Review

Schmallenberg Virus: Pathogenesis, Diagnostic Challenges, and Control Gap in Endemic Europe

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Abstract

Schmallenberg virus (SBV) has evolved from an emergent *Orthobunyavirus* identified in Europe in 2011 into an endemic pathogen with complex epidemiological dynamics. This review focuses on three key aspects: pathogenesis and fetal neurotropism, diagnostic limitations within the Simbu serogroup, and challenges in disease control. SBV pathogenesis is characterized by immune evasion mediated by the NSs protein and a marked tropism for the developing central nervous system, resulting in congenital malformations when infection occurs during critical gestational stages. Similar mechanisms are shared with other Simbu serogroup viruses, contributing to overlapping clinical presentations and complicating differential diagnosis. Diagnostic approaches are constrained by the short duration of viraemia and significant serological cross-reactivity among related viruses. While RT-qPCR is effective for detecting acute infections, its utility is limited for retrospective diagnosis, where fetal tissues and pre-colostral serology are required. Widely used ELISAs lack serogroup specificity, raising concerns about the potential under-recognition of co-circulating or emerging viruses. Despite advances in vaccine development, implementation remains limited, and vector control strategies provide only partial mitigation. SBV therefore represents a valuable model for understanding arbovirus persistence in temperate regions. Addressing current challenges will require improved diagnostic specificity, sustainable vaccination strategies, and integrated surveillance systems.

Keywords: Schmallenberg virus; Simbu serogroup; *Culicoides*; arbovirus epidemiology; congenital malformations; diagnostic limitations; vaccine uptake; climate change

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1. Introduction: Schmallenberg Virus as a Model of Endemic Arbovirus Persistence

Since its emergence in Europe in 2011, Schmallenberg virus (SBV) has transitioned from an acute epidemic threat to an endemic arbovirus characterized by recurrent, wave-like transmission dynamics. Initially identified in dairy cattle in Germany presenting with transient fever, reduced milk production, and diarrhea, SBV rapidly spread across Europe within a single vector season, demonstrating that temperate regions can sustain the emergence and persistence of novel arboviruses when competent vectors and susceptible host populations are present [1–3].

SBV belongs to the Simbu serogroup within the genus *Orthobunyavirus*, family *Peribunyaviridae*. This serogroup includes several antigenically and genetically related viruses of veterinary importance, such as Akabane virus, Aino virus, Shamonda virus, Peaton virus, Shuni virus, and others [4,5]. These viruses share key biological features, including a tripartite negative-sense RNA genome, transmission by *Culicoides* biting midges, and—for several members—the ability to cause congenital malformations when naïve pregnant ruminants are infected during critical stages of gestation [6].

The clinical importance of SBV lies less in acute disease in adult animals, which is usually mild, transient, or subclinical, and more in its teratogenic potential. Infection of naïve pregnant ruminants during defined gestational windows can result in transplacental transmission, fetal central nervous system damage, arthrogryposis, hydranencephaly, abortion, stillbirth, or the birth of non-viable malformed offspring [5,7,8].

Importantly, the congenital syndrome caused by SBV is not pathognomonic. Several Simbu serogroup viruses produce overlapping clinical and pathological outcomes, particularly the arthrogryposis–hydranencephaly complex [5,7]. This creates important diagnostic and surveillance challenges, especially in regions where multiple Simbu serogroup viruses may circulate simultaneously. In such settings, reliance on broadly reactive serological assays may obscure the emergence or re-emergence of related viruses and may lead to under-recognition of mixed or sequential circulation events [9,10].

Fifteen years after its first detection, SBV provides a useful model for understanding arbovirus emergence, endemic persistence, and control in temperate livestock systems. Its epidemiology is shaped by the interaction of vector ecology, livestock immunity, animal trade, climate variability, diagnostic capacity, and vaccine availability [2,3,6,11]. The following sections examine three areas where current knowledge gaps have direct implications for disease control: pathogenesis and fetal neurotropism, diagnostic limitations within the Simbu serogroup context, and practical constraints affecting vaccination and vector management.

2. Pathogenesis and Disease Mechanisms: From Vector Transmission to Fetal Damage

2.1. Transmission and Early Host Infection

SBV is transmitted predominantly by infected *Culicoides* biting midges. Following inoculation during blood feeding, the virus initially replicates at or near the site of entry and in associated lymphoid tissues before disseminating through the bloodstream [11–13]. In adult ruminants, this results in a short viremic phase, usually lasting only a few days, which explains both the transient nature of acute disease and the narrow diagnostic window for molecular detection in blood [8,14].

Clinical signs in adult cattle, sheep, and goats are generally non-specific and may include fever, diarrhea, reduced appetite, and decreased milk production [1,15]. However, the major pathogenic consequence of maternal infection occurs when viraemia coincides with pregnancy, allowing the virus to reach the placenta and infect the developing fetus [7,8,16].

2.2. Transplacental Transmission and Fetal Infection

A defining feature of SBV and several related Simbu serogroup viruses is the capacity for transplacental transmission. After maternal viraemia, SBV can infect placental tissues and subsequently enter the fetal circulation [7,8,16]. The consequences of fetal infection depend strongly on gestational age, because susceptibility is linked to the developmental stage of the fetal immune and nervous systems [5,7].

2.3. Neurotropism and the Mechanisms of Congenital Malformations

SBV shows marked tropism for fetal neural tissues. Experimental and field studies have demonstrated viral antigen and RNA predominantly in neurons of the brain and spinal cord, particularly in grey matter [7,16,17]. Viral replication in these cells leads to neuronal degeneration, necrosis, cerebral malacia, and disruption of normal CNS development [7,16,17].

The characteristic musculoskeletal lesions, especially arthrogryposis, are secondary to CNS damage rather than the result of primary viral replication in muscle. Destruction of spinal motor neurons disrupts neuromuscular signaling, leading to neurogenic muscle atrophy, reduced fetal movement, and fixed limb contractures [5,7]. This mechanism closely resembles that described for Akabane virus and other teratogenic Simbu serogroup viruses [5,6] (Figure 1).

