Review Article

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# Bluetongue Disease

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## Abstract

A viral disease known as bluetongue (BT) can afflict ruminants, both domestic and wild. Arthropods, particularly species of Culicoides, disseminate it. The disease is brought on by the BT virus (BTV), which belongs to the genus Orbivirus and family Reoviridae. This review covers the etiology, epidemiology, pathogenesis, transmission, clinical signs, diagnosis, and management of the disease. BTV infection causes significant direct economic losses due to high morbidity, mortality, stillbirths, abortions, fetal abnormalities, low birth weight in young animals, decreased milk yield and fertility rate, weight loss, early culling, and loss of meat and fleece. Fever (105-106° F), serous to bloody nasal discharge, mucopurulent discharge later on, hyperemia and edema of the lips, face, tongue, ears, and submaxillary region (looking like a monkey face), oral erosions and ulcers, and in rare cases, cyanosis of the tongue are the most common clinical symptoms. The disease is diagnosed using either immune response detection or pathogen identification. The OIE recommends four serodiagnosis tests: CFT, AGID, competitive, and indirect ELISA. Vaccines that are inactivated pose a lower risk than those that are live attenuated. Because there are so many BTV serotypes and susceptible hosts, controlling BTV is very difficult.

**Keywords:** Bluetongue disease, Bluetongue virus, Culicoides, Diagnosis, Epidemiology.

## Introduction

Bluetongue (BT) is an infectious, non-contagious, viral disease that affects both domestic and wild ruminants. Arthropods spread it, and the BT virus (BTV), a member of the Reoviridae family and genus Orbivirus, causes it. *Culicoides* species are the primary vectors of BT (1). BTV infection results in significant direct and indirect economic losses (2, 3). Due to variations in the genome segment-2 (Seg-2) sequence and its translated protein VP2, 28 BTV serotypes have been identified up until recently (4, 5). One important group-specific antigen determinant is the BTV core VP7 protein (6). Notably, researchers discovered a novel BTV serotype (7) in a batch of commercially contaminated sheep pox vaccines. (7). Bloodsucking midges of the genus *Culicoides* and family *Ceratopogonidae* bite susceptible hosts, naturally dispersing the BTV (8), along with transplacental transmission, which results in severe birth defects (9). According to recent research on vectors, *Culicoides oxystoma* and *C. imicola* are primarily responsible of BTV transmission (1). Generally, BTV affects camelids, elephants, domestic and wild carnivores, ruminants (sheep, goats, and cattle), and wild (deer, pronghorn antelope, and bighorn sheep) carnivores (10, 11). While cattle, goats, and camelids typically exhibit asymptomatic or sub-clinical disease, sheep, white-tailed deer, pronghorn antelope, desert bighorn sheep, mouflon, llamas, and alpacas are the ruminants most commonly found with severe clinical disease (12,13). The incubation period of the disease is 4-8 days. Clinical manifestations include fever between 40.5°C and 41.11°C, bloody or serous to mucopurulent nasal discharge, hyperemia and edema of the lips, face, tongue, ears, and submaxillary region (appearing like a monkey face), oral erosions and ulcers, and in rare instances, cyanosis of the tongue. Following the pyretic phase, the animal exhibits laminitis, coronitis, paralysis of the muscles, and a deformed back while standing. In addition, respiratory distress, muscular necrosis, dermatitis, torticollis, and wool break may develop (2, 14, 15). Increased vascular permeability, hemorrhages, fluid exudations, thrombosis, and tissue infarction are the outcomes of BTV-induced lesions, which are caused by direct damage to the endothelial cells of the microvasculature (3). One can make an assumption-based diagnosis of the disease based on clinical signs and lesions. Pathogen identification, or immune response detection, is the basis for diagnosing BTV infection. Pathogen identification techniques include classical virus isolation, real-time RT-PCR, and RT-PCR (Reverse Transcriptase PCR), viral neutralization test (VNT, serotype-specific), agar gel immunodiffusion test (AGID), complement fixation test (CFT), and competitive enzyme-linked immunosorbent assay (c-ELISA, serogroup specific) are available for detecting the immune response in the host. The BT serotype-specific neutralizing antibodies are found using the Virus Neutralization Test (VNT). The competitive enzyme-linked immunosorbent assay (ELISA), indirect ELISA, agar gel

