesion distribution depends on exposure route and host factors: teat lesions suggest microtrauma during milking, while oral lesions in calves may follow suckling infected teats. In buffaloes, buffalopox lesions may affect the muzzle, udder, teats, inner thighs, scrotum, ears, and periocular regions. Overall,

tissue tropism centers on stratified squamous epithelium and is modified by host species, site, trauma, secondary infection, and husbandry conditions (Eltom et al., 2020; Martínez-Burnes et al., 2024; MacNeill et al., 2025).

5.4. Histopathological changes and host immune response

Histologically, bovine and buffalo pox-like lesions show typical poxvirus dermatitis, including epithelial hyperplasia, ballooning degeneration, hyperkeratosis, crusting, epithelial necrosis, intracytoplasmic inclusion bodies, and inflammatory infiltration. These changes support poxvirus infection but cannot identify the viral species; PCR, sequencing, or whole-genome analysis is required to distinguish CPXV from vaccinia-like orthopoxviruses, buffalopox virus, parapoxviruses, and other agents (MacNeill, 2022; MacNeill et al., 2025). Direct immune-response data for confirmed CPXV infection in cattle and buffalo are limited; interpretation should therefore be drawn cautiously from broader orthopoxvirus immunology. Host defense involves innate recognition, inflammatory and interferon pathways, and adaptive immunity. At the same time, CPXV encodes immunomodulatory proteins that interfere with antigen presentation, cytokine/chemokine signaling, NK-cell activity, apoptosis, complement, DNA sensing, NF-κB, interferon responses, and restriction factors. Disease outcome reflects a balance between host antiviral defense and viral immune evasion (Alzhanova & Früh, 2010; Hernáez & Alcamí, 2024; Xiang, 2025).

6. Differential Diagnosis of Pox-Like Lesions in Cattle and Buffalo

Differential diagnosis of pox-like lesions in cattle and buffalo is challenging because infectious and non-infectious conditions may produce overlapping papular, pustular, ulcerative, crusting, vesicular, proliferative, or nodular lesions. Lesion distribution, age, herd history, systemic signs, lactation status, and zoonotic context may guide suspicion, but gross appearance is insufficient for definitive diagnosis. Suspected CPXV cases, therefore, require PCR, sequencing, or whole-genome analysis to distinguish orthopoxviruses from parapoxviruses, lumpy skin disease virus, bovine herpes mammillitis, and non-infectious teat disorders (MacNeill et al., 2025; Graf et al., 2024; Makoga et al., 2024).

6.1. Buffalopox virus and vaccinia-like viruses

Buffalopox virus and other vaccinia-like orthopoxviruses are important differential diagnoses of cowpox-like disease, especially in buffalo-rearing regions. Buffalopox is a transmissible zoonotic disease primarily affecting Asian water buffaloes, with occasional infections in cattle and humans. Lesions may involve the udder, teats, muzzle, periocular region, ears, thighs, scrotum, and genital or perineal skin, often with painful mammary lesions, reduced milk yield, and secondary mastitis. Differentiating CPXV from BPXV or vaccinia-like viruses is essential for diagnosis, outbreak attribution, epidemiological interpretation, and zoonotic-risk assessment (Eltom et al., 2020; Martínez-Burnes et al., 2024; Pattanaik et al., 2024).

6.2. Pseudocowpox virus and bovine papular stomatitis virus

Pseudocowpox virus and bovine papular stomatitis virus are major parapoxvirus differentials because their lesions may resemble orthopoxvirus infection. PCPV usually affects dairy-cattle teats, producing papular, pustular, and scab-forming lesions. At the same time, BPSV more often causes papular, erosive, or ulcerative lesions of the lips, muzzle, nostrils, tongue, and oral cavity, especially in calves. However, lesion distribution is not definitive, and coinfection or sequential detection may occur. PCR, sequencing, or genome-scale analysis is therefore needed for reliable species-level differentiation (Graf et al., 2024; Sindryakova et al., 2024; Shimizu et al., 2020; Aytoğlu et al., 2025).

6.3. Lumpy skin disease virus and bovine herpes mammillitis

Lumpy skin disease virus should be considered when lesions are nodular, generalized, or associated with fever, lymphadenopathy, ocular or nasal discharge, reduced appetite, and decreased milk production. Although systemic signs and widespread nodules may help distinguish LSD from localized mammary pox-like lesions, atypical cases require molecular confirmation. Bovine herpes mammillitis, caused by bovine alphaherpesvirus 2, is another important differential in lactating cows, producing erosive-ulcerative, self-limiting teat and udder lesions that may resemble crusted pox lesions. Therefore, molecular confirmation is essential before assigning cattle or buffalo lesions to a specific poxvirus etiology (Haider et al., 2024; Makoga et al., 2024; Lanave et al., 2020).

6.4. Non-infectious conditions resembling pox-like lesions

Not all pox-like lesions are viral. Non-infectious teat and skin disorders may produce ulcerative, crusting, fissured, hyperkeratotic, necrotic, or open lesions resembling poxvirus infection. Teat open lesions in dairy herds may be linked to dry teat skin, environmental exposure, mechanical irritation, chemical injury, thermal stress, or milking-related factors. They may interfere with milking behavior (Virkler & Wieland, 2023). Because crusting or ulcerative teat lesions are not pathognomonic for poxvirus infection, differential diagnosis should include herd history, lesion chronology, clinical assessment, and virological testing. Altered teat skin condition has also been associated with an increased risk of clinical mastitis, underscoring the herd-health importance of non-infectious teat damage (Wieland et al., 2024; Virkler & Wieland, 2023; MacNeill et al., 2025).

7. Laboratory Diagnosis, Genomic Confirmation, and Molecular Epidemiology

Laboratory diagnosis is indispensable in suspected CPXV infection because pox-like lesions in cattle and buffalo are not etiologically specific. Lesions suspected to represent one poxvirus may be caused by another poxvirus or a different agent with overlapping morphology. This is particularly important because viruses historically grouped as CPXV are genetically heterogeneous and should not be treated as a uniform lineage. Contemporary investigation should therefore move from clinical suspicion to molecular confirmation and, when relevant, genome-scale characterization (Mauldin et al., 2017; Diaz-Cánova et al., 2022).