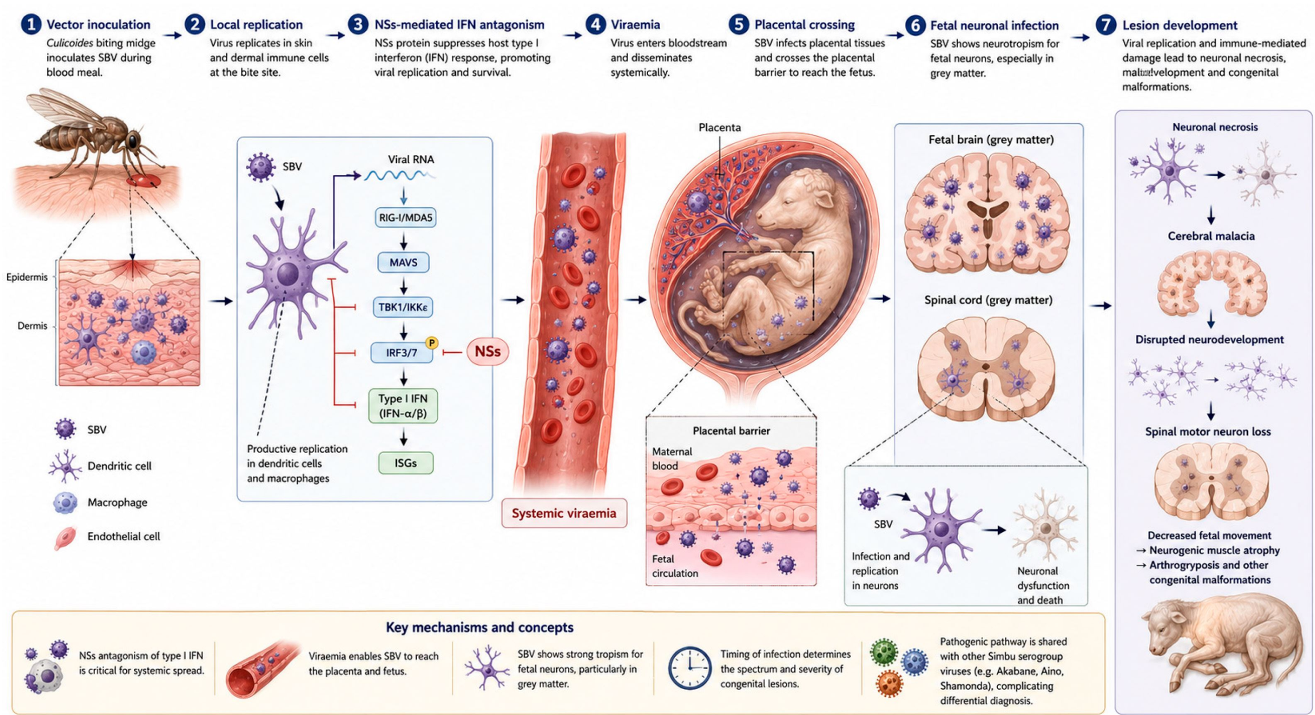

Figure 1. Cellular and molecular pathogenesis of SBV.

Because these lesions are shared across several Simbu viruses, clinical presentation alone cannot reliably distinguish SBV from Akabane, Aino, Shamonda, Peaton, or Shuni virus infections. Laboratory confirmation is therefore essential, particularly in areas where multiple Simbu serogroup viruses may circulate [5,6,9,10].

2.4. NSs-Mediated Immune Evasion

The non-structural protein NSs is a major SBV virulence factor. Reverse genetics studies have shown that deletion of NSs markedly attenuates SBV, confirming its importance in viral pathogenesis. NSs antagonizes the host type I interferon response by interfering with host transcriptional machinery, thereby suppressing interferon and interferon-stimulated gene expression [18,19] (Figure 2). This immune evasion strategy allows SBV to establish systemic infection despite early innate immune defenses. Similar NSs-mediated interferon antagonism has been described for other orthobunyaviruses, indicating that suppression of the innate antiviral response is a conserved mechanism within this group [4,18,19].