immunodiffusion (AGID), and complement fixation test are the serodiagnosis tests that the OIE recommends (16-18). The best strategies for managing and eliminating BT include mass immunization, vector control, rigorous entomological and serological monitoring, creating restricted areas, and sentinel initiatives (19-21). The current review provides an overview of this economically significant viral disease's etiology, epidemiology, transmission, pathogenesis, clinical signs, diagnosis, and management.

**Epidemiology**

In the 18th century, bluetongue was first reported in South Africa with the importation of fine wool sheep from Europe (22). Hutcheon's annual report in 1880 included information on the disease's clinical aspects. Still, the illness known as (Epizootic catarrh) or (Malarial catarrhal fever), was not documented in scientific journals until 1902 (23). Farmers in South Africa first used the African term "bluetongue" (bloutong) to characterize the cyanosis of the tongue in clinically infected animals. The outbreak of disease is influenced by various climatic conditions, sheep populations, and animal breeds. Globally, BTV is present in tropical and subtropical regions. It is also present in certain regions outside of this range, such as parts of California (8, 15, 24, 25). The widespread presence of mosquito vectors belonging to the genus Culicoides (26). There are endemic areas in Africa, Europe, the Middle East, North and South America, Asia, and numerous islands, including Australia, the South Pacific, and the Caribbean. Different species are responsible for different regions' transmission of the disease: *C. imicola* in Africa and Asia, *C. brevitarsis* in Australia, *C. sonorensis* in America, and *C. obsoletus*, *C. scoticus*, and *C. pulicaris* in Northern Europe are the most likely transmitters (17). There are reports of 28 serotypes of BTV worldwide. In 2014, BTV-27 was isolated from goats on the French island of Corsica. Meanwhile, in Palestine, BTV-28 was isolated from tainted live-attenuated sheep pox and lumpy skin disease vaccines (4- 6, 27).

**Etiology**

The Bluetongue Virus (BTV) is a member of the Reoviridae family and the Sedoreovirinae subfamily within the Orbivirus genus. The Office International des Epizootics (OIE) has classified bluetongue as a multispecies disease. The viral genome is made up of ten separate pieces of double-stranded RNA. These pieces code for at least four non-structural proteins (NS1–NS3/NS3A and NS4) and seven structural proteins (VP1–VP7).The length of BTV's entire genome is approximately 19.2 kbp, with ds RNA segments ranging from 822 to 3954bp. Following their observation of the cyanosis of the tongue in sheep that were clinically afflicted, Afrikaans farmers coined the term (bloutong) or (Blaauwtong), which was later translated as (bluetongue) by Spreull in 1905. The Afrikaans word for mouth sicknesses, or (Bekziekte), was also used by farmers to refer to oral lesions. Clinical signs of the disease were similar to those of foot-and-mouth disease when it was first reported in cattle in 1933 (28). Because of

this, the illness was also known as (sore mouth), (pseudo-foot-and-mouth disease), or (seer-beck) (9, 29-31). The following figure (Figures 1 and 2), shows a schematic structure of the BTV core particle and vector of the Bluetongue Virus (32).

**Transmission**

Most cases of bluetongue are spread by an amplifier host, which can be any of the several species of haematophagus-biting midges that are part of the family *Ceratopogonidae*, order *Diptera*, and genus *Culicoides*. Moreover, the illness can spread orally (by consuming contaminated placenta), transplacentally (leading to abortions, stillbirths, and unviable fetuses), directly through vertical and venereal routes, and indirectly through mechanical means (some arthropods, such as sheep ked (*Melophagus ovinus*), mosquitoes, and ticks, can act as mechanical vectors for BTV), (Figure 3). While this mode of transmission may not have any clear epidemiological significance (17, 33-35).