7.1. Clinical and field diagnosis

Clinical and field diagnoses should be considered presumptive. Lesion morphology, distribution, stage, systemic signs, herd history, host species, and exposure history can help identify suspected cases, but cannot reliably determine the causative virus at the species level. This limitation is important because orthopoxvirus infections, parapoxvirus infections, lumpy skin disease, bovine herpes mammillitis, and non-infectious teat disorders may overlap clinically (Gelaye et al., 2017; Lanave et al., 2020). Molecular studies confirm the need for laboratory testing: multiplex PCR and high-resolution melting assays can differentiate CPXV, LSDV, pseudocowpox virus, and BPSV, while field investigations show that LSD-suspected outbreaks may include BPSV. Field diagnosis should therefore focus on early recognition, lesion documentation, representative sampling, epidemiological recording, and biosecurity before molecular confirmation (Gelaye et al., 2017; Makoga et al., 2024).

7.2. Sample collection, pre-analytical handling, and biosafety considerations

For suspected orthopoxvirus infection, lesion-derived material is the most valuable specimen because viral DNA is usually abundant in active lesions, crusts, scabs, lesion roofs, or lesion swabs. CPXV investigations have confirmed the value of skin-lesion material through virus isolation and electron-microscopic detection of brick-shaped particles. Although recent specimen-performance evidence largely comes from mpox studies, higher viral loads in skin lesions than respiratory samples support lesion-based PCR diagnosis in orthopoxvirus cutaneous disease. Samples should be collected from representative lesions, preserved under cold-chain conditions when possible, and processed in laboratories prepared for suspected orthopoxvirus material. Virus isolation should be restricted to reference or research laboratories because it involves infectious viruses and is primarily used for viable virus recovery, phenotypic characterization, and subsequent antigenic or genomic work (Cardeti et al., 2011; Andreani et al., 2019; Lim et al., 2023).

7.3. Electron microscopy, virus isolation, serology, and PCR-based methods

Electron microscopy can rapidly demonstrate poxvirus-like particles but cannot definitively identify CPXV. Confirmation requires virus isolation, PCR, sequencing, serology, or whole-genome analysis. Serology may support exposure assessment, but strong cross-reactivity among orthopoxviruses limits species-level specificity. PCR remains central, beginning with broad poxvirus or orthopoxvirus screening followed by genus-, species-, or lineage-specific assays when needed. In veterinary diagnosis, multiplex PCR and high-resolution melting assays are valuable for differentiating CPXV from LSDV, pseudocowpox virus, BPSV, and other poxviruses. CPXV-specific real-time PCR further improves discrimination from closely related orthopoxviruses (Cardeti et al., 2011; Andreani et al., 2019; Grossegesse et al., 2023; Uhteg & Mostafa, 2023; Gelaye et al., 2017; Gavrilova et al., 2010; Maksyutov et al., 2015).

7.4. Whole-genome sequencing, comparative genomics, and phylogenetic analysis

Whole-genome sequencing is essential in modern CPXV research because CPXV represents a genetically diverse and taxonomically complex group rather than a uniform entity. Complete-genome studies show that CPXV-related viruses have large genomes of approximately 220–222 kbp with more than 200 predicted open reading frames and segregate into multiple phylogenetic clusters. Compared with single-gene typing, comparative genomics more effectively assesses nucleotide variation, indels, gene-content differences, recombination signals, and phylogenetic placement, especially in variable terminal regions. It also improves differentiation between clinically similar but taxonomically distinct poxviruses, including bovine parapoxviruses (Mauldin et al., 2017; Antwerpen et al., 2019; Diaz-Cánova et al., 2022; Graf et al., 2024).

7.5. Molecular epidemiology and genomic tracing

Molecular epidemiology combines viral genomic data with host, geographic, temporal, and exposure information to clarify transmission and outbreak relatedness. For CPXV, this is critical because clinically similar cases may belong to distinct lineages, while short markers may miss true outbreak structure. Whole-genome sequencing outperforms hemagglutinin-gene analysis for CPXV traceback by identifying clonal clusters and refining the interpretation of transmission. Genomic tracing also helps distinguish single from multiple introductions, detect divergent lineages, place isolates within CPXV evolutionary

diversity, and assess diagnostic-target suitability. Thus, WGS moves CPXV investigation from detection to high-resolution epidemiological and evolutionary interpretation (Antwerpen et al., 2019; Diaz-Cánova et al., 2022).

8. Poxvirus Infections in the Middle East and Iraq

8.1. Overview of animal poxviruses in the Middle East

Animal poxviruses remain important veterinary and zoonotic pathogens in the Middle East because they affect livestock, wildlife interfaces, and occasionally humans. The regional poxvirus landscape includes capripoxviruses such as LSDV and sheep/goat pox viruses, orthopoxviruses such as camelpox virus and cowpox-related or vaccinia-like viruses, and parapoxviruses affecting ruminants. This diversity creates diagnostic complexity because lesions caused by different viral genera may overlap clinically. Therefore, suspected cowpox-like disease in cattle and buffalo should be interpreted within a broad differential-diagnosis framework and confirmed by laboratory methods (Al-Eitan et al., 2024; Gelaye et al., 2017).

8.2. Livestock-associated poxvirus infections in the region

In the Middle East, livestock-associated poxvirus infections are strongly shaped by capripoxvirus diseases, especially lumpy skin disease in cattle. Regional analyses show that LSD outbreaks were influenced by environmental conditions, livestock density, and production systems, supporting its inclusion as a key differential diagnosis of bovine pox-like disease. The regional picture also includes camelpox in camel-rearing areas and buffalopox or vaccinia-like orthopoxviruses in buffalo-associated systems. Because buffalopox is zoonotic and primarily affects Asian water buffaloes, with occasional cattle and human involvement, pox-like lesions in buffaloes or cattle should not be attributed to classical CPXV without virological confirmation (Alkhamis & VanderWaal, 2016; Eltom et al., 2020; Martínez-Burnes et al., 2024).