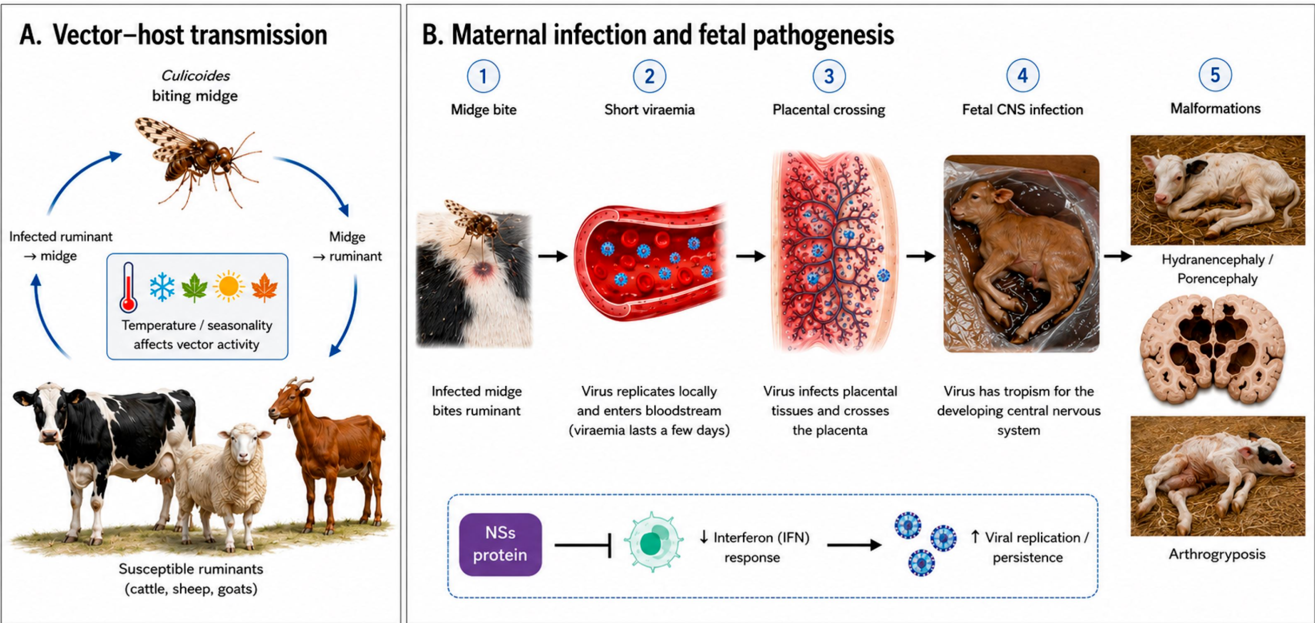

Figure 2. Schmallenberg virus transmission and pathogenesis. (**A**) Schmallenberg virus (SBV) is maintained in nature through a transmission cycle between infected *Culicoides* biting midges and susceptible ruminants. Vector activity and transmission are influenced by temperature and seasonality. (**B**) After a midge bite, SBV replicates locally and causes a short viraemia. During pregnancy, the virus can cross the placenta and infect the fetus, with a marked tropism for the developing central nervous system. Infection during critical gestational windows may result in congenital malformations such as hydranencephaly, porencephaly, and arthrogryposis. The viral NSs protein inhibits the host interferon response, thereby enhancing viral replication.

2.5. Gestational Timing and Lesion Spectrum

The type and severity of lesions depend strongly on the timing of fetal infection. Earlier fetal infection is more likely to cause severe CNS destruction, including hydranencephaly and porencephaly, whereas later infection more commonly results in arthrogryposis, spinal cord lesions, or milder neurological signs [5,7,8].

In cattle, infections occurring approximately between 80 and 120 days of gestation are commonly associated with severe cerebral lesions, while infections later in gestation may produce arthrogryposis, scoliosis, torticollis, or calves born alive with neurological deficits [5,8]. In sheep and goats, the shorter gestational period shifts the equivalent susceptibility window earlier [5].

A useful pathological feature in the differential diagnosis of Simbu serogroup infections is the relative absence of cerebellar lesions, which can help distinguish these infections from other teratogenic viruses such as bovine viral diarrhea virus [5].

Comparative Analysis of Gestational Windows Across Ruminant Species

The differences in susceptibility windows between ruminant species reflect species-specific rates of fetal neurodevelopment and maturation of the blood–brain barrier. In sheep, the compressed gestational period (~147 days) and early development of spinal motor neurons (peak vulnerability days 28–42) create a narrower window. In cattle (~282 days gestation), the extended period of cerebellar and cerebral cortical development (~80–150 days) produces a broader window. Goats (~150 days gestation) show patterns similar to sheep, though data are more limited [5]. Comparative neurodevelopmental studies indicate that the timing of oligodendrocyte precursor differentiation and blood–brain barrier tight junction formation correlates with susceptibility to SBV-induced lesions across species.

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Species-specific differences in placental trophoblast expression of viral entry receptors (yet to be fully characterized) may also contribute.

Table 1 summarizes the key gestational parameters.

Table 1. Gestational parameters and lesion timing in SBV infection.

Species	Gestation Length (Days)	Critical Window (Days)	Peak Neuronal Vulnerability	Primary Lesion Type If Infected Early vs. Late
Cattle	~282	80–150	Cortical neurogenesis (80–120)	Early: hydranencephaly; Late: arthrogryposis
Sheep	~147	28–56	Spinal motor neurons (28–42)	Early: porencephaly; Late: arthrogryposis
Goat	~150	30–60 (estimated)	Similar to sheep	Limited data; pattern presumed similar to sheep

2.6. SBV Within the Broader Simbu Serogroup Context

SBV should not be considered in isolation. Although SBV is currently the principal Simbu serogroup virus recognized in Europe, related viruses have caused similar congenital syndromes in Asia, Africa, Australia, and the Middle East [5,6,10]. Some, such as *Akabane* virus, are well-established teratogenic pathogens, whereas others, including *Shuni* and *Shamonda* viruses, have been increasingly recognized in association with neurological disease or congenital abnormalities [6,10,20,21]. In particular, *Shuni* virus has been associated with fatal encephalitis in calves [22].

Antigenic relationships among Simbu serogroup viruses are complex. The nucleocapsid (N) protein is highly conserved (∼85–95% amino acid identity across the serogroup), explaining the extensive cross-reactivity observed in N-based ELISAs. In contrast, the surface glycoproteins Gn and Gc show greater diversity (∼60–75% identity), and neutralizing antibody responses are largely type-specific. Phylogenetic analysis places SBV within the Simbu serogroup's 'Simbu-like' clade, most closely related to *Sathuperi* and *Shamonda* viruses. The Gc protein, which mediates host cell attachment and membrane fusion, contains variable domains that determine serotype specificity.

Table 2 provides a systematic comparison of selected Simbu serogroup viruses.

Table 2. Comparative features of selected Simbu serogroup viruses of veterinary importance.

Feature	SBV	Akabane Virus	Shuni Virus	Aino Virus	Shamonda Virus
Geographic distribution	Europe	Africa, Asia, Australia, Middle East	Africa, Middle East	Asia, Africa	Africa, Asia
Primary livestock impact	Cattle, sheep, goats	Cattle, sheep, goats	Cattle, sheep	Cattle	Cattle
Congenital malformation risk	High	High	Documented	High	Documented
Abortion/stillbirth reported	Yes	Yes	Yes	Yes	Yes
Adult clinical disease	Mild/febrile	Usually subclinical	Neurologic (calves)	Subclinical	Subclinical
Diagnostic cross-reactivity (ELISA)	High	High	High	High	High
VNT distinguishability	Yes	Yes	Yes	Yes	Yes
Vaccine cross-protection	Limited	Limited	Unknown	Unknown	Unknown
NSs immune evasion documented	Yes	Yes	Presumed	Yes	Presumed
Confirmed in Europe	Yes	No (serological only)	No	No	No

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This broader context has two important consequences. First, the clinical and pathological overlap among Simbu serogroup viruses requires diagnostic approaches capable of distinguishing between them. Second, serological cross-reactivity may lead to underdetection of emerging or co-circulating viruses if surveillance relies only on non-specific commercial ELISAs [9,10]. For this reason, virus neutralization tests and molecular assays remain essential tools for specific identification in areas where multiple Simbu serogroup viruses may be present [9,10].