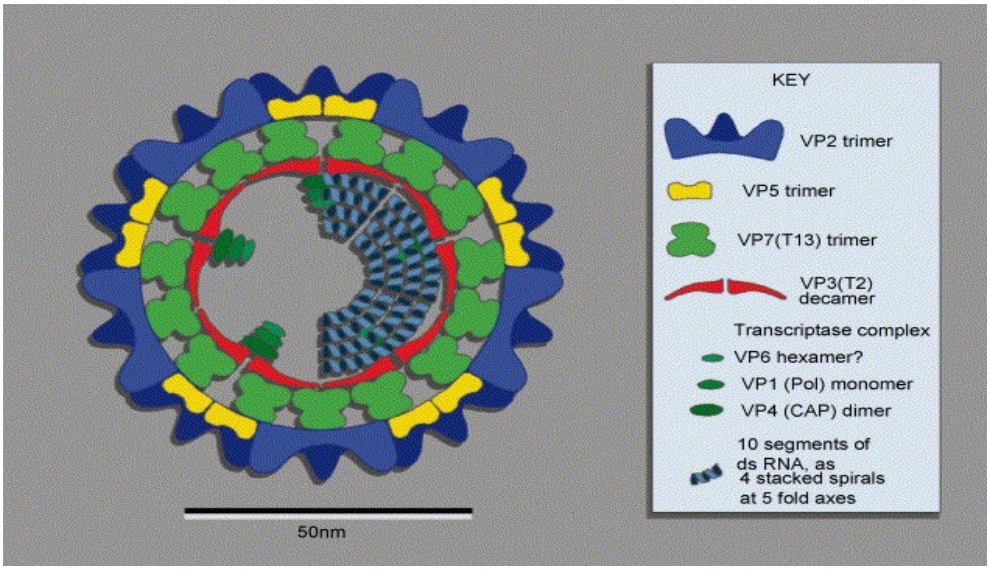


**Figure 1: Structure of Bluetongue Virus Core Particle (32)**

**Pathogenesis**

After the insect vector bite, the virus travels to the lymph nodes, where it begins to replicate. Dendritic cells then help the virus spread from the skin to lymph nodes. The site of virus replication is the endothelial cells line the blood vessels. The virus then enters the bloodstream and attaches itself to erythrocytes, causing necrosis, vascular thrombosis, and tissue infarction (3). BTV primarily binds to platelets and erythrocytes during the viremia's duration of at least 30 days in sheep and up to 100 days in cattle (30). Additionally, the virus spreads to the secondary site of replication, which includes the lungs, spleen, and lymph nodes, through the lymphatic and vascular systems. In

animals with BT infection, the spleen serves as the primary location for secondary viral replication. Following the spleen's release of BTV, a secondary viremia with a strong cell association was observed. Through the activation of p38 MAP kinase, which results in vascular permeability and increased blood production of thromboxane and prostacyclin, BT infection causes cell apoptosis, necrosis, and an exaggerated inflammatory response (36). The animal develops immunity against the particular serotype of the infection after the disease progresses naturally, but it still has the potential to contract another serotype (30). As shown in (Figure 4).