8.3. Importance of cattle and buffalo production in Iraq

Cattle and buffalo production contribute to Iraqi livestock systems, food supply, and rural livelihoods. In contrast, buffalo husbandry has particular ecological and cultural importance in the southern marshlands of Basra, Maysan, and Dhi Qar. Water buffalo production is closely linked to marshland livelihoods and dairy production, and restoration-related work emphasized the need for improved fodder and veterinary services. Epidemiologically, close-contact management, teat and skin lesions, milking practices, animal movement, and limited diagnostic access may influence recognition and spread of pox-like diseases. However, cattle and buffalo should be viewed as important host populations for investigation rather than proven CPXV reservoirs; etiological attribution requires molecular confirmation (Ayied & Reiss, 2019).

8.4. Diagnostic limitations and knowledge gaps in Iraq

Available Iraqi studies indicate that field diagnosis alone is insufficient for reliable classification of pox-like lesions in cattle and buffalo. Published work has used PCR, sequencing, histopathology, and phylogenetic analysis to differentiate LSDV, pseudocowpox virus, and BPSV, reflecting clinical overlap and the inability of lesion morphology to determine genus- or species-level identity. Iraqi peer-reviewed literature has focused mainly on LSDV and parapoxviruses, while published genomic evidence for classical CPXV in Iraq remains limited. This limitation in published evidence should not be interpreted as evidence of epidemiological absence but rather as a knowledge gap that justifies whole-genome characterization of suspected cowpox-like cases in Iraqi cattle and buffalo (Gharban et al., 2019; Karim et al., 2019; Khudhair et al., 2024; Mauldin et al., 2017; Diaz-Cánova et al., 2022).

9. Economic, Public Health, Prevention, and Control Aspects

Pox-like orthopoxvirus infections in cattle and buffalo have veterinary, economic, and public-health importance because they affect milk production, animal welfare, farm management, occupational exposure, and surveillance. Udder and teat lesions may interfere with milking, cause pain, reduce productivity, predispose to mastitis, and facilitate transmission through handling or milking equipment. Milkers, animal handlers, veterinarians, and laboratory workers may also be exposed to lesions, crusts, or contaminated materials. Therefore, bovine and buffalo orthopoxvirus-like diseases should be addressed within a veterinary and One Health framework rather than viewed only as localized skin conditions (MacNeill et al., 2025; De Pascali et al., 2024).

9.1. Effects on milk production and animal welfare

In dairy cattle and buffalo, pox-like mammary lesions involving teats and udder can impair milking, suckling, productivity, and welfare. In cattle, bovine vaccinia and vaccinia-like orthopoxvirus infections may cause painful teat and udder lesions, sometimes complicated by mastitis, secondary infection, and reduced milk yield. In buffalo, most evidence relates to buffalopox rather than classical CPXV, but udder and teat involvement similarly causes pain, milking difficulty, mastitis, and production

loss. Thus, impact should be evaluated not only by mortality but also by pain, teat damage, secondary complications, and impaired udder function (Matos et al., 2018; Eltom et al., 2020; Martínez-Burnes et al., 2024).

9.2. Economic losses at herd level

At the herd level, economic losses from pox-like orthopoxvirus disease arise mainly from reduced milk production, disrupted milking, increased labor, veterinary care, supportive treatment, and secondary mastitis, rather than from mortality alone. Additional losses may include discarded milk, reduced milk quality, prolonged recovery, animal separation, enhanced disinfection, altered milking order, and biosecurity costs. In zoonotic outbreaks, infection or exposure among milkers and handlers may reduce workforce availability and necessitate occupational health measures. Thus, the economic impact includes production losses, welfare costs, labor disruption, biosecurity expenditures, and public health consequences (Matos et al., 2018; Eltom et al., 2020; De Pascali et al., 2024; Pattanaik et al., 2024).

9.3. Occupational exposure and zoonotic implications

Orthopoxvirus-like diseases in cattle and buffalo have important zoonotic implications, especially buffalopox and bovine vaccinia/vaccinia-like infections. Human infection is commonly linked to direct contact with affected animals during milking, lesion handling, or close care, making milkers, handlers, veterinarians, and laboratory personnel key risk groups. The post-smallpox-vaccination era increases concern because reduced cross-protective immunity may heighten susceptibility to zoonotic orthopoxviruses. Suspected orthopoxvirus-like disease should therefore be managed through a One Health approach, including animal diagnosis, worker protection, exposure assessment, safe sample handling, and risk communication (Eltom et al., 2020; Pattanaik et al., 2024; Gieryńska et al., 2023; De Pascali et al., 2024).

9.4. Farm-level prevention, control, and biosecurity

Farm-level control should begin with early recognition, temporary separation of affected animals, strict milking hygiene, and reduced contact with lesions, crusts, or contaminated materials. In close-contact dairy systems, transmission may occur through infected teats, contaminated hands, cloths, equipment, or animal contact; therefore, milking management is central. Practical measures include milking affected animals after healthy ones, using gloves, avoiding reuse of contaminated towels or instruments, disinfecting hands and equipment, minimizing manipulation of ulcerated teats, and improving environmental hygiene. Where wildlife or rodent exposure is possible, reducing contact should also be included to interrupt transmission at the animal–handler–environment interface (Eltom et al., 2020; Pattanaik et al., 2024; Bruneau et al., 2023; Al-Eitan et al., 2024).