3. Epidemiology in an Endemic System: Vector Ecology, Trade, and Cyclic Re-Emergence

The endemic epidemiology of SBV reflects a dynamic equilibrium among three interacting components: (1) vector ecology and environmental suitability, (2) host immunity and demographic turnover, and (3) anthropogenic factors including livestock movement. This section examines each component in sequence, then integrates them to explain wave-like re-emergence patterns and the implications of the broader Simbu serogroup context.

3.1. Vector Competence and Environmental Constraints

SBV transmission is tightly linked to the ecology of *Culicoides* biting midges. In Europe, several species within the *Culicoides obsoletus* and *Culicoides pulicaris* complexes have been implicated in SBV transmission [11,12]. Following ingestion of infected blood, the virus replicates within the vector and, after an extrinsic incubation period, is transmitted to new hosts through saliva during subsequent feeding [11,12].

Unlike many arboviruses confined to tropical regions, SBV demonstrated that European *Culicoides* species can sustain viral transmission under temperate climatic conditions, including relatively low temperatures. This adaptation has facilitated the establishment of SBV as an endemic pathogen in Europe [2,6].

3.2. Climate Change and a Year-Round Transmission Potential

Climatic factors play a central role in shaping SBV epidemiology. Temperature influences vector abundance, feeding frequency, and viral replication within the insect. Warmer conditions accelerate the extrinsic incubation period and increase the proportion of infectious vectors, thereby enhancing transmission efficiency [6,23,24].

Recent studies have challenged the traditional concept of a “vector-free period” during winter months. Evidence from Central Europe indicates that *Culicoides* midges remain active at low temperatures and are frequently detected inside livestock buildings, where microclimatic conditions provide refugia [6,25]. This raises the possibility of low-level, continuous transmission during winter, which has important implications for surveillance systems and trade regulations that assume seasonal interruption of virus circulation.

3.3. Livestock Movement and the Role of Trade

The rapid spread of SBV across Europe following its emergence highlighted the potential role of livestock movement and trade networks in facilitating arbovirus dissemination. Although vector-borne transmission is the primary route of infection, the movement of infected animals—particularly during the viremic phase—can introduce the virus into new areas where competent vectors are present [2,6,26]. A retrospective study by Gache et al. [27] demonstrated that herds receiving animals from SBV-affected regions during the 2011–2012 transmission season had 2.4-fold higher odds of seropositivity. Similarly, the French SBV surveillance system showed that introduction of pregnant animals from high-incidence areas was associated with increased farm-level infection risk [27]. A bulk milk tank study in Ireland further demonstrated the widespread introduction and spread of SBV in dairy herds, highlighting the role of animal movements [28]. Notably, vector-borne

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transmission remains the primary route, and trade-associated introduction is conditional upon the presence of competent vectors at the destination. The epidemiological significance of animal movement is therefore context-dependent.

Within Europe, the high density of ruminant populations and frequent movement of animals between regions create conditions that favor rapid geographic expansion. In addition, trade in germplasm (semen and embryos) may pose a theoretical risk, although its epidemiological significance remains less clearly defined.

Beyond Europe, serological evidence of SBV or related viruses has been reported in regions such as Africa and Asia, including Ethiopia and China [6]. While not all reports confirm active viral circulation, these findings raise concerns about silent spread or independent emergence of related Simbu serogroup viruses. The situation in the Middle East, where multiple Simbu serogroup viruses have been detected serologically, further underscores the importance of robust surveillance systems capable of distinguishing between closely related viruses [10].

3.4. Endemic Stability and Wave-like Re-Emergence

Following the initial pandemic phase (2011–2013), SBV became established as an endemic infection in many parts of Europe. Its epidemiology is now characterized by periodic wave-like re-emergence, driven primarily by changes in herd immunity [2,3,6].

After large outbreaks, a high proportion of the ruminant population becomes immune, reducing transmission in subsequent seasons. Over time, however, this population-level immunity declines due to the birth of susceptible animals, replacement of immune individuals, and possible waning of antibody levels. When the proportion of susceptible hosts reaches a critical threshold, and vector activity resumes under favorable climatic conditions, new transmission waves occur [2,6].

This dynamic equilibrium between host immunity and vector activity explains why SBV persists without continuous large-scale outbreaks yet retains the capacity to cause sporadic epidemics of congenital disease, particularly when naïve pregnant animals are exposed.

3.5. Epidemiological Implications of the Simbu Serogroup Context

The epidemiology of SBV cannot be fully understood without considering the broader Simbu serogroup. In regions where multiple Simbu viruses circulate, epidemiological patterns may be more complex due to cross-protective immunity, sequential infections, and serological cross-reactivity.

Evidence from Africa and the Middle East suggests that co-circulation of multiple Simbu serogroup viruses is common, which may alter transmission dynamics and complicate interpretation of serological surveys [9,10]. In contrast, Europe has largely reported SBV as the dominant circulating Simbu virus. However, reliance on non-specific diagnostic tools raises the possibility that additional Simbu viruses may go undetected, particularly if they produce similar clinical outcomes but are not specifically targeted by surveillance programs [9,10].

3.6. Wildlife Hosts: Current Evidence and Research Gaps

Serological evidence indicates that wild ruminants (e.g., red deer, roe deer, wild boar) can be exposed to SBV, but their contribution to viral persistence, spatial spread, and reintroduction into domestic populations is unclear [6,29]. A systematic review of European studies shows seroprevalences ranging from 0–15% in wild deer [29–31], with higher rates in areas of high domestic livestock density [29]. However, active viral circulation in wildlife has not been confirmed, and the duration of antibodies in wild species is unknown. Targeted

longitudinal studies with repeated sampling of marked individuals are needed to determine whether wildlife can act as a true reservoir or merely as incidental spillover hosts.

