

Lumpy Skin Disease in Cattle and Buffaloes: Pathogenesis, Immunopathology, Diagnosis, and Vaccination in India

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Abstract

Lumpy skin disease (LSD) has become endemic in India following its introduction in 2019 and the extensive 2022 epidemic. A structured narrative search of peer-reviewed and authoritative sources informed this review, which examines current evidence on LSD virus epidemiology, pathogenesis, pathology, immunity, diagnosis, and vaccination, with emphasis on cattle and water buffaloes in India. The characteristic skin nodule is associated with viral tropism for epithelial and vascular cells, necrotising fibrinoid vasculitis, thrombosis, and ischaemic necrosis. Intracytoplasmic inclusions support the diagnosis but may be sparse. Buffaloes usually develop mild or subclinical infection and require species-specific validation of serological tests. Lesion tissue, scabs, and nasal swabs generally provide better molecular diagnostic yield than whole blood. India's homologous live-attenuated vaccine, Lumpi-ProVacInd, includes a deletion that may support differentiation of infected from vaccinated animals. Priorities include standardised lesion grading, buffalo-specific diagnostics, whole-genome surveillance, and robust field studies of vaccine effectiveness.

Keywords: Cattle, Diagnosis, Immunopathology, India, Lumpy Skin Disease Virus, Vaccination, Vasculitis, Water Buffalo.

Introduction

Lumpy skin disease is caused by lumpy skin disease virus (LSDV), a member of the genus Capripoxvirus in the family Poxviridae, and is listed by the World Organisation for Animal Health (WOAH) as a notifiable transboundary disease. For most of the twentieth century it was an African problem, first recognised in Zambia in 1929 and confined largely to sub-Saharan Africa. From 2013 onwards it moved rapidly through the Middle East, into Turkey, the Balkans and Russia, and then east into Asia. Bangladesh reported the first South Asian outbreak in July 2019; India followed within weeks (Sudhakar *et al.*, 2020; Tuppurainen and Oura, 2012; WOAH, 2024). India remains particularly vulnerable because of its large bovine population, predominantly smallholder production systems, high animal density, informal animal movement, year-round arthropod activity, and uneven biosecurity. The economic consequences include reduced milk production, hide damage, reproductive losses, mortality, and direct treatment costs (Kumar and Tripathi, 2022; Naidu *et al.*, 2025). For veterinary pathologists, LSD presents an important differential-diagnostic problem. Nodular skin lesions in Indian cattle and buffaloes may also occur with pseudo-lumpy skin disease caused by bovine herpesvirus 2, dermatophilosis, dermatophytosis, demodicosis, besnoitiosis, insect-bite hypersensitivity, urticaria, onchocerciasis, and cutaneous neoplasia. Accurate diagnosis is necessary because notification, movement restrictions, and vaccination measures can be costly and disruptive (Namazi and Khodakaram Tafti, 2021; Toker *et al.*, 2026; WOAH, 2024).

This review covers the virus and its lineage structure, the epidemiology of LSD in India from incursion to endemicity, the pathogenesis and pathology of the disease in cattle and buffaloes, its immunopathology, the current diagnostic toolkit, and the state of vaccination policy and vaccine development. Throughout, the emphasis is on what is known from Indian material and what remains unresolved here.

Literature Search Methodology

A structured narrative literature search was conducted to identify evidence on lumpy skin disease virus epidemiology, pathogenesis, pathology, immunology, diagnosis, vaccination, and control, with particular emphasis on India and water buffaloes. PubMed, Google Scholar, and the reference lists of relevant articles were searched for English-language publications available up to 31 August 2026. Search terms were used alone and in combination, including ‘lumpy skin disease’, ‘LSDV’, ‘India’, ‘cattle’, ‘buffalo’, ‘pathogenesis’, ‘histopathology’, ‘immunopathology’, ‘diagnosis’, ‘PCR’, ‘vaccine’, ‘Lumpi-ProVacInd’, ‘epidemiology’, and ‘economic impact’. Official documents from the World Organisation for Animal Health, the Food and Agriculture Organization of the United Nations, and the Government of India were also examined. Original research, authoritative technical guidance, and recent reviews directly relevant to the review objectives were included; duplicate records, non-scholarly summaries, and publications without relevant primary or synthesis data were excluded. Priority was given to Indian field and laboratory studies, followed by international evidence where Indian data were limited. Because the purpose was a critical narrative synthesis rather than estimation of a pooled effect, formal risk-of-bias scoring and meta-analysis were not performed.

The Virus: Genome, Lineage Structure and the Indian Isolates

Genome Organisation

LSDV has a linear double-stranded DNA genome of approximately 151 kilobases containing about 156 putative open reading frames, flanked by inverted terminal repeats (Tulman *et al.*, 2001). Around 146 genes are conserved and encode the machinery of transcription, messenger RNA biogenesis, virion structure and assembly. The central genomic region is highly conserved across capripoxviruses; the variable terminal regions house the virulence and host-range determinants, including ankyrin-repeat and kelch-like protein genes, and it is here that most of the mutations distinguishing attenuated from virulent strains accumulate (Biswas *et al.*, 2020; Tulman *et al.*, 2001).

LSDV shares 96 to 97 per cent nucleotide identity with sheeppox virus and goatpox virus. That closeness has two practical consequences. It underpins the cross-protection exploited by heterologous vaccination, and it makes species-level discrimination a real diagnostic challenge — pan-capripoxvirus assays cannot distinguish the three viruses, which matters in mixed small-ruminant and bovine holdings common across India. The estimated substitution rate for LSDV is low, of the order of 7.4×10^{-6} substitutions per site per year, consistent with a large DNA virus; evolution is driven less by drift than by recombination and by selection on the terminal variable regions

(Biswas *et al.*, 2020; Reddy *et al.*, 2015; Tulman *et al.*, 2001).

Global Lineage Architecture

Before 2017, whole-genome analysis divided circulating LSDV into two clusters. Cluster 1.1 comprises historical South African isolates and the Neethling vaccine strains. Cluster 1.2 contains the Kenyan strains identified in the 1950s, together with Middle Eastern, Balkan, Greek, Turkish and Russian isolates recovered before 2017 (Anwar *et al.*, 2022; Bayyappa *et al.*, 2025a).

The identification of Saratov/2017 in Russia altered this classification. The virus was a recombinant with genomic segments related to the Neethling vaccine strain and a Kenyan sheep and goat pox vaccine strain. Subsequent recombinant vaccine-like strains, including Udmurtiya/2019, Kostanay/2018, Tyumen/2019, and the China 2019 lineage, are now placed in cluster 2, with clades 2.1-2.6. Available evidence indicates that homologous recombination between live-attenuated vaccine strains during vaccine production contributed to their emergence, highlighting the need for strict manufacturing controls (Krotova *et al.*, 2023; Sendow *et al.*, 2024). Clade 2.5 has spread most widely, dominating outbreaks in China, Vietnam, Thailand, Indonesia and elsewhere in Southeast Asia. Evidence is accumulating that clade 2 strains transmit efficiently by direct and indirect contact as well as by mechanical vectors, which distinguishes them epidemiologically from classical clade 1 viruses and has implications for how outbreaks are contained (Anwar *et al.*, 2022; Sendow *et al.*, 2024).