**Figure 2: Vector of Bluetongue Virus (32).**

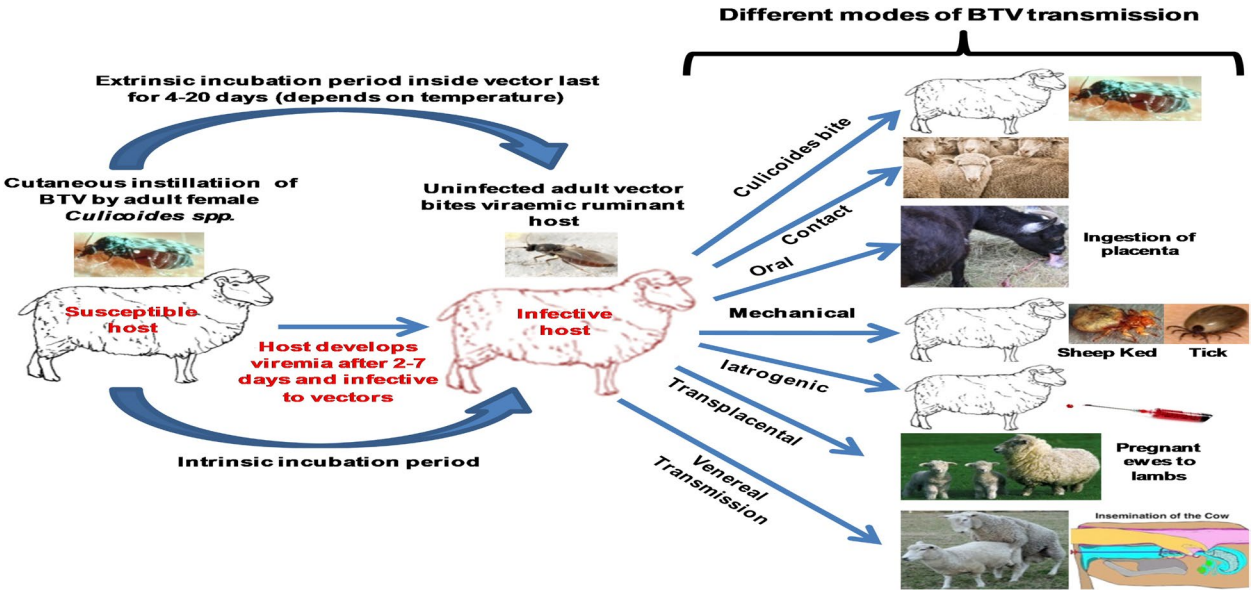


**Figure 3: Various routes of transmission of bluetongue virus (3)**

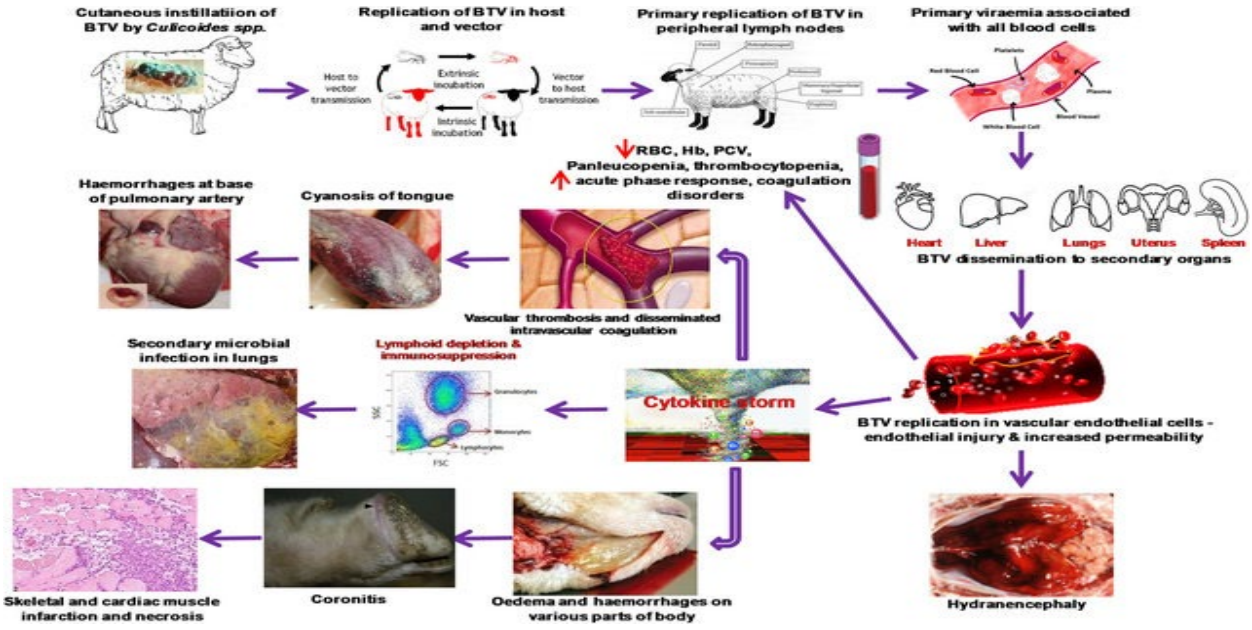


**Figure 4: Pathogenesis of bluetongue virus in ruminants (3).**

## Clinical signs

The incubation period of four to twelve days is followed by the clinical signs and symptoms of bluetongue, which differ based on the viral strain and animal breed. Sheep, whose clinical illness is more severe, typically experience fever (up to 42.0°C), conjunctivitis, lacrimation, nasal and oral mucosal congestion, and facial and lips edema. While the clinical signs may not worsen in some instances, they usually lead to more severe clinical features such as mucopurulent nasal discharge, severe facial edema, erosions, ulcerations, and hemorrhages in the lips, tongue, and nose. The majority of BT lesions are hemorrhagic, erosive, and edematous. The disease's name comes from cyanosis of the tongue, which can occasionally accompany these symptoms.The majority of severe cases show respiratory distress along with paresis of the pharynx and esophagus. Coronitis usually appears 8-14 days after infection in sheep. Multiple limb lameness of varying intensity and diffused redness in the hoof coronary band are the hallmarks of this condition. In the worst situations, animals appear bent or kneeling, unable to stand or move, and serum discharge is visible around the coronary band. Dermatitis, torticollis, and wool breakage are also possible.During the breeding season, congenital deformities (cerebral malformations), abortion, stillbirth, and infection can account for a considerable portion of early embryonic losses in sheep, and the animals may return to estrus irregularly (Figure 5). When infected, goats, cattle, and wild ruminants such as deer can all appear healthy. Midges that feed on the infected animals may contribute to the silent spread. Compared to sheep, cattle typically have substantially lower mortality rates. Other than pyrexia, anorexia, and

depression, signs in cattle are typically less severe than in sheep, and only one or two signs appear. In certain situations, cocirculation of multiple BTV serotypes in one area may exacerbate clinical symptoms in cattle (11, 32, 37, 38).