4. Diagnosis Challenge in the Simbu Serogroup Context

4.1. Molecular Detection: Strengths and Limitations

Reverse transcription quantitative PCR (RT-qPCR) is the primary method for detecting SBV RNA during acute infection. It provides high sensitivity and specificity when samples are collected during the short viremic phase, typically within a few days post-infection [8,16]. Multiplex RT-qPCR assays have also been developed to enable simultaneous detection and differentiation of SBV and other Simbu serogroup viruses, particularly in regions where co-circulation may occur [26].

However, this narrow diagnostic window represents a major limitation. In adult animals, viraemia is transient, and failure to sample at the appropriate time can lead to false-negative results. This is particularly relevant in field conditions, where clinical signs may be mild or go unnoticed [8].

In cases of congenital infection, molecular detection remains valuable even after maternal viraemia has resolved. Viral RNA can be detected in fetal tissues, especially brain, spinal cord, and meconium. These tissues provide the highest diagnostic yield and are considered optimal for confirming in utero infection [16].

4.2. Retrospective Diagnosis and Fetal Testing

The short duration of viraemia in adult animals makes retrospective diagnosis challenging. In many cases, infection is only recognized after the birth of malformed offspring. Under these circumstances, diagnosis relies on detection of viral RNA in fetal tissues and identification of antibodies in pre-colostral serum. The detection of antibodies in pre-colostral serum is particularly important, as it indicates *in utero* infection, given that maternal antibodies are not transferred across the placenta in ruminants [5,8,32]. Serological surveys in Italy have also used such approaches to confirm past SBV exposure in livestock [33].

4.3. Serological Assays: Utility and Critical Limitations

Serological testing plays a central role in SBV surveillance, particularly for assessing herd immunity and detecting past exposure [34]. Virus neutralization tests (VNT) are the reference standard due to their high specificity and ability to distinguish between closely related viruses [8].

However, VNT requires specialized laboratory facilities and is not suitable for large-scale screening. As a result, enzyme-linked immunosorbent assays (ELISAs), particularly those based on the nucleocapsid (N) protein, are widely used in routine diagnostics [8].

Despite their practicality, commercial ELISAs have important limitations, especially in the context of the Simbu serogroup. Several studies have demonstrated that these assays are not strictly serogroup-specific, leading to cross-reactivity between antibodies directed against different Simbu viruses [9,10,35].

Antigenic Basis of ELISA Cross-Reactivity

The extensive cross-reactivity observed in commercial SBV ELISAs has a well-defined molecular basis. Most assays use recombinant N protein as the antigen, chosen for its high immunogenicity and ease of production [32,36]. However, the N protein is among the most conserved proteins within the Simbu serogroup, exhibiting high amino acid identity across species [8,36]. Phylogenetic analyses have shown that the SBV N gene is most closely related to that of *Shamonda* virus, with nucleotide sequence identities reaching 96.7% [37]. Structural

analysis shows that the immunodominant epitopes recognized by host antibodies during infection map to regions of the N protein that are particularly conserved [36]. Consequently, antibodies raised against Akabane, Aino, Shuni, or Shamonda viruses frequently cross-react with SBV N protein in ELISA format [3,36]. Specifically, N-specific monoclonal antibodies have been shown to detect not only all tested SBV isolates, but also several other viruses of the Simbu serogroup, with one antibody recognizing all tested Simbu serogroup viruses [36]. The Gc glycoprotein, in contrast, shows greater diversity and contains serotype-specific neutralizing epitopes [32,36]. The N-terminal variable part of the Gc protein (Gc head) is highly immunogenic and the major target of neutralizing antibodies [36]. In contrast to N-specific antibodies, Gc-specific monoclonal antibodies detected different SBV isolates as well as two closely related members of the Simbu serogroup, while one antibody showed highly specific reactivity with the homologous SBV strain only [36]. Experimental Gc-based assays achieve improved specificity but are more challenging to produce and may have lower sensitivity. For instance, a recently developed glycoprotein Gc-based triplex ELISA for the detection and differentiation of antibodies against SBV, *Akabane* virus (AKAV), and *Shuni* virus (SHUV) showed overall diagnostic specificities of 84.56% for SBV, 94.68% for AKAV and 89.39% for SHUV, with sensitivities of 89.08%, 69.44% and 84.91%, respectively, and only slight effects of serological cross-reactivity on diagnostic specificity [35].

4.4. Implications for Surveillance and Emerging Virus Detection

The reliance on broadly reactive serological assays in Europe, where SBV is currently considered the dominant Simbu virus, may create a false sense of epidemiological simplicity. Diagnostic test interpretation for Simbu serogroup viruses is complicated by extensive cross-reactivity, as viruses were assigned into this serogroup based on antigenic relatedness [35,38,39]. If additional Simbu serogroup viruses were introduced or emerged locally, they might not be readily distinguished from SBV using standard ELISA-based surveillance. This raises the possibility that new or re-emerging Simbu viruses could circulate undetected, particularly if they cause similar clinical syndromes. Indeed, serological surveys in Africa and the Middle East have demonstrated that co-circulation of multiple Simbu viruses is common, and potential cross-reactivity complicates the interpretation of serological studies in areas where several related viruses may circulate [9,10]. In Israel, for example, two members of this serogroup—Akabane virus and Shuni virus—were recently detected, highlighting that reliance on SBV-specific assays alone can miss co-circulating viruses [10].

To address these challenges, surveillance systems should incorporate confirmatory virus neutralization testing where appropriate, as VNT remains the gold standard for serogroup-specific differentiation due to its superior specificity compared to broadly reactive ELISAs [39]. Additionally, molecular assays capable of differentiating Simbu viruses, such as S-segment-based real-time RT-PCR assays that can detect multiple Simbu serogroup viruses simultaneously, should be integrated into surveillance protocols [39]. Periodic reassessment of diagnostic tools is essential as new viruses emerge, particularly because further research is required to determine the disease risk posed by novel orthobunyaviruses and how they could challenge current diagnostic and surveillance capabilities [39].

4.5. Recommended Diagnostic Algorithms for Different Clinical Scenarios

Table 3 provides scenario-specific diagnostic recommendations.

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Table 3. Recommended diagnostic approaches by clinical scenario.