The Indian Lineage

Indian isolates have consistently fallen within cluster 1.2. The 2019 Odisha viruses were shown to be closely related to historical Kenyan NI-2490/KSGP-like field strains, carrying unique signature substitutions (Sudhakar *et al.*, 2020, 2022). Subsequent characterisation confirmed the persistence of a wild-type field lineage rather than any vaccine-derived virus. Recent isolates from the 2025 outbreaks in Maharashtra and Karnataka formed a closely related monophyletic clade with more than 99% nucleotide identity. They were most closely related to a 2022 Haryana strain and were distinct from the 2019 Jharkhand and 2020 Karnataka isolates (Tadakod *et al.*, 2026). All 2025 isolates contained two conserved nonsynonymous substitutions, P34T and P61T, in the G protein-coupled chemokine receptor gene; these substitutions were absent from earlier Indian strains and may be useful lineage markers. The findings are consistent with gradual divergence of an endemic mainland lineage associated with livestock movement (Bayyappa *et al.*, 2025a; Tadakod *et al.*, 2026).

A distinct finding was reported from Great Nicobar Island, where a virus collected during a 2022 outbreak resembled cluster 2.5 recombinant strains circulating in East and Southeast Asia. This detection indicates that recombinant Asian lineages can reach Indian territory and supports targeted genomic surveillance at ports, island territories, and eastern land borders (Sudhakar *et al.*, 2025b).

Epidemiology of LSD in India

From Incursion to Endemicity

India reported its first LSD outbreak in August 2019 from the Mayurbhanj, Bhadrak and Kendrapara districts of Odisha, with laboratory confirmation following in November of that year. Through 2020 and 2021 the disease spread quietly, producing sporadic and often under-recognised outbreaks across several states; vaccination coverage was negligible — in Karnataka it stood at under 1 per cent in 2021 (Reddy *et al.*, 2023; Sudhakar *et al.*, 2020).

The 2022 epidemic was substantially larger. Beginning in Gujarat and Rajasthan around May and accelerating during the monsoon, it had reached 15 states and 251 districts by late September. Published estimates indicate that approximately 2.4 million cattle were affected and more than 110,000 died, although totals vary by source and reporting period (Akther *et al.*, 2023; Kumar and Tripathi, 2022).

A systematic Indian pathology-led investigation of that epidemic examined 1,618 animals across seventy outbreaks, of which 513 were clinically suspect and 48 were subjected to post-mortem examination. Morbidity was 31.70 per cent, mortality 2.97 per cent, and the case fatality rate 9.37 per cent (Manjunathareddy *et al.*, 2024). These figures sit at the upper end of what has historically been reported for LSD, where case fatality is usually below 10 per cent,

and they are consistent with an immunologically naive population encountering a virulent field strain. Mass vaccination beginning in late 2022 was followed by a marked decline in reported incidence and mortality during 2023 and 2024. Nevertheless, outbreaks continued in 2025 and 2026, including post-monsoon clusters in Maharashtra and Karnataka. The current pattern is consistent with endemic, seasonally recurrent transmission in a partially immune population (Bayyappa *et al.*, 2025b; Tadakod *et al.*, 2026).

Karnataka surveillance data require cautious interpretation. The reported case-fatality rate increased from 0.15% in 2021-2022 to 13.8% in 2023-2024 in some northern agro-climatic zones despite high vaccination coverage. This pattern may reflect changes in case ascertainment and reporting, because mild or subclinical infections are less likely to enter passive surveillance after widespread vaccination. Active, structured sampling is needed before attributing the increase to vaccine failure or greater viral virulence (Bayyappa *et al.*, 2025b).

Table 1: Chronology and scale of lumpy skin disease in India, 2019–2026.

Period	Geographic extent	Key features	Vaccination
Aug–Nov 2019	Odisha (Mayurbhanj, Bhadrak, Kendrapara); subsequent spread to adjoining states	First Indian incursion; KSGP-like cluster 1.2 field strain	None
2020–2021	Sporadic across multiple states; presumptive cases in cattle and buffaloes around central Indian tiger reserves	Under-recognised; limited laboratory confirmation	Heterologous goatpox (Uttarkashi) authorised 2021; coverage minimal
2022	15 states, 251 districts by late September	Major epidemic from Gujarat and Rajasthan; ~2–2.4 million cattle affected; >110,000 deaths reported; morbidity 31.7%, CFR 9.37% in a 70-outbreak study	Emergency mass campaign with goatpox vaccine; Lumpi-ProVacInd technology released Aug 2022
2023–2024	Declining incidence nationally; persistent hotspots	Marked fall in mortality; ~182 million cattle vaccinated by Dec 2023; apparent rise in reported CFR in some zones, likely denominator-driven	Near-complete coverage in several states; CDSCO approval of commercial Lumpi-ProVacInd (2024)
2025–2026	Ten states reporting in 2025; post-monsoon clusters in Maharashtra, Karnataka, Rajasthan, Himachal Pradesh	Endemic, seasonally recrudescence pattern; genetically stable lineage related to the 2022 Haryana strain	Annual mass vaccination continuing; field effectiveness of the heterologous vaccine under active question

Sources: Bayyappa *et al.* (2025b), Kumar and Tripathi (2022), Manjunathareddy *et al.* (2024), Sudhakar *et al.* (2020), and Tadakod *et al.* (2026).

Transmission and Vector Ecology

LSDV is transmitted predominantly by mechanical rather than biological vector transmission. Blood-feeding arthropods carry virus on contaminated mouthparts between animals during interrupted feeding. Stable flies (*Stomoxys calcitrans*), horn flies (*Haematobia irritans*), mosquitoes (notably *Aedes aegypti*), *Culicoides* midges, and ixodid ticks of the genera *Rhipicephalus* and *Amblyomma* have all been implicated. Transstadial and transovarial passage in ticks has been demonstrated, raising the possibility of over-wintering or inter-epidemic maintenance. Vector competence has not been evaluated adequately in the *Stomoxys*, *Culicoides*, and *Rhipicephalus* populations present in Indian agro-ecosystems (Tuppurainen and Oura, 2012; WOA, 2024).

Direct and indirect transmission also occurs — through contaminated feed, water, shared equipment, and via semen, milk and colostrum — and appears to be more important for clade 2 recombinant strains than for the classical clade 1 viruses circulating in mainland India. Scabs shed from healing lesions contain high viral loads and remain infectious for extended periods, which makes disposal of shed scabs and contaminated bedding a practical control point that is routinely neglected (Bowden *et al.*, 2008; Roche *et al.*, 2020; Tuppurainen and Oura, 2012).

The Indian seasonal pattern follows vector abundance closely: cases rise with the monsoon and peak in the warm, humid post-monsoon months of roughly July to October. Spatial analyses from Karnataka and Uttar Pradesh have shown strong spatial autocorrelation with clustering in densely stocked, vector-favourable districts, and geographically weighted regression has identified temperature, humidity and land-cover variables as significant predictors of incidence. Livestock movement supplies the long-distance component: cattle fairs, informal trade networks and transhumance carry virus between agro-climatic zones that vectors alone would not connect (Bayyappa *et al.*, 2025b; Das *et al.*, 2025).

Host and Herd-Level Risk Factors

Cattle aged 1-5 years and females have been over-represented in Indian field studies. This may reflect both biological susceptibility and the age and sex structure of dairy herds. Exotic and crossbred cattle had 2.1-2.6-fold higher odds of infection than indigenous zebu breeds in a Karnataka analysis. Proposed explanations include differences in skin characteristics, vector exposure, metabolic demand, fly-avoidance behaviour, and host genetics, but these factors have not been separated experimentally (Bayyappa *et al.*, 2025b; Manjunatha Reddy *et al.*, 2025; Ochwo *et al.*, 2019).

Concurrent haemoprotozoan infection and helminth burden were associated with worse outcomes in analyses of Indian outbreaks. National programme guidance therefore recommends strategic deworming before vaccination to support an adequate immune response (Manjunatha Reddy *et al.*, 2025).