9.5. Challenges in prevention, treatment, and surveillance

Prevention and control of pox-like orthopoxvirus disease in cattle and buffalo remain challenging because clinical lesions are not etiologically specific, and delayed or inaccurate diagnosis may limit intervention. For buffalopox, no widely established commercial vaccine is available for routine control, so prevention depends mainly on early detection, biosecurity, management, and outbreak response. Control is further complicated by zoonotic transmission involving animal hosts, human exposure, environmental interfaces, and variable diagnostic capacity. Surveillance is also limited by underrecognition, misclassification, restricted geographic data, and insufficient genomic characterization. In the Middle East, strengthening biosafety, biosecurity, molecular diagnosis, occupational-health reporting, and veterinary surveillance is essential for improving poxvirus detection and control in cattle and buffalo (Pattanaik et al., 2024; Al-Eitan et al., 2024; De Pascali et al., 2024; MacNeill et al., 2025).

10. Conclusions

Cowpox virus (CPXV) is a zoonotic orthopoxvirus with a broad host range, and wild rodents are considered its primary natural reservoir, while cattle, buffaloes, and humans are incidental hosts. Because CPXV is genetically diverse and not a single monophyletic virus, molecular methods such as PCR, sequencing, and ideally whole-genome sequencing are essential for accurate identification and classification. Pox-like lesions in cattle and buffalo may result from several infectious agents, making clinical and histopathological findings alone insufficient for definitive diagnosis. These diseases can adversely affect animal welfare, milk production, and farm productivity, leading to significant economic losses. They also pose occupational risks to individuals in close contact with infected animals, highlighting the importance of a One Health approach integrating veterinary, public health, and biosecurity measures. In Iraq, published genomic evidence for classical CPXV remains limited and should be interpreted as a knowledge gap rather than evidence of epidemiological absence. Molecular and genomic investigation of suspected cowpox-like cases is therefore required to distinguish CPXV from other poxviruses circulating in livestock. An integrated diagnostic strategy combining field investigation with laboratory confirmation and phylogenetic analysis will improve disease surveillance and outbreak investigations. Overall, molecular characterization of cowpox-like disease in Iraqi cattle and buffalo will strengthen diagnosis, enhance epidemiological understanding, and contribute to regional One Health surveillance of emerging poxvirus infections.

11. Declarations

11.1. Ethical considerations

This article is a literature review and did not involve the collection of primary data from animals or human participants. Therefore, ethical committee approval was not required.

11.2. Use of artificial intelligence (AI)

Generative AI tool (ChatGPT, Open AI) was used solely for language refinement and paraphrasing assistance during manuscript revision. All scientific content, interpretation, and references were reviewed and approved by the authors, who take full responsibility for the final manuscript.

11.3. Conflict of interest

The authors declare no conflict of interest.

11.4. Funding

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References

Al-Eitan, L. N., Ali, H. O., Abu Kharmah, H. S., Alasmar, M. K., Khair, I. Y., & Mihyar, A. H. (2024). Addressing poxvirus challenges in the Middle East to enhance biosafety and biosecurity measures. *Journal of Biosafety and Biosecurity, 6*(3), 142–156. https://doi.org/10.1016/j.jobb.2024.06.003

Alkhamis, M. A., & VanderWaal, K. (2016). Spatial and temporal epidemiology of lumpy skin disease in the Middle East, 2012–2015. *Frontiers in Veterinary Science, 3*, 19. https://doi.org/10.3389/fvets.2016.00019

Alzhanova, D., & Früh, K. (2010). Modulation of the host immune response by cowpox virus. *Microbes and Infection, 12*(12–13), 900–909. https://doi.org/10.1016/j.micinf.2010.07.007

Andreani, J., Arnault, J.-P., Bou Khalil, J. Y., Abrahão, J., Tomei, E., Vial, E., Le Bideau, M., Raoult, D., & La Scola, B. (2019). Atypical cowpox virus infection in a smallpox-vaccinated patient, France. *Emerging Infectious Diseases, 25*(2), 212–219. https://doi.org/10.3201/eid2502.171433

Antwerpen, M. H., Georgi, E., Nikolic, A., Zoeller, G., Wohlsein, P., Baumgärtner, W., Peyrefitte, C., Charrel, R., & Meyer, H. (2019). Use of next generation sequencing to study two cowpox virus outbreaks. *PeerJ, 7*, e6561. https://doi.org/10.7717/peerj.6561

Ayied, A. Y., & Reiss, P. (2019). Impact of the Iraq Marshlands Restoration Program on livestock population and production in the southern marshes of Iraq. *Journal of Buffalo Science, 8*(2), 25–33. https://doi.org/10.6000/1927-520X.2019.08.02.1

Aytoğlu, G., Yaşar, M., Aybey, N., Mecitoğlu, Z., & Yeşilbağ, K. (2025). Molecular characterization of current field isolates of zoonotic parapoxviruses and their growth characteristics. *Gene Reports, 41*, 102328. https://doi.org/10.1016/j.genrep.2025.102328

Bourquain, D., Schrick, L., Tischer, B. K., Osterrieder, K., Schaade, L., & Nitsche, A. (2021). Replication of cowpox virus in macrophages is dependent on the host range factor p28/N1R. *Virology Journal, 18*, 173. https://doi.org/10.1186/s12985-021-01640-x

Broyles, S. S. (2003). Vaccinia virus transcription. *Journal of General Virology, 84*(9), 2293–2303. https://doi.org/10.1099/vir.0.18942-0

Bruneau, R. C., Tazi, L., & Rothenburg, S. (2023). Cowpox viruses: A zoo full of viral diversity and lurking threats. *Biomolecules, 13*(2), 325. https://doi.org/10.3390/biom13020325

Byrne, J., Saini, G., Garcia-Leon, A., Alalwan, D., Doran, P., Landay, A., Luong Nguyen, L. B., O'Broin, C., Savinelli, S., O'Halloran, J. A., Cotter, A., Horgan, M., Kelly, C., Sadlier, C., de Barra, E., Gautier, V., Mallon, P. W. G., Feeney, E. R., & All Ireland Infectious Diseases Cohort Study. (2025). Development and validation of a quantitative Orthopoxvirus immunoassay to evaluate and differentiate serological responses to Mpox infection and vaccination. *eBioMedicine, 113*, 105622. https://doi.org/10.1016/j.ebiom.2025.105622