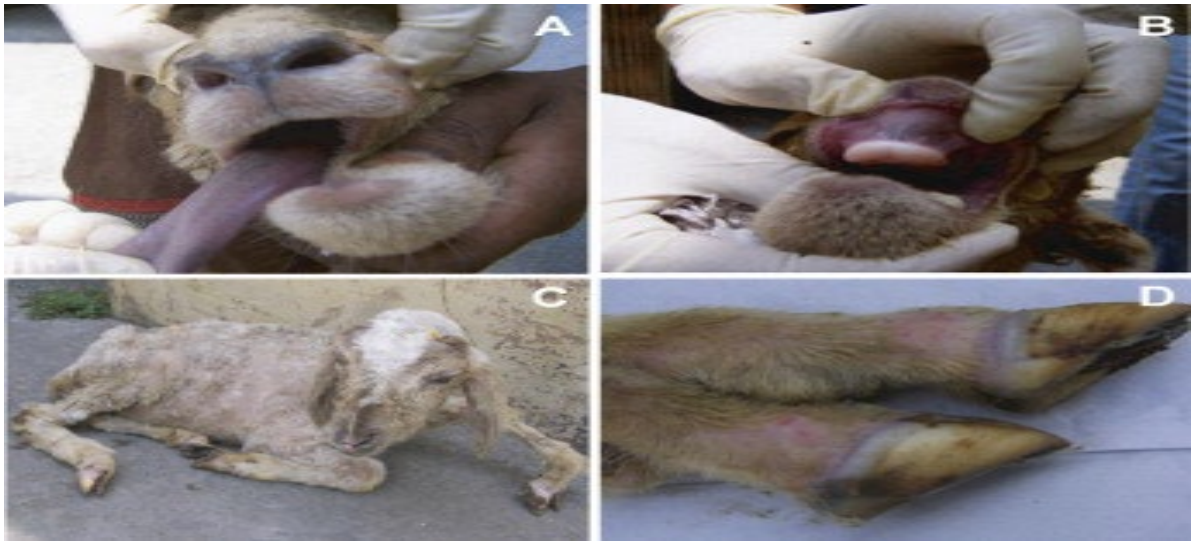


**Figure 5: Clinical signs in bluetongue virus-infected sheep (14).**

**Diagnosis**

**1-Clinical diagnosis**

**2-Laboratory diagnosis**

**A-Serological tests**

**1- Competitive ELISA**

According to (39), this technique was created to identify distinct antibodies to BTV This method works well for quickly identifying the organism in the first six days of infection (40).It can identify particular antibodies by utilizing a serogroup known as Mabs, which is unique to BTV.. Consequently, to bind with antigens, the serum antibody competes with the Mabs (41).

**2- Indirect ELISA (i-ELISA)**

This technique, which uses IgG anti-ruminant as the conjugate and VP7 protein as the substrate, is crucial for detecting the bluetongue virus in whole milk samples. Its sensitivity has reached 98% and is highly specific, up to 96% . According to (42), I-ELISA is superior to c-ELISA in that it can distinguish between infections that result from vaccinations (DIVA system) and those that are not, as well as in the detection of Bluetongue virus NS3 antibodies (43).

**3-Complement fixation test (CFT)**

Historically, this test was used for the first time to identify the Bluetongue virus from isolates in Australia (44). This method is crucial for determining the antibodiespresent in the infected ovine and bovine samples. For example, serotyping of isolates of the bluetongue virus has been limited by modified indirect CFT (45).

**4- Agar gel immuno-diffusion (AGID)**

The main characteristic of this procedure is the precipitation of soluble antigens following the addition of a specific antibody in a sterile medium. This test's simplicity in providing the required result and ease of use are what make it so important. However, this test's lower sensitivity and specificity are among its shortcomings, preventing it from being used to facilitate cross-border trade (35).

**5- Serum neutralization test (SNT)**

Antibodies against the Bluetongue disease virus are developed for different strains ; this test is used to identify them.. This approach results in a permanent variation in the test strain's reaction to the serum used. Next, mammalian culture inoculations are used to gauge how much of the treated virus neutralizes the virus that has not been serum-treated. SNT is crucial in preventing cross-reaction with other *Orbivirus* species due to its high specificity and sensitivity (35).

**B-Viral isolation**

It is possible to isolate the bluetongue virus from the right animal samples that are ill. As a result, samples of semen, blood, and tissues are used to isolate viruses. Furthermore, the virus has been detected in a variety of animal organs that have been infected (17). Typically, BTV is isolated by inoculating chicken embryonated eggs and Kc cell linesderived from *C. sonorensis* midges (46).

**C- Molecular diagnostic tests**

When compared to the serum neutralization test (SNT) and viral inhibition (VI), the reverse polymerase chain reaction (RT-PCR) has been shown to have excellent sensitivity and specificity for detecting the BTV genome using a variety of specimen types (47). According to (48), the capacity of RT-PCR to detect viral RNA even six months after infection is another crucial feature.

**1-Conventional RT-PCR**

Conventional RT-PCR is considered a more significant technique than other kinds of serological testing since it can distinguish the genome of distinct BTV strains (47).

**2-Nested PCR**

This approach is highly significant due to its superior sensitivity-roughly 100 times higher than small PCR-in identifying the minuscule genome (0.1 femtograms, or 5 particles) of BTV as well as its sophisticated use in epidemiological research. This nested PCR can quickly identify the BTV from the tissue specimen and cell culture by using primers based on VP7 and NS1 (49).