Lumpy Skin Disease in Water Buffaloes

India has approximately 110 million buffaloes, which contribute substantially to national milk production. The available evidence suggests that water buffaloes are susceptible to LSDV but generally develop milder disease than cattle (Di Felice *et al.*, 2024; Fagbo *et al.*, 2014; Sudhakar *et al.*, 2025a). Field observations from central India during 2020-2021 described presumptive LSD in Asian water buffaloes living near affected native cattle, with lower morbidity in buffaloes. In-contact buffaloes with mild, deep-seated nodules were negative for LSDV DNA at the time of sampling but had virus-neutralising antibody titres of 1:16-1:64, indicating previous exposure. Natural infection was later confirmed in buffaloes sampled across 12 states and one union territory during 2020-2023; clinical disease was usually mild to moderate, and many infected animals were asymptomatic (Pandey *et al.*, 2022; Sudhakar *et al.*, 2025a).

Experimental work in Mediterranean buffalo is consistent with this. Following inoculation with LSDV, buffaloes remained negative by real-time polymerase chain reaction on blood, swabs, biopsies and organs; three animals seroconverted on enzyme-linked immunosorbent assay between days 39 and 42, but all sera were negative by virus neutralisation test. In-contact cattle, by contrast, developed severe clinical disease, viraemia, virus shedding and unambiguous seroconversion on both assays (Di Felice *et al.*, 2024). These observations have three practical implications. First, buffaloes may be less efficient amplifying hosts than cattle, although their role in transmission has not been quantified. Second, disagreement between enzyme-linked immunosorbent assay and virus-neutralisation results suggests that assays validated in cattle should not be applied to buffalo serosurveys without species-specific validation. Third, mild or subclinical infection may be missed clinically; LSD should therefore remain a differential diagnosis in buffaloes with sparse, deep-seated dermal nodules (Di Felice *et al.*, 2024; Sudhakar *et al.*, 2025a).

Vaccination policy for buffaloes remains largely undefined in India. Immune response data for Lumpi-ProVacInd in buffaloes have been generated, but whether routine buffalo vaccination is epidemiologically justified — given their limited apparent role in transmission — or economically warranted has not been settled (Dhanda *et al.*, 2024).

Host Range Expansion

Two Indian reports have extended the recognised host range within the Bovini. LSD was confirmed in yak (*Bos grunniens*), interpreted as species spillover from cattle, and subsequently in mithun (*Bos frontalis*) — the first such evidence anywhere. Both findings matter for the Himalayan and North-Eastern states, where these species are economically and culturally central and where veterinary surveillance is thinnest. They also raise an unaddressed question about wild bovids: gaur (*Bos gaurus*) and wild buffalo (*Bubalus arnee*) share landscapes with infected

village cattle across central and north-eastern India, and no systematic surveillance of these populations has been undertaken (Manjunatha Reddy *et al.*, 2023; Reddy *et al.*, 2024).

Economic Burden

The economic burden of LSD in India has been estimated using stochastic modelling. Losses arise from mortality, reduced milk yield, treatment, hide damage, loss of draught power, abortion, infertility, reduced semen usability, and trade restrictions. For Karnataka, a vaccination programme estimated to cost approximately INR 2,729 million was projected to avert losses of about INR 58,930 million. Estimates for the 2022 epidemic vary substantially because they use different assumptions for mortality, milk loss, and under-reporting (Molla *et al.*, 2017; Naidu *et al.*, 2025).

Pathogenesis

Entry, Primary Replication and Viraemia

Virus is deposited into the dermis, usually by the contaminated mouthparts of a biting arthropod. Primary replication occurs locally in dermal fibroblasts, pericytes, macrophages and endothelial cells, producing the initial papule. Virus then drains to the regional lymph node, where further replication occurs, and enters the circulation as a transient, largely cell-associated viraemia carried in monocytes. Generalisation to distant skin, mucosae and viscera follows (Kumar *et al.*, 2021; Kumar *et al.*, 2025).

The incubation period is 4 to 14 days under experimental conditions and may extend to five weeks in the field. Fever is characteristically biphasic, with the first peak coinciding with viraemia and the second with lesion generalisation. Viraemia is brief and modest relative to viral loads in skin lesions, a pattern that informs diagnostic specimen selection (Kumar *et al.*, 2025; WOA, 2024).

Cellular Tropism

LSDV has epithelial tropism and also infects endothelial cells and pericytes. Viral antigen and inclusion bodies have been demonstrated in keratinocytes, follicular and glandular epithelium, sebaceous epithelium, macrophages, fibroblasts, pericytes, and vascular and lymphatic endothelium. Involvement of the microvasculature helps explain why LSD produces deep, full-thickness necrosis rather than a predominantly superficial pox lesion (Kumar *et al.*, 2025; Sanz-Bernardo *et al.*, 2020).

Evolution of the Cutaneous Lesion

The lesion begins as a papule and enlarges into a firm, raised, circumscribed nodule typically 10 to 50 millimetres in diameter, involving epidermis, full-thickness dermis, and frequently the subcutis and underlying musculature. Nodules may be few or number in the hundreds, and adjacent lesions coalesce into irregular plaques. As vascular injury progresses, the centre of the nodule undergoes necrosis and forms the characteristic sitfast: a firm, dry, sharply demarcated plug that separates and may leave a deep ulcer. Healing occurs through granulation tissue and fibrosis, often producing a permanent scar and hide defect. The wedge-shaped coagulative necrosis observed histologically is consistent with ischaemic injury downstream of vasculitis and thrombosis (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020).

Systemic and Mucosal Lesions

Nodules develop on mucous membranes of the muzzle, nares, oral cavity, pharynx, oesophagus, trachea and, less commonly, the lungs; in the gastrointestinal tract they favour the abomasum and rumen. Superficial lymph nodes — prescapular, precrucial, parotid, submandibular — enlarge markedly, sometimes to ten times normal size, and this generalised lymphadenomegaly in the presence of skin nodules is a useful clinical discriminator. Subcutaneous oedema of the brisket, ventral abdomen and distal limbs is common, reflecting lymphangitis and lymphatic obstruction as much as vascular leakage (Namazi and Khodakaram Tafti, 2021; WOA, 2024).

Respiratory involvement is a leading cause of death. Tracheal and laryngeal nodules can obstruct the airway; pulmonary lesions include primary viral interstitial pneumonia and, more commonly in fatal cases, secondary

bacterial bronchopneumonia. Ocular lesions — conjunctivitis progressing to keratitis and occasionally corneal opacity — accompany the mucopurulent ocular discharge of the generalised phase. Myocardial and epicardial haemorrhage with interstitial mononuclear infiltration has been described in Indian and Southeast Asian material (Manjunathareddy *et al.*, 2024; Mathewos *et al.*, 2022).

Reproductive and Mammary Involvement

Bulls develop orchitis and testicular degeneration, and virus is shed in semen for extended periods after clinical recovery — an important consideration for artificial insemination centers and semen stations, and a route by which LSDV can cross considerable distances. In cows, nodules on the udder and teats predispose to ascending bacterial mastitis, and teat lesions make milking painful, compounding the direct viral effect on yield. Abortion, stillbirth, and temporary or permanent infertility are recognised sequelae (Kumar *et al.*, 2025; Namazi and Khodakaram Tafti, 2021).

Determinants of Severity and Cause of Death

Disease severity is influenced by viral strain, breed, age, immune status, vector exposure, nutrition, and concurrent disease. Fatal cases commonly involve secondary bacterial bronchopneumonia, complicated mastitis, myiasis, reduced feed intake due to oral or pharyngeal lesions, cachexia, or septicaemia associated with extensive ulceration. Accordingly, supportive care, wound management, and fly control may reduce case fatality even when specific antiviral treatment is unavailable (Manjunathareddy *et al.*, 2024; Mathewos *et al.*, 2022).