Campe, H., Zimmermann, P., Glos, K., Bayer, M., Bergemann, H., Dreweck, C., Graf, P., Weber, B. K., Meyer, H., Büttner, M., Busch, U., & Sing, A. (2009). Cowpox virus transmission from pet rats to humans, Germany. *Emerging Infectious Diseases, 15*(5), 777–780. https://doi.org/10.3201/eid1505.090159

Cardeti, G., Brozzi, A., Eleni, C., Polici, N., D'Alterio, G., Carletti, F., Scicluna, M. T., Castilletti, C., Capobianchi, M. R., Di Caro, A., Autorino, G. L., & Amaddeo, D. (2011). Cowpox virus in a llama, Italy. *Emerging Infectious Diseases, 17*(8), 1513–1515. https://doi.org/10.3201/eid1708.101912

Carroll, D. S., Emerson, G. L., Li, Y., Sammons, S., Olson, V., Frace, M., Nakazawa, Y., Czerny, C. P., Tryland, M., Kolodziejek, J., Nowotny, N., Olsen-Rasmussen, M., Khristova, M., Govil, D., Karem, K., Damon, I. K., & Meyer, H. (2011). Chasing Jenner's vaccine: Revisiting cowpox virus classification. *PLoS ONE, 6*(8), e23086. https://doi.org/10.1371/journal.pone.0023086

Carslake, D., Bennett, M., Hazel, S. L., Macdonald, D. W., & Begon, M. (2006). Inference of cowpox virus transmission rates between wild rodent host classes using space–time interaction. *Proceedings of the Royal Society B: Biological Sciences, 273*(1588), 775–782. https://doi.org/10.1098/rspb.2005.3400

Chantrey, J., Meyer, H., Baxby, D., Begon, M., Bown, K. J., Hazel, S. M., Jones, T., Montgomery, W. I., & Bennett, M. (1999). Cowpox: Reservoir hosts and geographic range. *Epidemiology and Infection, 122*(3), 455–460. https://doi.org/10.1017/S0950268899002423

Condit, R. C., Moussatche, N., & Traktman, P. (2006). In a nutshell: Structure and assembly of the vaccinia virion. *Advances in Virus Research, 66*, 31–124. https://doi.org/10.1016/S0065-3527(06)66002-8

Costa, T., Stidworthy, M. F., Ehmann, R., Denk, D., Ashpole, I., Drake, G., Maciuca, I., Zoeller, G., Meyer, H., & Chantrey, J. (2023). Cowpox in zoo and wild animals in the United Kingdom. *Journal of Comparative Pathology, 204*, 39–46. https://doi.org/10.1016/j.jcpa.2023.05.002

Dabrowski, P. W., Radonić, A., Kurth, A., & Nitsche, A. (2013). Genome-wide comparison of cowpox viruses reveals a new clade related to variola virus. *PLoS ONE, 8*(12), e79953. https://doi.org/10.1371/journal.pone.0079953

De Pascali, A. M., Brandolini, M., Peli, L., Sambri, V., Cricca, M., & Scagliarini, A. (2024). Zoonotic orthopoxviruses after smallpox eradication: A shift from crisis response to a One Health approach. *IJID One Health, 2*, 100018. https://doi.org/10.1016/j.ijidoh.2024.100018

Deng, Y., Navarro-Forero, S., & Yang, Z. (2025). Temporal expression classes and functions of vaccinia virus and mpox (monkeypox) virus genes. *mBio, 16*(4), e03809-24. https://doi.org/10.1128/mbio.03809-24

Díaz-Cánova, D., Mavian, C., Brinkmann, A., Nitsche, A., Moens, U., & Okeke, M. I. (2022). Genomic sequencing and phylogenomics of cowpox virus. *Viruses, 14*(10), 2134. https://doi.org/10.3390/v14102134

Eltom, K. H., Samy, A. M., Abd El Wahed, A., & Czerny, C.-P. (2020). Buffalopox virus: An emerging virus in livestock and humans. *Pathogens, 9*(9), 676. https://doi.org/10.3390/pathogens9090676

Esteban, D. J., & Hutchinson, A. P. (2011). Genes in the terminal regions of orthopoxvirus genomes experience adaptive molecular evolution. *BMC Genomics, 12*, 261. https://doi.org/10.1186/1471-2164-12-261

Ferrier, A., Frenois-Veyrat, G., Schvoerer, E., Henard, S., Jarjaval, F., Drouet, I., Timera, H., Boutin, L., Mosca, E., Peyrefitte, C., & Ferraris, O. (2021). Fatal cowpox virus infection in human fetus, France, 2017. *Emerging Infectious Diseases, 27*(10), 2570–2577. https://doi.org/10.3201/eid2710.204818

Franke, A., Pfaff, F., Jenckel, M., Hoffmann, B., Höper, D., Antwerpen, M., Meyer, H., Beer, M., & Hoffmann, D. (2017). Classification of cowpox viruses into several distinct clades and identification of a novel lineage. *Viruses, 9*(6), 142. https://doi.org/10.3390/v9060142

Gavrilova, E. V., Shcherbakov, D. N., Maksyutov, R. A., & Shchelkunov, S. N. (2010). Development of real-time PCR assay for specific detection of cowpox virus. *Journal of Clinical Virology, 49*(1), 37–40. https://doi.org/10.1016/j.jcv.2010.06.003

Gelaye, E., Mach, L., Kolodziejek, J., Grabherr, R., Loitsch, A., Achenbach, J. E., Nowotny, N., Diallo, A., & Lamien, C. E. (2017). A novel HRM assay for the simultaneous detection and differentiation of eight poxviruses of medical and veterinary importance. *Scientific Reports, 7*, 42892. https://doi.org/10.1038/srep42892

Gharban, H. A. J., Al-Shaeli, S. J. J., Al-Fattli, H. H. H., & Altaee, M. N. K. (2019). Molecular and histopathological confirmation of clinically diagnosed lumpy skin disease in cattle, Baghdad Province of Iraq. *Veterinary World, 12*(11), 1826–1832. https://doi.org/10.14202/vetworld.2019.1826-1832