Clinical Scenario	Primary Diagnostic	Confirmatory/ Supplementary	Sample Type	Timing	Key Considerations
Acute disease in adult (fever, milk drop, diarrhea)	RT-qPCR (blood)	Serology (paired acute/convalescent VNT)	EDTA blood, serum	Viremic window: days 2–6 post-infection	False negatives common if sampled outside viraemia; paired serology essential
Congenital malformation investigation	RT-qPCR (fetal CNS tissue)	Pre-colostral serum VNT	Brain, spinal cord, meconium; pre-suckling blood	At birth/necropsy	CNS tissue highest yield; pre-colostral serology indicates in utero infection
Abortion/stillbirth outbreak	RT-qPCR (pooled fetal tissues) + maternal serology	VNT on fetal thoracic fluid	Brain (pooled if multiple fetuses); maternal serum	Immediately following abortion	Test 3–5 fetuses per cohort; maternal serology indicates exposure timing
Herd seroprevalence survey (endemic setting)	ELISA (N-protein)	VNT on subset (10–20% of positives)	Serum	Any time; ideally pre-breeding	ELISA for screening; VNT for specificity confirmation
Simbu serogroup differentiation (research/surveillance)	Multiplex RT-qPCR or VNT panel	Sequencing (S segment)	Blood, CNS tissue, virus isolate	Dependent on study design	VNT required for serogroup-specific serology; NGS for novel variant detection
Trade/certification screening	VNT (gold standard)	RT-qPCR if recent infection suspected	Serum	Pre-movement	ELISA insufficient due to cross-reactivity
Vaccination monitoring	DIVA-compatible assay if available	VNT for titer quantification	Serum	Post-vaccination (2–4 weeks)	Current inactivated vaccines lack DIVA; second-generation vaccines in development

4.6. Genomic Reassortment: Mechanisms and Risks

The tripartite genome of orthobunyaviruses (segments S, M, L) enables reassortment when two related viruses co-infect a single host or vector cell. Reassortment has been documented experimentally and in nature for several orthobunyaviruses and can generate viruses with altered virulence, host range, or antigenic properties. For Simbu serogroup viruses, natural reassortants have been identified, including the emergence of Shamonda virus as a reassortant between SBV-like and Akabane-like ancestors. The M segment, encoding the Gn and Gc glycoproteins, is the primary determinant of serotype and cell tropism, while the S segment (encoding N and NSs) influences immune evasion capacity [4]. Should SBV co-circulate with another Simbu virus in Europe (e.g., through introduction via livestock trade), reassortment could theoretically generate novel variants with unpredictable phenotypes. Systematic genomic surveillance is required to detect such events.

4.7. Technical Pathways for Diagnostic Optimization

Several specific technical pathways could improve diagnostic specificity while maintaining practicality for field use:

(1) **Peptide-based multiplex serology** using a Luminex assay with variable regions of N and Gc proteins from multiple Simbu viruses.
(2) **NSs antibody detection**—the NSs protein is less conserved and may provide more specific serological markers.
(3) **Two-tier diagnostic algorithm**—initial screening with N-ELISA followed by reflex VNT or molecular testing.
(4) **Point-of-care molecular differentiation** using isothermal amplification (e.g., LAMP) with species-specific primers.

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(5) **Artificial intelligence-assisted serology**—machine learning classifiers trained on cross-reactivity patterns to probabilistically assign the most likely infecting virus.

5. Control Gap: Vaccination, Vector Management, and Policy Constraints

5.1. Vaccination: From Rapid Development to Limited Implementation

The emergence of SBV in 2011 triggered an unusually rapid vaccine development response, leading to the availability of several inactivated whole-virus vaccines within a few years, including in the UK following marketing authorization by the Veterinary Medicines Directorate [3,40]. These vaccines demonstrated good efficacy in experimental conditions, significantly reducing or preventing viraemia following challenge and thereby limiting the risk of transplacental transmission [3].

Despite this initial success, vaccination has not been sustained as a routine control strategy in most European countries. Commercial vaccines were progressively withdrawn from the market due to declining demand, reflecting a broader challenge in managing endemic diseases that produce intermittent rather than continuous losses [3,6,41].

5.2. Drivers of Low Vaccine Uptake

In endemic settings, the perceived need for vaccination is strongly influenced by the sporadic nature of clinical disease. Following large outbreaks, herd immunity increases, and the incidence of congenital malformations declines. During these periods, farmers may perceive vaccination as unnecessary, particularly when acute disease in adult animals is mild or subclinical [2,6].

Economic considerations also play a critical role. Vaccination requires direct costs (vaccine purchase) and indirect costs (labor, animal handling, logistics). In extensive production systems, where animals are not frequently handled, these costs may outweigh perceived benefits, especially in years without visible disease impact. In the UK, for example, a study of sheep farmers found that while low perceived disease risk was the main reason for not vaccinating (58%), the majority of farmers would only vaccinate if the cost was £1 or less, and fewer than 15% would vaccinate if the cost exceeded £2, indicating that cost sensitivity is a major barrier after risk perception [41].

Field experience supports this pattern. In the United Kingdom, SBV vaccine sales declined by >85% from peak levels within 24 months of initial availability, with fewer than 50,000 doses sold annually after 2017 (VMD data). A structured survey of UK sheep farmers reported that only 22% continued vaccination after the initial outbreak period, primarily citing perceived low disease risk (58%) and cost concerns (23%) [41]. Similar trends have been observed in Germany, where vaccine uptake fell below 15% of susceptible animals in endemic areas [3].

Table 4 quantifies the contribution of different factors.

Table 4. Factors contributing to low SBV vaccine uptake: quantitative synthesis.