**3- Reverse transcriptase-polymerase chain reaction (RT-PCR)**

A reliable, quick, and highly sensitive method was established by (50). By amplifying the outer-capsid protein VP2 in conjunction with nucleotide sequencing, this method serves as a typing assay for every BTV serotype. These highly specific primers are used in phylogenetic analyses to identify 26 BTV strains and serotypes. Furthermore,

when amplification is performed with a remarkable 25 strains, no cross-reaction is seen (3).

**Quantitative real-time - Polymerase chain reaction (qRT-PCR)**

This kind of molecular method uses primers for Seg-1/VP1, Seg-5/NS1, Seg-2/VP2, and Seg-10/NS3 to identify the BTV. Nonetheless, due to its conservation, Seg-5 is favored for detecting all BTVs. It is more sophisticated than the traditional method in identifying the virus in all samples, including cultures, tissues, and semen from afflicted animals. It also makes use of the highly sensitive Taq-Man fluorescence probe (51)

**Control and prevention**

Due to the existence of asymptomatic infections, protracted viremia in cattle, and virus persistence in the vector population that keeps the virus in the environment, control and eradication of BT are extremely unlikely. Furthermore, it is very difficult to stamp out the diseased animals and impose movement restrictions (8). The primary methods of controlling bluetongue are vector control, management techniques, and animal immunization. Although the goal may be to keep vulnerable animals away from the Culicoides vector, this is not always feasible. Applying *Culicoides* insecticides can be one method of controlling vectors. Vaccines may contain live attenuated viruses or inactivated viruses. To avoid fetal infections, live attenuated vaccines must be administered before the reproductive stage (26, 52).

Vaccination is an economical and sustainable approach controlling the vector-borne diseases like BT (21). Prophylactic vaccination has contributed to BT control and significantly reduced the economic losses caused by morbidity, mortality, reproductive problems, and reduced milk production (20). There are 28 existing BTV serotypes, which show little cross-protection. Currently, live attenuated and inactivated BTV vaccines are available for a limited number of serotypes, but these vaccines have their pros and cons, including the inability to do DIVA. Intensified and continuous monitoring of BTV serotypes is required to know the exact prevalence of BTV serotypes in different states and their inclusion in vaccine development. Even though studies have confirmed that recombinant vaccination technologies are practically applicable in the field of prevention of BTV infection in ruminants, the expression of immunogenic proteins is challenging due to the different conformational structures of each epitope/immunogen, poor stability during storage, and serotype-specific immune responses (53, 54).

**Live attenuated vaccines**

The first live attenuated monovalent BTV vaccine was developed by serial passaging in sheep and this vaccine was used from 1907 to 1943. However, this vaccine failed to provide immunity against many other serotypes of BTV that circulate in South Africa. Hence, this vaccine was discontinued. The currently used live attenuated BTV vaccine in the United States (only vaccination in sheep), South Africa,

Italy, Israel, Bulgaria, India, France, Spain, and Turkey contains five different combinations of serotypes of BTV attenuated by continuous passaging in ECEs and BHK-21 cells (21, 53, 55).

**Killed or inactivated vaccines**

In 1975, researchers first developed killed vaccines against BTV by inactivating whole BTV with ultraviolet radiation, heat, or chemicals using binary ethylenimine (BEI) or hydroxylamine (56, 57).In Europe, the BTV-2 vaccine was commercially introduced in 2005 (54). Subsequently, inactivated polyvalent vaccines were developed by including BTV-1, -4, -8, and -9 (53, 54).

**Subunit vaccines**

Recently, a subunit vaccine containing purified VP2, NS1, and NS2 proteins of BTV expressed in *baculovirus* and *E. coli* and an adjuvant with the immunostimulating complex AbISCO-300 was developed and evaluated in cattle. This vaccine-induced sufficient humoral and CMI responses after booster vaccination and protected against different serotypes of BTV (59). Further, this vaccine was evaluated in calves and protected against BTV-8 challenge, 3 weeks after booster vaccination. The CMI response (T-lymphocytes) directed against NS1 and NS2 proteins of BTV provided cross-protection to varying VP2 serotypes (59).