Gieryńska, M., Szulc-Dąbrowska, L., Struzik, J., Gregorczyk-Zboroch, K. P., Mielcarska, M. B., Toka, F. N., Schollenberger, A., & Biernacka, Z. (2023). Orthopoxvirus zoonoses—Do we still remember and are ready to fight? *Pathogens, 12*(3), 363. https://doi.org/10.3390/pathogens12030363

Graf, A., Rziha, H.-J., Krebs, S., Wolf, E., Blum, H., & Büttner, M. (2024). Parapoxvirus species revisited by whole genome sequencing: A retrospective analysis of bovine virus isolates. *Virus Research, 346*, 199404. https://doi.org/10.1016/j.virusres.2024.199404

Greseth, M. D., & Traktman, P. (2022). The life cycle of the vaccinia virus genome. *Annual Review of Virology, 9*, 239–259. https://doi.org/10.1146/annurev-virology-091919-104752

Grimm, C., Hillen, H. S., Bedenk, K., Bartuli, J., Neyer, S., Zhang, Q., Hüttenhofer, A., Erlacher, M., Dienemann, C., Schlosser, A., Urlaub, H., Böttcher, B., Szalay, A. A., Cramer, P., & Fischer, U. (2019). Structural basis of poxvirus transcription: Vaccinia RNA polymerase complexes. *Cell, 179*(7), 1537–1550.e19. https://doi.org/10.1016/j.cell.2019.11.024

Grossegesse, M., Stern, D., Hofmann, N., Surtees, R., Kohl, C., Michel, J., & Nitsche, A. (2023). Serological methods for the detection of antibodies against monkeypox virus applicable for laboratories with different biosafety levels. *Journal of Medical Virology, 95*(12), e29261. https://doi.org/10.1002/jmv.29261

Gruber, C. E. M., Giombini, E., Selleri, M., Tausch, S. H., Androusch, A., Tyshaieva, A., Cardeti, G., Lorenzetti, R., De Marco, L., Carletti, F., Nitsche, A., Capobianchi, M. R., Ippolito, G., Autorino, G. L., & Castilletti, C. (2018). Whole genome characterization of *Orthopoxvirus* Abatino, a zoonotic virus representing a putative novel clade of Old World orthopoxviruses. *Viruses, 10*(10), 546. https://doi.org/10.3390/v10100546

Gubser, C., Hué, S., Kellam, P., & Smith, G. L. (2004). Poxvirus genomes: A phylogenetic analysis. *Journal of General Virology, 85*(1), 105–117. https://doi.org/10.1099/vir.0.19565-0

Haider, A., Abbas, Z., Taqveem, A., Ali, A., Khurshid, M., El Naggar, R. F., Rohaim, M. A., & Munir, M. (2024). Lumpy skin disease: Insights into molecular pathogenesis and control strategies. *Veterinary Sciences, 11*(11), 561. https://doi.org/10.3390/vetsci11110561

Haller, S. L., Peng, C., McFadden, G., & Rothenburg, S. (2014). Poxviruses and the evolution of host range and virulence. *Infection, Genetics and Evolution, 21*, 15–40. https://doi.org/10.1016/j.meegid.2013.10.014

Hazel, S. M., Bennett, M., Chantrey, J., Bown, K., Cavanagh, R., Jones, T. R., Baxby, D., & Begon, M. (2000). A longitudinal study of an endemic disease in its wildlife reservoir: Cowpox and wild rodents. *Epidemiology and Infection, 124*(3), 551–562. https://doi.org/10.1017/S0950268899003799

Hendrickson, R. C., Wang, C., Hatcher, E. L., & Lefkowitz, E. J. (2010). Orthopoxvirus genome evolution: The role of gene loss. *Viruses, 2*(9), 1933–1967. https://doi.org/10.3390/v2091933

Hernáez, B., & Alcamí, A. (2024). Poxvirus immune evasion. *Annual Review of Immunology, 42*, 509–537. https://doi.org/10.1146/annurev-immunol-090222-110227

Hyun, J. K. (2022). Poxvirus under the eyes of electron microscope. *Applied Microscopy, 52*, 11. https://doi.org/10.1186/s42649-022-00080-3

Iyer, R. F., Edwards, D. M., Kolb, P., Raué, H. P., Nelson, C. A., Epperson, M. L., Slifka, M. K., Nolz, J. C., Hengel, H., Fremont, D. H., & Früh, K. (2022). The secreted protein Cowpox Virus 14 contributes to viral virulence and immune evasion by engaging Fc-gamma-receptors. *PLOS Pathogens, 18*(9), e1010783. https://doi.org/10.1371/journal.ppat.1010783

Karim, S. M., Mansour, K. A., Janabi, A. H., & Al-Nakeeb, N. K. (2019). First phylogenetic characterization of *Pseudocowpox* virus from cattle in Al-Qadisiyah province/Iraq. *Iraqi Journal of Veterinary Sciences, 33*(1), 123–126. https://doi.org/10.33899/ijvs.2019.125525.1047

Kaysser, P., von Bomhard, W., Dobrzykowski, L., & Meyer, H. (2010). Genetic diversity of feline cowpox virus, Germany 2000–2008. *Veterinary Microbiology, 141*(3–4), 282–288. https://doi.org/10.1016/j.vetmic.2009.09.029

Khudhair, Y. I., Rhyif, A. G., Mayea, K. Q., & Ben Said, M. (2024). Prevalence, clinico-epidemiological features, and molecular characterization of bovine papular stomatitis virus in cattle in Iraq. *Archives of Virology, 169*, 152. https://doi.org/10.1007/s00705-024-06061-z

Kurth, A., Wibbelt, G., Gerber, H. P., Petschelis, A., Pauli, G., & Nitsche, A. (2008). Rat-to-elephant-to-human transmission of cowpox virus. *Emerging Infectious Diseases, 14*(4), 670–671. https://doi.org/10.3201/eid1404.070817