Pathogenesis in Buffaloes

Pathogenesis in *Bubalus bubalis* may differ quantitatively from that in cattle. Available studies indicate restricted replication, little or no detectable viraemia, limited shedding, and fewer or less conspicuous skin lesions. The mechanisms remain unknown and may involve differences in viral entry, early innate restriction, or interactions between viral host-range proteins and buffalo cellular factors. Comparative studies using bovine and buffalo dermal cells are needed (Di Felice *et al.*, 2024; Sudhakar *et al.*, 2025a).

Pathology

Gross Pathology

At necropsy the defining findings are multifocal to coalescing, firm, raised, circumscribed cutaneous nodules distributed over the whole-body surface with predilection for the head, neck, perineum, udder, scrotum and limbs. On cut surface the nodule is grey-white, firm and homogeneous, extending through the full dermal thickness into the subcutis and often into underlying fascia and muscle, with a well-demarcated necrotic core in more advanced lesions. Some nodules show a targetoid appearance with concentric zonation (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020).

Regional lymph nodes are markedly enlarged, oedematous and often haemorrhagic on section. Nodular lesions are found on the mucosa of the nasal cavity, pharynx, larynx, trachea, oesophagus, abomasum and rumen, and occasionally on the pleural and peritoneal surfaces. The lungs may show focal firm nodules, interstitial oedema and, in animals dying after a protracted course, cranioventral consolidation of bacterial bronchopneumonia. Subcutaneous and intermuscular oedema is common. Hepatic and renal changes are non-specific (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020).

Histopathology

Histological findings vary with lesion age. The description below integrates Indian field observations, experimental studies, and the World Organisation for Animal Health case description (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020; WOA, 2024). In early lesions the epidermis shows spongiosis with widened intercellular spaces and ruptured intercellular bridges, intracellular oedema and ballooning degeneration of the stratum spinosum, microvesicle formation, and scattered single or small clusters of necrotic keratinocytes with shrunken hyper eosinophilic cytoplasm and pyknotic, hyperbasophilic nuclei. Orthokeratotic hyperkeratosis is variable. The

superficial dermis is oedematous with a perivascular infiltrate. Large stellate to epithelioid cells with abundant pale cytoplasm — the cellules claveleuses of Borrel, familiar from sheeppox — may be present (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020).

In the fully developed acute nodular lesion the diagnostic change is necrotising fibrinoid vasculitis of dermal and subcutaneous arterioles and small muscular arteries. Vessel walls are disrupted and replaced by brightly eosinophilic fibrinoid material admixed with mononuclear inflammatory cells, and lumina are frequently thrombosed. Lymphatics show endothelial hypertrophy and proliferation with mural and perivascular infiltration — lymphangitis. A mixed inflammatory infiltrate of macrophages, lymphocytes, plasma cells, neutrophils and eosinophils permeates the dermis, accompanied by oedema and haemorrhage. Dermal–epidermal separation may occur (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020). The necrotic stage is defined by wedge-shaped zones of coagulative necrosis — infarcts — whose apices point towards the occluded feeder vessel. In fully evolved lesions the necrotic core is sequestered, sharply demarcated from surrounding viable tissue, and progressively rimmed by granulation tissue. Deep folliculitis and furunculosis are common, and bacterial colonies are frequently visible within necrotic tissue. Martius scarlet blue or a comparable fibrin stain is useful for confirming the fibrinoid nature of the vascular lesion when haematoxylin and eosin is equivocal (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020).

Table 2: Stage-wise histopathological lesion profile in bovine lumpy skin disease.

Stage	Epidermis	Dermis and Vasculature	Inclusion Bodies	Deep Tissue
Early (approx. 0–7 days)	Spongiosis; intra- and intercellular oedema; ballooning degeneration of stratum spinosum; microvesicles; scattered keratinocyte necrosis; variable orthokeratotic hyperkeratosis	Superficial dermal oedema; perivascular mononuclear cuffing; early endothelial swelling; cellules clavele uses of Borrel	Infrequent; occasional in keratinocytes	Minimal involvement
Acute nodular (approx. 7–14 days)	Full-thickness degeneration and necrosis; vesiculation; ulceration where the surface is lost	Necrotising fibrinoid vasculitis with mural fibrin and mononuclear infiltration; thrombosis; lymphangitis with endothelial hypertrophy; mixed infiltrate of macrophages, lymphocytes, plasma cells, neutrophils, eosinophils; oedema and haemorrhage	Most numerous at this stage; keratinocytes, follicular and sebaceous epithelium, macrophages, fibroblasts, pericytes, endothelium	Subcutaneous oedema; myositis and myonecrosis in severe cases
Necrotic / sitfast (approx. 14–28 days)	Loss of epidermis; dermal–epidermal separation at margins	Wedge-shaped coagulative necrosis (infarction); sequestrum formation; deep folliculitis and furunculosis; bacterial colonies; early granulation tissue rim	Diminishing; degenerate and difficult to identify	Extension into fascia and muscle; secondary bacterial invasion
Chronic (>28 days)	Re-epithelialisation from lesion margins	Granulation tissue; perivascular fibroplasia; progressive mature collagenous fibrosis; residual vascular remodelling	Absent	Scar with permanent hide defect; sequestrum extruded or encapsulated

Sources: Manjunathareddy *et al.* (2024), Sanz-Bernardo *et al.* (2020), and Vigneshwar *et al.* (2026).

Chronic lesions consist of granulation tissue, perivascular fibroplasia and progressively mature collagenous fibrosis replacing the infarcted dermis, with the sequestrum either extruded or encapsulated. Eosinophilic intracytoplasmic inclusion bodies are a characteristic diagnostic feature. They may occur in keratinocytes, follicular and sebaceous epithelium, macrophages, fibroblasts, pericytes, and endothelial cells and are most readily detected in acute lesions.

Because inclusions may be sparse, their absence does not exclude LSD; multiple sections and careful high-power examination may be required. They should be distinguished from the intranuclear inclusions and syncytia associated with bovine herpesvirus 2 (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020).

Lymph nodes show marked lymphoid hyperplasia with prominent germinal centres, sinus histiocytosis, subcapsular oedema and haemorrhage; inclusion bodies are occasionally identifiable in sinus macrophages. Pulmonary lesions comprise interstitial pneumonia with alveolar septal thickening, type II pneumocyte hyperplasia, alveolar oedema and, where secondary infection has supervened, suppurative bronchopneumonia. Nodular mucosal lesions in the alimentary and respiratory tracts recapitulate the cutaneous histology, with vasculitis and epithelial necrosis (Manjunathareddy *et al.*, 2024; Mathewos *et al.*, 2022).

Ancillary Techniques

Immunohistochemistry using antibodies directed against capripoxvirus structural antigens, most commonly the P32 (ORF074) envelope protein, localises antigen to keratinocytes, macrophages, fibroblasts, pericytes, and endothelium and is particularly useful when inclusion bodies are not detected. Demonstration of antigen in endothelial cells also supports the interpretation of vascular tropism (Sanz-Bernardo *et al.*, 2020; WOA, 2024).