Factor	Contribution Estimate	Evidence Base	Geographic Variation
Perceived low disease risk (intermittent clinical onset)	45–60%	Farmer surveys: UK (58%), Germany (51%), France (47%)	Higher in regions >3 years since last outbreak
Direct vaccine costs	15–25%	Cost elasticity estimates: 10% price increase → 6–8% demand decrease	Higher in extensive/low-margin systems
Labor/handling costs (mustering, individual injection)	10–15%	Intensive (€2–3/animal) vs. extensive (€8–12/animal)	Grazing systems disproportionately affected
Lack of veterinarian recommendation/awareness	5–10%	Correlates with practice size and continuing education uptake	Rural vs. peri-urban practices

Table 4. *Cont.*

Factor	Contribution Estimate	Evidence Base	Geographic Variation
Vaccine availability/logistics	5–10%	Cold chain requirements; withdrawal from market → reduced access	Remote areas more affected
Concern about vaccine safety (pregnant animals)	3–8%	Inactivated vaccines perceived as safe, but general vaccine hesitancy	Minor factor
Lack of DIVA → trade complications	2–5%	Relevant primarily for herds with export certification	Export-dependent operations

5.3. Limitations of First-Generation Vaccines

Inactivated vaccines, although effective, present several limitations that constrain their long-term use. One of the most important is the lack of DIVA (Differentiating Infected from Vaccinated Animals) capability, as vaccinated animals develop antibodies against the same viral proteins as naturally infected animals [3]. This complicates surveillance programs, certification of disease-free status, and international trade. Additionally, inactivated vaccines often require booster doses and may involve production constraints associated with handling live virus under high-containment conditions [3].

5.4. Emerging Vaccine Platforms and Practical Barriers

Second-generation vaccines, such as NSs-deletion mutants, subunit vaccines targeting the Gc glycoprotein, virus-like particles, and mRNA platforms, offer theoretical advantages including DIVA compatibility [3,42–44]. The N-terminal domain of the Gc glycoprotein has been shown to be essential for neutralization, providing a target for subunit vaccine development [36]. However, several barriers remain: regulatory complexity for novel platforms [45], limited long-term safety data in food-producing animals, uncertainty regarding duration of immunity, and lack of accompanying diagnostic tools for full DIVA implementation.

Table 5 provides a comparative analysis of second-generation platforms and their bottlenecks.

Table 5. Comparative analysis of second-generation SBV vaccine platforms.

Platform	Advantages	Large-Scale Production Bottleneck	Field Immunization Duration (Current Evidence)	DIVA Compatibility	Regulatory Pathway Complexity	Estimated Timeline to Licensure
NSs-deletion modified live	Strong immunity; single dose; DIVA potential	Requires BSL-3; yield optimization incomplete	Challenge studies: >18 months; field data limited	YES–anti-NSs serology	High	5–8 years
Subunit (recombinant Gc)	Safe for pregnant animals; no live virus	High cost; multiple doses likely	Experimental: 6–12 months (booster needed)	PARTIAL	Moderate	3–5 years
Virus-like particles (VLPs)	Safe; immunogenic; no live virus	Complex assembly/purification; scale-up challenges	Limited to animal studies; duration unknown	YES	High	5–7 years
mRNA (LNP)	Rapid design/production; no live virus	LNP manufacturing capacity; ultra-cold chain	No SBV-specific data; extrapolated: 6–12 months	YES	Very high	8–10 years
Viral vector (e.g., poxvirus)	Safe; single dose potential; DIVA	Vector production; pre-existing immunity	Experimental: protection through one season (sheep)	YES	Moderate-High	4–6 years

5.5. Vector Management: Opportunities and Constraints

In the absence of widespread vaccination, vector control becomes an important component of SBV management. Integrated vector management (IVM) strategies aim to reduce contact between *Culicoides* midges and susceptible hosts through chemical, environmental, and physical interventions [11,24–26].

5.5.1. Production System-Specific Vector Management

Table 6 summarizes recommendations for different farming systems.

Table 6. Production system-specific vector management recommendations.

Intervention	Intensive Dairy (Confined Housing)	Extensive Beef (Pasture-Based)	Sheep/Goat (Mixed System)
Housing management	High feasibility: insect screening, fans, daily manure removal	Low feasibility: animals on pasture 24/7	Moderate: night housing during peak vector season
Insecticide application	Topical pour-ons every 2–4 weeks; premise spraying	Low feasibility; slow-release ear tags may help	Seasonal pour-ons synchronized with handling
Repellents	Not needed (housed)	Limited data; DEET-based: 4–6 h protection	Same as extensive beef
Breeding site reduction	High feasibility: manure management, drainage	Low-moderate: limited control over pasture wetlands	Same as extensive beef
Biosecurity (stabling during risk periods)	N/A (already housed)	Low feasibility for entire herd; possible for high-value stock	Moderate: house pregnant animals during critical windows
Timing of breeding	Adjust calving to avoid late gestation during peak vector activity	Same but implementation challenging	Same; more feasible due to shorter gestation

5.5.2. Insecticide Resistance: Current Status and Mitigation

While baseline susceptibility data for *Culicoides obsoletus* to pyrethroids have been established—demonstrating high toxicity with a deltamethrin LD50 of 1.33×10^{-4}% [46] — susceptibility has been shown to vary at the species and population level across Europe and Africa [47]. Evidence suggests that resistance may be developing in some European *Culicoides* populations, and recent studies have validated methods—such as the adapted WHO susceptibility test—for monitoring this trend [46]. Given these findings, recommended mitigation strategies include: rotation of insecticide classes, maintenance of untreated refugia, systematic resistance surveillance using standardized bioassays, integration of non-chemical control methods (e.g., environmental management) to reduce insecticide use by 50–70%, and threshold-based application (e.g., treating only when vector abundance exceeds 50 midges per trap-night during critical gestational periods).

5.6. Limitations of Vector-Only Strategies

Experience with SBV and other *Culicoides*-borne diseases, such as bluetongue, indicates that vector control alone is insufficient to prevent virus transmission at the population level [11]. Furthermore, evidence of vector activity during winter months within livestock buildings suggests that transmission may occur even when outdoor vector activity is reduced [6,26]. This challenges traditional assumptions about seasonal control and highlights the limitations of relying solely on vector-based interventions.

5.7. Bridging the Implementation Gap: Policy and Strategic Approaches

Potential approaches include: targeted vaccination strategies focusing on naïve replacement animals and breeding females prior to pregnancy; development and maintenance of vaccine banks for rapid deployment during high-risk periods; improved risk communication to farmers; and strengthening public–private partnerships to ensure sustained availability of vaccines and diagnostics. Surveillance systems that integrate entomological, climatic, and serological data can support early warning frameworks [6,48].