Lanave, G., Larocca, V., Losurdo, M., Catella, C., Capozza, P., Tempesta, M., Martella, V., Buonavoglia, C., & Camero, M. (2020). Isolation and characterization of bovine alphaherpesvirus 2 strain from an outbreak of bovine herpetic mammillitis in a dairy farm. *BMC Veterinary Research, 16*, 103. https://doi.org/10.1186/s12917-020-02325-3

Lim, C. K., McKenzie, C., Deerain, J., Chow, E. P. F., Towns, J., Chen, M. Y., Fairley, C. K., Tran, T., & Williamson, D. A. (2023). Correlation between monkeypox viral load and infectious virus in clinical specimens. *Journal of Clinical Virology, 161*, 105421. https://doi.org/10.1016/j.jcv.2023.105421

Limon, G., Gamawa, A. A., Ahmed, A. I., Lyons, N. A., & Beard, P. M. (2020). Epidemiological characteristics and economic impact of lumpy skin disease, sheep pox and goat pox among subsistence farmers in northeast Nigeria. *Frontiers in Veterinary Science, 7*, 8. https://doi.org/10.3389/fvets.2020.00008

Liu, L., Cooper, T., Howley, P. M., & Hayball, J. D. (2014). From crescent to mature virion: Vaccinia virus assembly and maturation. *Viruses, 6*(10), 3787–3808. https://doi.org/10.3390/v6103787

MacNeill, A. L. (2022). Comparative pathology of zoonotic orthopoxviruses. *Pathogens, 11*(8), 892. https://doi.org/10.3390/pathogens11080892

MacNeill, A. L., Micheloud, J. F., Parvin, R., Gjessing, M., Airas, N. A., de Sant'Ana, F. J. F., & Adamek, M. (2025). Poxvirus pathology and pathogenesis in agriculturally important species. *Veterinary Pathology, 62*(6), 849–866. https://doi.org/10.1177/03009858251338854

Makoga, F. T., Chang'a, J. S., Meki, I. K., Mayenga, C., Settypalli, T. B. K., Bitanyi, S., Magidanga, B., Peter, E., Chengula, A., Cattoli, G., & Lamien, C. E. (2024). Detection and molecular characterization of lumpy skin disease and bovine papular stomatitis viruses in lumpy skin disease-suspected outbreaks in Tanzania. *Virology Journal, 21*, 276. https://doi.org/10.1186/s12985-024-02558-w

Maksyutov, R. A., Gavrilova, E. V., Meyer, H., & Shchelkunov, S. N. (2015). Real-time PCR assay for specific detection of cowpox virus. *Journal of Virological Methods, 211*, 8–11. https://doi.org/10.1016/j.jviromet.2014.10.004

Martínez-Burnes, J., Barrios-García, H., Carvajal-de la Fuente, V., Corona-González, B., Obregón Alvarez, D., & Romero-Salas, D. (2024). Viral diseases in water buffalo (*Bubalus bubalis*): New insights and perspectives. *Animals, 14*(6), 845. https://doi.org/10.3390/ani14060845

Matos, A. C. D., Rehfeld, I. S., Guedes, M. I. M. C., & Lobato, Z. I. P. (2018). Bovine vaccinia: Insights into the disease in cattle. *Viruses, 10*(3), 120. https://doi.org/10.3390/v10030120

Mauldin, M. R., Antwerpen, M., Emerson, G. L., Li, Y., Zoeller, G., Carroll, D. S., & Meyer, H. (2017). Cowpox virus: What is in a name? *Viruses, 9*(5), 101. https://doi.org/10.3390/v9050101

McInnes, C. J., Damon, I. K., Smith, G. L., McFadden, G., Isaacs, S. N., Roper, R. L., Evans, D. H., Damaso, C. R., Carulei, O., Wise, L. M., & Lefkowitz, E. J. (2023). ICTV virus taxonomy profile: Poxviridae 2023. *Journal of General Virology, 104*(5), 001849. https://doi.org/10.1099/jgv.0.001849

Molteni, C., Forni, D., Cagliani, R., Clerici, M., & Sironi, M. (2022). Genetic ancestry and population structure of vaccinia virus. *npj Vaccines, 7*, 92. https://doi.org/10.1038/s41541-022-00519-4

Molteni, C., Forni, D., Cagliani, R., Mozzi, A., Clerici, M., & Sironi, M. (2023). Evolution of the orthopoxvirus core genome. *Virus Research, 323*, 198975. https://doi.org/10.1016/j.virusres.2022.198975

Moss, B. (2013). Poxvirus DNA replication. *Cold Spring Harbor Perspectives in Biology, 5*(9), a010199. https://doi.org/10.1101/cshperspect.a010199

Moss, B. (2015). Poxvirus membrane biogenesis. *Virology, 479–480*, 619–626. https://doi.org/10.1016/j.virol.2015.02.003

Möstl, K., Addie, D., Belák, S., Boucraut-Baralon, C., Egberink, H., Frymus, T., Gruffydd-Jones, T., Hartmann, K., Hosie, M. J., Lloret, A., Lutz, H., Marsilio, F., Pennisi, M. G., Radford, A. D., Thiry, E., Truyen, U., & Horzinek, M. C. (2013). Cowpox virus infection in cats: ABCD guidelines on prevention and management. *Journal of Feline Medicine and Surgery, 15*(7), 557–559. https://doi.org/10.1177/1098612X13489212

Ninove, L., Domart, Y., Vervel, C., Voinot, C., Salez, N., Raoult, D., & Meyer, H. (2009). Cowpox virus transmission from pet rats to humans, France. *Emerging Infectious Diseases, 15*(5), 781–784. https://doi.org/10.3201/eid1505.090235

Oliveira, G. P., Rodrigues, R. A. L., Lima, M. T., Drumond, B. P., & Abrahão, J. S. (2017). Poxvirus host range genes and virus–host spectrum: A critical review. *Viruses, 9*(11), 331. https://doi.org/10.3390/v9110331