Transmission electron microscopy of negatively stained lesion material demonstrates brick-shaped poxvirus particles of approximately 230 by 290 nanometres with a characteristic surface tubular structure; capripoxvirions can be distinguished morphologically from the ovoid parapoxvirus particles of pseudocowpox and bovine papular stomatitis, though not from sheeppox and goatpox virus. Virus isolation on lamb testis cells, Madin-Darby bovine kidney cells or primary bovine dermis cultures produces cytopathic effect with cell rounding, vacuolation, ballooning degeneration, syncytium formation and eventual cytolysis, often only after six to ten passages, together with intracytoplasmic inclusions — in contrast to bovine herpesvirus 2, which produces syncytia with intranuclear inclusions (Haegeman *et al.*, 2020; Kumar *et al.*, 2021).

Differential Dermatopathology

The single most important differential is pseudo-lumpy skin disease caused by bovine herpesvirus 2. Its lesions are superficial, transient, resolve within a few weeks without sit fast formation, and histologically show intranuclear rather than intracytoplasmic inclusions with syncytial cell formation and no significant vasculitis. Other differentials that arise in Indian material include dermatophilosis (exudative, with the characteristic tramline branching filaments of *Dermatophilus congolensis* in crusts), dermatophytosis, demodicosis, besnoitiosis (thick-walled *Besnoitia* cysts in dermis and scleral conjunctiva), onchocerciasis, hypodermosis, insect-bite hypersensitivity and urticaria, photosensitisation dermatitis, cutaneous tuberculosis, bovine papillomatosis and cutaneous lymphoma (Namazi and Khodakaram Tafti, 2021; Toker *et al.*, 2026; WOA, 2024).

The combination that discriminates LSD is deep, full-thickness, vasculitis-centered necrosis together with eosinophilic intracytoplasmic inclusion bodies. Neither feature alone is sufficient, and in practice the vascular lesion is the more consistent of the two (Sanz-Bernardo *et al.*, 2020).

Immunopathology

Innate Sensing and Interferon Antagonism

As a cytoplasmically replicating double-stranded DNA virus, LSDV is sensed principally through cyclic GMP-AMP synthase, which on detecting cytosolic viral DNA generates cyclic GMP-AMP; this binds the endoplasmic reticulum adaptor STING (also known as MITA), driving its oligomerisation and trafficking, recruitment of TANK-binding kinase 1, activation of interferon regulatory factor 3, and induction of type I interferons and interferon-stimulated genes (Chen *et al.*, 2025).

LSDV interferes with this axis at multiple points, and recent functional work has begun to identify the responsible gene products. The protein encoded by LSDV 001/156, located in the inverted terminal repeat, binds interferon regulatory factor 3 and prevents its dimerisation and nuclear translocation, blunting interferon production; deletion of this gene reduces replication and virulence in cattle. LSDV122 acts downstream, binding both subunits of the

type I interferon receptor and disrupting their assembly so that Janus kinase 1 and tyrosine kinase 2 cannot be recruited — with the result that LSDV-infected bovine kidney cells fail to induce interferon-stimulated genes such as IFI44, ISG56, RSAD2 and MX2 even in the presence of interferon-beta. Interestingly, LSDV087 appears to work in the opposite direction, promoting STING oligomerisation and enhancing signalling, while also functioning as a decapping enzyme; whether this reflects an unintended consequence of a replication function or a genuine element of a host-virus equilibrium is unresolved (Li *et al.*, 2025; Sun *et al.*, 2026; Zhang *et al.*, 2025).

Together, these mechanisms may create an early permissive period for viral replication in dermal cells. The mature lesion is therefore likely to reflect both direct viral injury and a delayed host inflammatory response (Chen *et al.*, 2025; Zhang *et al.*, 2025).

Virokines, Viroceptors and Local Immune Subversion

LSDV encodes several secreted or membrane-associated immunomodulatory proteins. These include LSDV005, an interleukin-10 homologue; LSDV006 and LSDV013, interleukin-1 receptor-like proteins that may function as decoy receptors; and LSDV011, a G protein-coupled CC chemokine receptor homologue. A CD47-like membrane protein may also inhibit macrophage clearance through signal regulatory protein-alpha, although its role in LSDV infection requires direct functional confirmation (Chen *et al.*, 2025; Tulman *et al.*, 2001). Targeted knockout of putative immunomodulatory genes has been investigated as a route to attenuated capripoxvirus vaccines with an intrinsic serological marker (Kara *et al.*, 2018; Williamson, 2025).

Vascular Immunopathology

The vascular lesion probably reflects both direct infection of endothelial cells and host-mediated injury. Cytotoxic T-cell activity, complement activation, and immune-complex deposition have been proposed as contributors to fibrinoid necrosis and thrombosis, but their relative importance has not been demonstrated conclusively. The resulting ischaemia accounts for much of the lesion depth, oedema, lymphangitis, and scarring (Badr *et al.*, 2022; Sanz-Bernardo *et al.*, 2020).

Cell-mediated Immunity

Protection against poxviruses is dominated by cell-mediated rather than humoral immunity, and LSDV is no exception. Studies of peripheral blood mononuclear cells from cattle recovered from natural LSDV infection have shown increased CD8-positive T-cell counts on antigenic restimulation without significant change in CD4-positive counts, and sensitised cells cleared LSDV infection more effectively than unsensitised cells — evidence for a central role of CD8-positive T cells in viral clearance. Both CD4-positive and CD8-positive subsets contribute to interferon-gamma production, demonstrable by enzyme-linked immunospot assay and intracellular cytokine staining following vaccination or challenge. The kinetics and magnitude of these responses, whether they differ between clinical and subclinical infection, how long they persist, and which subpopulations dominate interferon-gamma production, are all still open questions (Fay *et al.*, 2022).

A seronegative vaccinated animal may still be protected because cell-mediated responses contribute substantially to immunity. Post-vaccination seroconversion should therefore not be interpreted as a stand-alone measure of vaccine effectiveness (Dhanda *et al.*, 2024; Fay *et al.*, 2022).

Humoral Immunity

Neutralising antibody is generally detected within 2-3 weeks after infection and subsequently declines. Natural infection is associated with long-lasting immunity, but the duration has not been defined precisely. Maternal antibody may persist for several months and can influence the timing of calf vaccination. Virus-neutralisation tests may fail to detect low antibody titres after mild or subclinical infection, particularly in buffaloes (Fay *et al.*, 2022; Tuppurainen and Oura, 2012).

Cytokine Dysregulation in Natural Disease

Studies of naturally infected Indian cattle have compared expression of pro-inflammatory cytokines, including interleukin-2, interferon-gamma, and granulocyte-macrophage colony-stimulating factor, with anti-inflammatory

cytokines such as interleukin-4 and interleukin-10. The reported stage-related shift towards an anti-inflammatory profile during later disease is compatible with viral immune modulation, although longitudinal studies are needed to establish the kinetics (Badr *et al.*, 2022; Vigneshwar *et al.*, 2026).

Systemic Immunosuppression, Haematology and Comorbidity

Naturally infected cattle show measurable transient immunosuppression: depressed lymphocyte transformation, reduced phagocytic percentage and reduced killing percentage, most marked within the first two weeks after infection. Haematologically, a macrocytic hypochromic anaemia develops around days 10 to 14, with leucocytosis and neutrophilia later in the course, particularly where secondary bacterial infection has supervened. Serum biochemistry typically shows hypoproteinaemia and hypoalbuminaemia with an altered albumin-to-globulin ratio, hyperfibrinogenaemia, and elevations in aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase reflecting muscle and hepatic involvement (Mathewos *et al.*, 2022; Vigneshwar *et al.*, 2026).

Transient immunosuppression may compound endemic haemoprotozoan and helminth infections and contribute to secondary bacterial complications in fatal cases. These observations support the national recommendation for deworming before vaccination and the use of supportive care and vector control during outbreaks (Manjunatha Reddy *et al.*, 2025; Vigneshwar *et al.*, 2026).