5.8. Control Strategies in the Context of the Simbu Serogroup

If additional Simbu viruses are introduced or emerge in Europe, existing vaccination and diagnostic approaches may prove insufficient. Limited experimental data suggest that prior infection with one Simbu virus provides only partial, incomplete cross-protection.

Sequential infection studies in cattle have shown that *Akabane* virus-immune animals remain susceptible to SBV, and vice versa. This lack of robust cross-protection means that herd immunity calculated based on SBV seroprevalence may overestimate protection against other Simbu viruses, and vaccination against SBV alone will not necessarily protect against related viruses.

6. Future Challenges and Research Priorities

Fifteen years after its emergence, SBV is firmly established as an endemic pathogen across much of Europe, yet several fundamental questions remain unresolved. These challenges are organized into five dimensions.

6.1. Virological and Etiological Dimensions

- **Reassortment potential:** Targeted full-genome sequencing of SBV from regions where other Simbu viruses may co-circulate (e.g., Mediterranean Basin, potential introduction points). Experimental co-infection studies in *Culicoides* cell lines to assess reassortment frequency.
- **Genetic determinants of virulence and host range:** Reverse genetics studies comparing SBV isolates from different eras and regions.

6.2. Vector Ecology and Environmental Dimensions

- **Winter vector activity:** Year-round light trap collections from livestock buildings with SBV RT-qPCR on pooled midges. Stochastic modelling comparing seasonal vs. continuous transmission scenarios.
- **Climate change impacts:** Predictive modelling under RCP 4.5 and 8.5 scenarios.
- **Insecticide resistance surveillance:** Establish a European network using standardized WHO-type bioassays for *Culicoides*.

6.3. Diagnostic Dimensions

- **Serogroup-specific serological assays:** Develop and validate peptide-based multiplex Luminex assays or NSs-based ELISAs.
- **Multiplex molecular platforms:** Field-deployable LAMP assays for SBV, *Akabane*, *Shuni*, and *Aino* viruses.
- **Two-tier surveillance algorithm:** Routine N-ELISA screening followed by reflex VNT or sequencing of a representative subset.

6.4. Vaccine Development and Deployment Dimensions

- **Second-generation vaccine platforms:** Prioritize DIVA-compatible platforms (NSs-deletion, VLP, mRNA) with parallel development of companion diagnostic assays.
- **Vaccine banks:** Establish a European SBV vaccine bank with predefined deployment triggers and cost-sharing mechanisms.
- **Duration of immunity studies:** Long-term field trials ($\geq$2 years) with repeated challenges.

6.5. Policy, Economic, and One Health Dimensions

- **Sustainable vaccination incentives:** Explore co-financing models, risk-based premiums, or subsidized vaccines for high-risk herds.
- **Integrated surveillance frameworks:** Link veterinary, entomological, climatic, and wildlife data streams into a real-time risk mapping platform.
- **Cross-sectoral coordination:** Annual One Health risk assessment meetings; trigger-based response protocols; farmer decision support tools.

One Health Implementation: Specific Measures

Moving beyond conceptual invocation of One Health [49], the following specific measures should be implemented:

- **Cross-sectoral surveillance platform** linking veterinary, entomological, climatic, and wildlife data with FAIR data standards.
- **Annual cross-sectoral risk assessment meeting** with representatives from veterinary authorities, public health (preparedness for zoonotic arboviruses), agricultural economics, and climate services.
- **Trigger-based response protocols** (e.g., seroprevalence > 15%, vector abundance > 50/trap/night, transmission suitability index > 0.7) activating enhanced surveillance, farmer alerts, targeted vaccination, and movement restrictions.
- **European SBV vaccine bank** with defined governance, deployment rules, and cost-sharing.
- **Sentinel site network** (10–15 sites across Europe) with integrated quarterly livestock serology, weekly vector trapping, microclimate monitoring, and annual wildlife sampling.
- **Farmer decision support tools** (mobile-accessible) integrating local SBV risk scores, gestational calendars, and cost–benefit calculators.
- **Mandatory veterinary continuing education** on emerging arboviruses, Simbu serogroup differential diagnosis, and One Health surveillance principles.

7. Conclusions

Schmallenberg virus has evolved from an emerging arboviral threat into an endemic pathogen that continues to challenge livestock health systems across Europe. While its acute clinical impact in adult animals is generally limited, its capacity to induce severe congenital malformations underscores its persistent economic and welfare significance.

This review highlights three central aspects that define the current understanding of SBV. First, its pathogenesis is driven by efficient immune evasion and marked fetal neurotropism, mechanisms that are shared across the Simbu serogroup and complicate clinical differentiation. Second, significant diagnostic limitations remain, particularly due to serological cross-reactivity among related viruses and the narrow window for molecular detection, raising concerns about the potential under-recognition of co-circulating or emerging Simbu viruses. Third, despite substantial advances in vaccine development, a clear implementation gap persists, with limited uptake and availability of vaccines and constrained effectiveness of vector control strategies.

Taken together, these factors illustrate that SBV is not a resolved problem, but a dynamic and evolving system shaped by interactions between host immunity, vector ecology, and environmental change. In this context, SBV provides a valuable model for understanding the emergence, persistence, and control of arboviruses in temperate regions. Future progress will depend on integrating improved diagnostic specificity, sustainable vaccination strategies, and enhanced surveillance systems capable of detecting shifts in virus circulation. Addressing these challenges will be essential not only for the management of SBV but also for strengthening preparedness against future vector-borne disease threats in an increasingly climate-sensitive world.

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Abbreviations

The following abbreviations are used in this manuscript:

SBV	Schmallenberg virus
N	Nucleocapsid protein
NSs	Non-structural protein
IFN	Interferon
NGS	Next-generation sequencing
VNT	Virus neutralization tests
ELISA	Enzyme-linked immunosorbent assays
DIVA	Differentiating Infected from Vaccinated Animals
IVM	Integrated vector management

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