Pattanaik, A., Lodha, L., Marate, S., Dhanya, K., Bhandarkar, B. S., Sreelakshmi, V., Ashtaputre, N., & Mani, R. S. (2024). Buffalopox: An emerging zoonotic challenge. *Infectious Diseases Now, 54*(6), 104954. https://doi.org/10.1016/j.idnow.2024.104954

Reynolds, M. G., Guagliardo, S. A. J., Nakazawa, Y. J., Doty, J. B., & Mauldin, M. R. (2018). Understanding orthopoxvirus host range and evolution: From the enigmatic to the usual suspects. *Current Opinion in Virology, 28*, 108–115. https://doi.org/10.1016/j.coviro.2017.11.012

Riedel, S. (2005). Edward Jenner and the history of smallpox and vaccination. *Baylor University Medical Center Proceedings, 18*(1), 21–25. https://doi.org/10.1080/08998280.2005.11928028

Roberts, K. L., & Smith, G. L. (2008). Vaccinia virus morphogenesis and dissemination. *Trends in Microbiology, 16*(10), 472–479. https://doi.org/10.1016/j.tim.2008.07.009

Schrick, L., Tausch, S. H., Dabrowski, P. W., Damaso, C. R., Esparza, J., Nitsche, A., & Drake, J. W. (2017). An early American smallpox vaccine based on horsepox. *New England Journal of Medicine, 377*(15), 1491–1492. https://doi.org/10.1056/NEJMc1707600

Shimizu, K., Badr, Y., Okada, A., & Inoshima, Y. (2020). Bovine papular stomatitis virus and pseudocowpox virus coinfection in dairy calves in Japan. *Archives of Virology, 165*, 2659–2664. https://doi.org/10.1007/s00705-020-04792-3

Silva, N. I. O., de Oliveira, J. S., Kroon, E. G., Trindade, G. S., & Drumond, B. P. (2021). Here, there, and everywhere: The wide host range and geographic distribution of zoonotic orthopoxviruses. *Viruses, 13*(1), 43. https://doi.org/10.3390/v13010043

Sindryakova, I., Blokhin, A., Lyska, V., & Titov, I. (2024). Description of zoonotic pseudocowpoxvirus infection of cattle in Russia. *Animals, 14*(6), 969. https://doi.org/10.3390/ani14060969

Stagegaard, J., Kurth, A., Stern, D., Dabrowski, P. W., Pocknell, A., Nitsche, A., & Schrick, L. (2017). Seasonal recurrence of cowpox virus outbreaks in captive cheetahs (*Acinonyx jubatus*). *PLOS ONE, 12*(11), e0187089. https://doi.org/10.1371/journal.pone.0187089

Tseng, K. K., Koehler, H., Becker, D. J., Gibb, R., Carlson, C. J., Fernandez, M. del P., & Seifert, S. N. (2025). Viral genomic features predict orthopoxvirus reservoir hosts. *Communications Biology, 8*, 309. https://doi.org/10.1038/s42003-025-07746-0

Uhteg, K., & Mostafa, H. H. (2023). Validation and implementation of an orthopoxvirus qualitative real-time PCR for the diagnosis of monkeypox in the clinical laboratory. *Journal of Clinical Virology, 158*, 105327. https://doi.org/10.1016/j.jcv.2022.105327

Virkler, P. D., & Wieland, M. (2023). Teat open lesions can lead to challenges at milking time on dairies in the Northeast United States. *Journal of the American Veterinary Medical Association, 261*(S1), S103–S108. https://doi.org/10.2460/javma.22.12.0567

Vogel, S., Sárdy, M., Glos, K., Korting, H. C., Ruzicka, T., & Wollenberg, A. (2012). The Munich outbreak of cutaneous cowpox infection: Transmission by infected pet rats. *Acta Dermato-Venereologica, 92*(2), 126–131. https://doi.org/10.2340/00015555-1227

Walsh, D. (2017). Poxviruses: Slipping and sliding through transcription and translation. *PLOS Pathogens, 13*(11), e1006634. https://doi.org/10.1371/journal.ppat.1006634

Wieland, M., Basran, P. S., Virkler, P. D., & Heuwieser, W. (2024). An observational study to investigate the association of teat skin condition with clinical mastitis risk. *JDS Communications, 5*(6), 654–658. https://doi.org/10.3168/jdsc.2024-0577

Xiang, Y. (2025). Poxvirus host-range determinants: SAMD9/9L and beyond. *Annual Review of Virology, 12*(1), 93–114. https://doi.org/10.1146/annurev-virology-092623-104658

Yang, Z., Bruno, D. P., Martens, C. A., Porcella, S. F., & Moss, B. (2010). Simultaneous high-resolution analysis of vaccinia virus and host cell transcriptomes by deep RNA sequencing. *Proceedings of the National Academy of Sciences of the United States of America, 107*(25), 11513–11518. https://doi.org/10.1073/pnas.1006594107

Yu, H., Resch, W., & Moss, B. (2025). Poxvirus structural biology for application to vaccine design. *Trends in Immunology, 46*(6), 455–470. https://doi.org/10.1016/j.it.2025.04.002

Yu, Z., Zhang, W., Fu, H., Zou, X., Zhao, M., Liang, S., Gu, C., Yang, Q., He, M., Xiao, Q., Xiao, W., He, L., & Lü, M. (2021). Genomic analysis of Poxviridae and exploring qualified gene sequences for phylogenetics. *Computational and Structural Biotechnology Journal, 19*, 5479–5486. https://doi.org/10.1016/j.csbj.2021.09.031

Zhu, J., Zhang, Z., Fang, Y., Xu, J., Jiang, Z., Li, H., Xie, S., Niu, K., Jing, Z., Song, B., Wu, W., & Peng, C. (2025). Poxvirus H5 mediates the formation of liquid-liquid phase separation condensates which promote virus factory assembly. *PLOS Pathogens, 21*(11), e1013708. https://doi.org/10.1371/journal.ppat.1013708