Advances in Diagnosis

Clinical Case Definition and Sampling Strategy

A presumptive field diagnosis rests on the combination of biphasic fever, generalised superficial lymphadenomegaly, multifocal firm cutaneous nodules involving the full skin thickness, mucopurulent nasal and ocular discharge, limb and brisket oedema, and a sharp fall in milk yield. Laboratory confirmation is required for notification and for outbreak response (Toker *et al.*, 2026; WOA, 2024). Specimen selection strongly influences diagnostic sensitivity. During Indian outbreaks in 2025, PCR positivity was 95% for nasal swabs, 82% for tissue biopsies or scabs, and 55% for whole blood. This pattern is consistent with transient, low-level viraemia and more persistent viral DNA in skin lesions and respiratory secretions. Whole blood is therefore a lower-yield specimen once the early febrile phase has passed (Das *et al.*, 2025; Tadakod *et al.*, 2026).

For a complete diagnostic submission the recommended package is: a fresh skin nodule or scab in viral transport medium under cold chain for molecular testing and virus isolation; a nasal swab in viral transport medium; a full-thickness skin biopsy including the lesion margin and adjacent normal skin fixed in 10 per cent neutral buffered formalin for histopathology and immunohistochemistry; ethylenediaminetetraacetic acid blood only if the animal is in the early febrile phase; and paired sera collected 21 days apart (Bhat *et al.*, 2025; Haegeman *et al.*, 2020; WOA, 2024).

Histopathology and Immunohistochemistry in the Diagnostic Pathway

Histopathology retains a defined role despite the primacy of molecular assays. It is the tool of choice for investigating mortality, where the question is not whether LSDV was present but what actually killed the animal; for distinguishing LSD from pseudo-lumpy skin disease and the other nodular dermatoses; and for late chronic lesions in which viral DNA may no longer be recoverable but the vasculitis-and-fibrosis picture remains readable. Immunohistochemistry adds antigen localisation where inclusion bodies are absent (Sanz-Bernardo *et al.*, 2020; WOA, 2024).

Molecular Detection

Conventional polymerase chain reaction targeting the P32 (ORF074) gene provides a rapid, inexpensive genus-level confirmation of capripoxvirus and remains the workhorse in Indian laboratories. Probe-based real-time polymerase chain reaction targeting the LSDV126 region is the World Organisation for Animal Health-recommended method and offers species-level specificity with high sensitivity, and it is the assay against which newer platforms are benchmarked. Additional targets used for characterisation and differentiation include the G protein-coupled chemokine receptor gene (ORF011), RPO30, the extracellular enveloped virus gene, and B22R (Haegeman *et al.*,

2020; Pestova *et al.*, 2018; WOA, 2024).

Genotyping and DIVA

Differentiating field virus from vaccine virus is essential during annual vaccination with live-attenuated products because this distinction separates field infection from vaccine-associated reactions or vaccine-derived virus. Several approaches are available. A duplex real-time polymerase chain reaction has been developed and validated that differentiates Neethling-based vaccine strains from both classical and Asian recombinant wild-type strains (Haegeman *et al.*, 2023). A 705-base-pair region within ORF134 (LW134) containing thirteen informative single nucleotide polymorphisms accurately assigns recombinant vaccine-like strains to their clusters from a single sequencing run (Krotova *et al.*, 2023). Multi-locus real-time polymerase chain reaction with high-resolution melting analysis differentiates wild-type, Asian recombinant and vaccine strains in a rapid, low-cost format. For lineage assignment, sequencing the C-terminal region of B22R, or a concatenated GPCR–RPO30–P32–EEV–B22R alignment, has been shown to reproduce whole-genome clustering (Byadovskaya *et al.*, 2021; Haegeman *et al.*, 2023; Krotova *et al.*, 2023).

Lumpi-ProVacInd was derived from LSDV/Cattle/India/2019/Ranchi after 50 passages in Vero cells and contains a unique 801-nucleotide deletion in the 5-prime inverted terminal repeat. This difference has been used in a high-resolution-melting gap quantitative PCR assay and in an indirect ELISA based on recombinant ORF154, which is present in field viruses but disrupted in the vaccine strain. Further field validation could make serological DIVA testing useful for monitoring vaccination and field infection in India (Kumar *et al.*, 2023b; Nokhwal *et al.*, 2025).

Field-deployable and Emerging Platforms

Isothermal amplification removes the requirement for a thermal cycler and brings molecular detection within reach of district and field laboratories. Loop-mediated isothermal amplification is recommended by the World Organisation for Animal Health alongside polymerase chain reaction methods. Recombinase polymerase amplification offers comparable advantages with shorter run times. A saltatory rolling circle amplification approach developed on Indian material from Meghalaya achieved a limit of detection of 10 copies per microlitre — better than the real-time polymerase chain reaction comparator in that study — using World Organisation for Animal Health-recommended conventional primers, with visual endpoint reading. CRISPR-Cas12a fluorescence and lateral flow assays, and nanopore sequencing for rapid characterisation, are all now described for LSDV (Bhat *et al.*, 2025; Das *et al.*, 2025; WOA, 2024).

Important constraints under field conditions include reagent cold-chain requirements, contamination risk in open-tube isothermal assays, and the need for trained personnel. Decentralised molecular testing should therefore include standard operating procedures, external quality assessment, and inter-laboratory proficiency testing before results are used for official notification (Bhat *et al.*, 2025; Das *et al.*, 2025).

Serology

The virus neutralisation test remains the reference standard but is laborious, requires cell culture facilities and biosafety containment, and lacks sensitivity in mild and subclinical infection. Indirect and double-antigen enzyme-linked immunosorbent assays are available commercially and are the practical tools for seroprevalence work; reported apparent seroprevalence figures from Indian studies include 11.5 per cent in Meghalaya and 19.6 per cent across Madhya Pradesh and Telangana. Immunoperoxidase monolayer assay and indirect fluorescent antibody test are used in reference settings. Cross-reactivity within the genus means that a positive capripoxvirus serological result in a mixed holding must be interpreted in the light of species and vaccination history, and — as discussed above — assay performance in buffaloes cannot be assumed to match performance in cattle (Di Felice *et al.*, 2024; Haegeman *et al.*, 2020; Ochwo *et al.*, 2019).

The Indian Diagnostic Architecture

Under India's Livestock Health and Disease Control Programme, state animal husbandry departments report outbreaks to the Department of Animal Husbandry and Dairying, and reference confirmation is supported by national laboratories including ICAR-NIVEDI. Expanding accredited district-level molecular testing, with

standardised sampling and referral pathways, external quality assessment, and validated procedures, could shorten the time to confirmation and improve the timing of movement controls and vaccination (Das *et al.*, 2025; Press Information Bureau, 2022).

Table 3: Diagnostic methods for lumpy skin disease and their practical position in the Indian setting.