**Virus-like particles**

Virus-like particles (VLPs) are non-infectious molecules that closely resemble viruses. The VLPs are self-assembling viral structural subunits, and virus replication and gene expression cannot occur due to a lack of nucleic acids (60). Vaccines containing VLPs provide strong immunogenicity as wild-type viruses without producing any clinical disease. Further, VLPs are highly suitable for the presentation of foreign antigens on their surface and efficient delivery to antigen-presenting cells (60).

**DNA vaccines**

The DNA vaccines utilize novel technology by which injection of genetically engineered DNA is aimed to produce efficient humoral and CMI responses. The strategies involved in DNA vaccines are to use DNA plasmids expressing one or more antigens to induce protective immune responses against viruses (21, 55).

**Disabled unfectious single animal vaccine**

Disabled unfectious single animal (DISA) vaccines have been developed using reverse genetics technology. In this vaccine, one important gene is deleted from the engineered virus, creating an immunogenic vaccine virus virus (21, 55).

**Disabled infectious single-cycle vaccine**

Like DISA vaccines, disabled infectious single-cycle (DISC) vaccine viruses are produced by reverse genetics technology. DISC virus particles infect the target cells of vaccinated animals only once due to the deletion of important genes. The DISC viruses are highly protective, have DIVA capability, and act as promising alternative vaccine agents against currently available

killed and MLV vaccines. The DISC BTV vaccines produce an aborted infection, resulting in viral protein expression in the vaccinated animals being similar to that of MLVs and having the same safety as that of inactivated vaccines (19, 20).

## Conflicts of interest

The authors declare that there is no conflict of interest.

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# مرض اللسان الأزرق

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## الخلاصة

اللسان الأزرق هو مرض فايروسي يصيب المجترات المستأنسة والبرية. ينتشر عن طريق المفصليات، وخصوصًا أنواع البعوض من جنس Culicoides. مسبب المرض هو فيروس BT (BTV)، والذي ينتمي إلى جنس Orbivirus وفصيلة Reoviridae. تغطي هذه المراجعة علم الأسباب والوبائيات وميكانيكية الإصابة والنقل والعلامات السريرية والتشخيص وإدارة المرض. تسبب عدوى BTV خسائر اقتصادية مباشرة كبيرة بسبب الإصابة العالية والهلاكات والولادات السابقة لأوانها والإجهاض التشوهات الخلقية للجنين والوزن المنخفض عند الحيوانات الصغيرة وانخفاض إنتاج الحليب ومعدل الخصوبة وفقدان الوزن التخلص المبكر من الحيوانات المصابة وخسائر اللحوم والصوف. تعتبر الحمى (105-106° F) والافرازات الأنفية المصلية إلى الدموية والافرازات المخاطية القيحية لاحقًا والاحمرار والوذمة في الشفتين والوجه واللسان والأذنين والمنطقة تحت الفك (تشبه وجه القرد) والتآكل والقرح الفموية وفي حالات نادرة، يعتبر ازرقاق للسان أكثر الأعراض السريرية شيوعًا. يتم تشخيص المرض باستخدام كشف الاستجابة المناعية أو تحديد الطفيلي. توصي المنظمة الدولية للصحة الحيوانية بأربع اختبارات لتشخيص المصل: CFT، AGID، المنافسة، و ELISA غير المباشرة. اللقاحات المعطلة أقل فعالية من اللقاحات التي تحتوي على أجسام مضادة حية. بسبب وجود العديد من أنواع BTV والمضيفين القابلين للإصابة، يعد التحكم في BTV أمرًا صعبًا للغاية.

**الكلمات المفتاحية:** مرض اللسان الأزرق ، فيروس اللسان الأزرق ، Culicoides ، التشخيص ، علم الأوبئة.