Method	Target or principle	Preferred sample	Practical position
Histopathology	Vasculitis-centred necrosis; intracytoplasmic inclusion bodies	Full-thickness skin biopsy in 10% NBF	Mortality investigation; differentiation from pseudo-LSD and other nodular dermatoses; late chronic lesions
Immunohistochemistry	Capripoxvirus antigen (commonly P32/ORF074)	Formalin-fixed paraffin-embedded skin, lymph node	Antigen localisation where inclusions cannot be found; demonstrates endothelial tropism
Virus isolation	CPE in lamb testis, MDBK or primary bovine dermis cells	Nodule or scab in VTM, chilled	Reference laboratories only; slow (CPE often at passage 6–10); needed for strain banking and challenge studies
Conventional PCR	P32 (ORF074), GPCR (ORF011)	Nasal swab, scab, tissue	Rapid genus-level confirmation; widely available in Indian state laboratories
Real-time PCR	LSDV126 (WOAH-recommended probe assay)	Nasal swab, scab, tissue	Reference confirmatory method; highest sensitivity and specificity
Molecular DIVA	801-nt ITR deletion (Lumpi-ProVacInd); duplex real-time PCR; ORF134 region	Nasal swab, scab, tissue	Distinguishes vaccine from field virus — essential under annual mass live-vaccine campaigns
Serological DIVA	Recombinant ORF154 indirect ELISA	Serum	Scalable audit of vaccination coverage and demonstration of freedom from field infection
Isothermal amplification	LAMP, RPA, saltatory rolling circle amplification	Nasal swab, scab	Field and district laboratory use; SRCA reported at 10 copies/μL on Indian material; needs QA framework
CRISPR-Cas12a	Cas12a collateral cleavage with fluorescence or lateral flow readout	Nasal swab, scab	Emerging; high sensitivity with minimal instrumentation
ELISA (serology)	Indirect or double-antigen antibody detection	Serum, paired 21 days apart	Seroprevalence and post-vaccination monitoring; genus cross-reactivity; performance in buffalo not established
Virus neutralisation test	Neutralisation of infectivity in cell culture	Serum	Reference standard; laborious; insensitive in mild, subclinical and buffalo cases

Sources: Bhat *et al.* (2025), Das *et al.* (2025), Haegeman *et al.* (2020), and WOAH (2024).

Advances in Vaccination

The Heterologous Goatpox Vaccine

In 2021, in the absence of a licensed homologous product, India authorised the use of the live-attenuated goat pox vaccine based on the Uttarkashi strain for immunisation of cattle against LSD. The rationale was sound in principle — capripox viruses share antigens and heterologous protection has been demonstrated for other strain combinations — and the practical advantages were considerable, since manufacturing capacity and cold chain already existed at scale (Kumar *et al.*, 2026; Toker *et al.*, 2026). Evidence for field performance is mixed. State-level analyses have

associated goatpox vaccination with reduced mortality, whereas experimental work and farm-level investigations have reported inadequate protection by the Uttarkashi strain. These findings are not directly comparable because programme-level trends may also reflect movement restrictions, supportive treatment, vector control, and the natural decline of an epidemic. Protection should not be assumed to be equivalent across different sheep pox or goat pox vaccine strains (Kumar *et al.*, 2026; Toker *et al.*, 2026).

Lumpi-ProVacInd: the Homologous Indian Vaccine

Lumpi-ProVacInd was developed at the National Centre for Veterinary Type Cultures, ICAR-National Research Centre on Equines, Hisar, in collaboration with ICAR-Indian Veterinary Research Institute, Izatnagar, by serial passage of the local isolate LSDV/Cattle/India/2019/Ranchi fifty times in Vero cells. The technology was released in August 2022. Whole-genome comparison of the P50 vaccine strain with the P0 virulent parent identified mutations in the DNA-dependent RNA polymerase, kelch-like protein, extracellular enveloped virus membrane phosphoglycoprotein, CD47-like putative membrane protein and G protein-coupled receptor genes — several of which are also mutated in other attenuated capripoxvirus vaccine strains — together with the unique 801-base-pair inverted terminal repeat deletion (Kumar *et al.*, 2023a).

A single dose contains $10^{3.5}$ median tissue culture infectious doses of live-attenuated virus; the product is stored at 2-8 °C, must be shipped on ice, and should be used within a few hours of reconstitution. Immunity induced by homologous live-attenuated LSD vaccines generally persists for at least one year. The vaccine has been reported to induce LSDV-specific antibody and cell-mediated immune responses and to protect against lethal challenge. Non-exclusive commercial rights were granted to Biovet, Bengaluru; Indian Immunologicals, Hyderabad; Hester Biosciences, Ahmedabad; and the Institute of Veterinary Biological Products, Pune. The Central Drugs Standard Control Organisation approved commercial production by Biovet in 2024 (Kumar *et al.*, 2023a; Press Information Bureau, 2022).

A built-in DIVA Marker

The 801-nucleotide inverted terminal repeat deletion gives Lumpi-ProVacInd a potential DIVA advantage over many live-attenuated capripoxvirus vaccines. Molecular differentiation is possible with a high-resolution-melting gap quantitative PCR assay, and an ORF154-based indirect ELISA has been developed for serological differentiation. These tools could support surveillance in vaccinated populations if their performance is confirmed under field conditions (Kumar *et al.*, 2023b; Nokhwal *et al.*, 2025).

Safety and the Recombination Question

A recognised limitation of homologous live-attenuated LSD vaccines is the "Neethling response" — local injection-site reactions, generalised micronodules, transient fever and a temporary drop in milk yield in a proportion of vaccinated animals. These reactions are a significant obstacle to farmer acceptance in dairy systems, where a measurable milk loss following vaccination is immediately visible. The Ranchi-strain vaccine has been reported as free of these effects, which if sustained under large-scale use is a meaningful advantage; systematic post-marketing pharmacovigilance would be needed to confirm it (Kumar *et al.*, 2023a; Toker *et al.*, 2026).

The possibility of recombination requires careful manufacturing controls. Cluster 2 recombinant vaccine-like viruses circulating in Southeast Asia have been linked to recombination between live-attenuated strains. Where capripoxvirus vaccines are produced in the same facility, risk controls should include strict strain segregation, whole-genome sequencing of seed and production lots, and genotyping of suspected vaccine-associated events (Krotova *et al.*, 2023; Sendow *et al.*, 2024).

Determinants of Field Effectiveness

Vaccine efficacy under controlled challenge conditions does not necessarily predict effectiveness in the field. Important determinants include coverage, completion of campaigns before peak vector activity, booster policy, vaccination of animals entering the population, cold-chain integrity, correct reconstitution and use, animal health at vaccination, and monitoring of adverse events (Kumar *et al.*, 2026; Toker *et al.*, 2026).

Next-generation Candidates

Targeted deletion of putative immunomodulatory genes offers rational attenuation with a built-in serological marker, in contrast to the random mutation accumulation of serial passage. Inactivated adjuvanted vaccines may be useful where vaccination must not complicate disease-free status, although the duration of immunity remains uncertain. Subunit and multi-epitope approaches based on the immunodominant P32, A4L, A33R, and L1R proteins have been designed computationally, expressed recombinantly, and shown to elicit humoral and cell-mediated responses in mice. A genome-wide screen has also identified LSDV103 as a highly immunogenic protein with potential as both a DIVA antigen and a vaccine candidate. Messenger RNA vaccine candidates against LSDV have been designed and evaluated as alternatives to live-attenuated products (Gu *et al.*, 2025; Kara *et al.*, 2018; Kumar *et al.*, 2025; Williamson, 2025; Yuan *et al.*, 2025).

For India specifically, the criteria that matter for any successor product are thermostability adequate for village-level cold chain, intrinsic DIVA capability, single-dose administration with at least twelve months of protection, safety in pregnant and lactating animals, demonstrated immunogenicity in buffaloes as well as cattle, and a cost per dose that remains viable when multiplied across a bovine population approaching 300 million (Gu *et al.*, 2025; Williamson, 2025).

Table 4: Vaccines used and under development for lumpy skin disease with relevance to India.

Vaccine or approach	Type and strain	Status in India	Principal limitations
Goatpox vaccine (Uttarkashi)	Heterologous live-attenuated	Authorised 2021; basis of the 2022–2025 mass campaigns	Field and experimental evidence of inadequate protection in cattle; no DIVA capability
Lumpi-ProVacInd	Homologous live-attenuated; LSDV/Cattle/India/2019/Ranchi, Vero P50; $10^{3.5}$ TCID ₅₀ per dose	Technology released Aug 2022; transferred to four manufacturers; CDSCO approval of commercial production (Biovet) in 2024	Cold chain dependence; use within hours of reconstitution; theoretical recombination risk inherent to live capripoxvirus vaccines
Neethling-based homologous vaccines	Live-attenuated cluster 1.1	Not used in India; protective against clade 2.5 challenge in published trials	Neethling response (local reaction, micronodules, fever, milk drop); limited DIVA capability
Immunomodulatory gene knockouts	Rationally attenuated live virus with marker deletion	Experimental	Regulatory pathway for genetically modified live vaccines; scale-up
Inactivated adjuvanted	Whole inactivated virus	Experimental / not licensed in India	Duration of immunity; multiple doses; adjuvant reactogenicity
Subunit and multi-epitope	Recombinant P32, A4L, A33R, L1R; LSDV103	Preclinical (mouse) data available	Efficacy in cattle unproven; adjuvant and delivery optimisation; cost
mRNA candidates	Lipid nanoparticle-formulated mRNA	Design and preclinical stage	Thermostability and cost at Indian population scale

Sources: Gu *et al.* (2025), Kumar *et al.* (2023a), Kumar *et al.* (2026), Williamson (2025), and Yuan *et al.* (2025).

Control Policy and Programme Delivery in India

LSD is a notifiable disease in India and is addressed under the Assistance to States for Control of Animal Diseases component of the Livestock Health and Disease Control Programme, which supports vaccination, disease surveillance and veterinary infrastructure for state-prioritised diseases including LSD, alongside anthrax and rabies. National Action Plans set out the expected outbreak response: identification and notification of the affected area, isolation of affected animals, and implementation of biosecurity measures. Central expert teams provide technical

support through physical and virtual engagement, and confirmatory diagnosis is routed through ICAR-NIVEDI (Press Information Bureau, 2022, 2025).

Implementation depends on timely confirmation, effective movement control, and vector management. Cattle fairs and informal trade can undermine movement restrictions. Residual insecticide use, manure and slurry management, and treatment of animals may reduce vector exposure, while safe disposal of scabs, bedding, and carcasses limits environmental contamination. Compensation policy can also influence reporting and animal movement by affected farmers (Press Information Bureau, 2022; Roche *et al.*, 2020).

Karnataka used bulk short message service advisories to send approximately 2.4 million disease alerts and recommended actions to farmers in March 2025. This low-cost approach can reach smallholders directly. Geographic information system-based clustering analyses of Karnataka and Uttar Pradesh outbreak data can also identify persistent hotspots and help target pre-monsoon vaccination and vector control (Bayyappa *et al.*, 2025b).

LSD is not considered zoonotic, and available evidence does not indicate infection of people through contact with affected cattle or their products. Clear public communication is nevertheless important because misinformation during outbreaks can disrupt milk marketing and disease-control activities (Toker *et al.*, 2026; WOA, 2024).

Knowledge Gaps and Research Priorities

Several gaps are specific to the Indian situation and are tractable with existing institutional capacity.

1. **Genomic surveillance:** Indian characterisation continues to rely largely on single-gene analysis, principally of the GPCR gene. Whole-genome sequencing of a representative sample of isolates across seasons, states and host species is needed to detect recombination, monitor the terminal variable regions where virulence determinants sit, and provide early warning of any incursion of cluster 2 recombinant strains beyond the single Great Nicobar detection (Bayyappa *et al.*, 2025a; Sudhakar *et al.*, 2025b; Tadakod *et al.*, 2026).
2. **Buffaloes:** Species-specific validation of serological assays in *Bubalus bubalis*, structured seroprevalence surveys using validated tests, and a properly framed assessment of whether buffaloes contribute meaningfully to transmission — which would determine whether including them in vaccination campaigns is justified (Dhanda *et al.*, 2024; Di Felice *et al.*, 2024; Sudhakar *et al.*, 2025a).
3. **Standardised lesion grading:** No widely accepted semiquantitative system is available for grading LSD skin lesions, which limits comparison among studies and vaccine trials. A practical scheme could combine lesion number, distribution, maximum diameter, depth, and stage of evolution on a defined ordinal scale. Veterinary pathologists are well placed to develop and validate such a system (Manjunathareddy *et al.*, 2024; Sanz-Bernardo *et al.*, 2020).
4. **Correlates of protection:** Standardised assays of LSDV-specific cell-mediated immunity and a validated immune correlate of protection are needed. Serology alone does not adequately describe vaccine-induced protection (Dhanda *et al.*, 2024; Fay *et al.*, 2022).
5. **Vaccine effectiveness:** Well-designed observational studies — test-negative design or matched cohort — comparing homologous and heterologous vaccination under Indian field conditions, with genotyping of breakthrough cases to distinguish field infection from vaccine reaction (Kumar *et al.*, 2023a; Kumar *et al.*, 2026).
6. **Vector competence:** Laboratory and field studies of the *Stomoxys*, *Haematobia*, *Culicoides*, *Aedes* and *Rhipicephalus* populations actually present in Indian agro-ecosystems, including the question of tick-mediated inter-epidemic maintenance (Roche *et al.*, 2020; Tuppurainen and Oura, 2012).
7. **Host genetics:** The consistent finding that indigenous zebu breeds are less susceptible than exotic and crossbred cattle has not been mechanistically explained, and has obvious implications for breeding policy if the effect proves heritable and separable from management confounders (Bayyappa *et al.*, 2025b; Manjunatha Reddy *et al.*, 2025).

8. **Atypical and wild hosts:** Surveillance in yak, mithun, gaur and wild buffalo populations at the livestock–wildlife interface, which is currently absent (Manjunatha Reddy *et al.*, 2023; Reddy *et al.*, 2024).
9. **Diagnostic decentralisation with quality assurance:** Extension of validated molecular capacity to district level, supported by external quality assessment schemes and inter-laboratory ring trials (Bhat *et al.*, 2025; Das *et al.*, 2025).

Conclusion

Lumpy skin disease in India has progressed from introduction in 2019 to a major epidemic in 2022 and subsequently to endemic, seasonally recurrent transmission. The characteristic pathology reflects epithelial and vascular tropism, with necrotising fibrinoid vasculitis, thrombosis, and ischaemic necrosis producing deep skin lesions and permanent scarring. Severe outcomes are frequently associated with secondary infection, extensive mucosal disease, and poor body condition (Sanz-Bernardo *et al.*, 2020).

Water buffaloes are susceptible but usually show mild or subclinical infection, and diagnostic assays validated in cattle may perform differently in this species. Given the size and economic importance of India's buffalo population, species-specific diagnostic validation is a priority (Di Felice *et al.*, 2024; Sudhakar *et al.*, 2025a).

For molecular diagnosis, lesion material, scabs, and nasal swabs generally provide better diagnostic yield than whole blood. India now has a homologous live-attenuated vaccine with a potentially useful DIVA marker. Sustained control will require high pre-monsoon coverage, vector management, rigorous vaccine manufacturing controls, and genomic and field-effectiveness surveillance. Veterinary pathologists can contribute through mortality investigation, differential diagnosis, vaccine-safety assessment, and standardisation of lesion grading (Kumar *et al.*, 2026; Nokhwal *et al.*, 2025; Tadakod *et al.*, 2026).

Contribution by Authors

All the authors contributed equally to writing the manuscript. The final manuscript was read by all authors and consented to publication.

Conflict of Interests

There is no conflict of interest.

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