International Journal of African and Asian Studies www.iiste.org
ISSN 2409-6938 An International Peer-reviewed Journal
Vol.21, 2016

Blue Tongue in Sheep: A Systemic Review

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Abstract
Bluetongue is a non-contagious disease of domestic and wild ruminants caused by a virus within the Orbivirus genus of the family Reoviridae and transmitted by Culicoides biting midges. All ruminants are susceptible to infection with bluetongue, but clinical disease is most often manifested in sheep. In cattle an important role in the epidemiology of BTV because of prolonged viraemia.In past the endemic area of Bluetongue virus are world-wide within tropical and subtropical climates from approximately 35° S to 40° N, in accordance with the extension area of Culicoides imicola, which major vector of the virus in the "Old World, however, bluetongue has recently spread far beyond this traditional range. Since 2006 BTV serotype 8 has also been reported from the countries in Northern and Western Europe where Culicoides imicola has not been found. In such cases, BTV is transmitted by Palearctic biting midges, such as C. obsoletus or C. dewulfi. The economic losses due to direct losses are death, abortions and production loss and indirect losses are export restrictions of live animals and animal product.Anew strategy for prevention and control of the disease was developed to limit direct losses and to reduce indirect losses are the use of mass vaccination of all domestic ruminant species to limit the spread of BTV and the use of intensive active surveillance to limit spread. This reviewpresents comprehensive information on this dangerous disease including its history, spread, economic impact, modes of transmission and species effect, as well as the causative agent and pathogenesis,clinical sign, pathological change and diagnosis of the disease.It also deals with relevant preventive and control measures to be implemented in areas with endemic bluetongue outbreaks.
Keywords: Bluetongue, Culicoides, Orbivirus, Reoviridae

1 INTRODUCTION

Bluetongue (BT) is an infectious and non-contagious arthropod borne viral disease of domestic and wild ruminants namely sheep, goat, cattle, camels, llamas, deer and antelopes. BT primarily affects sheep and deer, but subclinical disease occurs in cattle and goat and wild ruminants. Bluetongue is usually considered to be a disease of improved breeds of sheep, particularly the fine-wool and mutton breeds (Merck, 2014).Bluetongue derives its name from the mechanism of action which primarily cell injury and necrosis leading to vascular thrombosis, edema and hemorrhage which can result in a cyanotic or bluetongue (Murphy, 2011). It is characterized by high fever, catarrhal inflammation of the buccal and nasal mucous membranes, and inflammation of the tongue, intestine and sensitive lamine of the foot. (Maclachlan, 2011)

Bluetongue has been known in South Africa for over a 100 years and endemic in wild ruminants. BT is endemic in an extensive band that includes tropical, subtropical, and temperate regions of the world between latitudes of approximately 40° North and 35° South that is, America, Africa, Australia and Asia where vectors (*Culicoides* sp.) are present (Bitew *et al*., 2013). BT is a disease of ruminants in temperate zones. However, clinical disease is reported in tropical and subtropical areas of the world when non-native breeds of ruminants are introduced in virus endemic area. The geographic restriction is in part related to the climatic and environmental conditions necessary to support the Culicoides vectors (Sukbed and Chintun. 2013).

Bluetongue virus is the type-species of the genus Orbivirus in the family Reoviridae (Maclachlan and Dubov**,** 2011).It has a 10-segment double-stranded RNA (dsRNA) genome (David, 2012). That encode seven structural (VP1-VP7) and four non-structural proteins (NS1, NS2, NS3, NS4) (Belhouchet and Huisman, 2011)

The course of the disease in small ruminates can vary from peracuteto chronic, with a mortality rate of 2%–90%. Clinical signs in younglambs are more apparent, and the mortality rate can be high up to 30%. The major production losses include deaths, unthrifteness during Prolonged, convalescence, wool breaks, and reproductive losses (Merck, 2014).

Laboratory confirmation is based on virus isolation in embryonated chicken eggs or mammalian and insect cell cultures or on identification of viral RNA by PCR. The identity of isolates may be confirmed by the group-specific antigen capture ELISA. This c-ELISA is highly sensitive and specificity, this specificity is gained by the use of the monoclonal anti-VP7, which is the protein that distinguishes the BT serogroup from other Orbivirus serogroups (Khalid *et al.*, 2012)

There is no specific treatment for animals with bluetongue apart from rest, provision of soft food, and good husbandry.The basic control strategy was based on strict movement controls of the susceptible animals from zones considered infected and vaccination was limited to sheep that were exposed in the protection zones. Intensive clinical, serological and entomological surveillance were used to define the areas that were subject to

movement restrictions (Giovannini, 2004).The control of vectors by using insecticides or protection from vectors may lower the numberof Culicoides bites and subsequently the risk of exposure to Bluetongue Virus infection (Merck, 2014).

In recent years, the global distribution and nature of BTV infection has changed significantly. Climate change has been implicated as a potential cause of this dramatic event observed globally. Bluetongue infection constitutes one of the major unresolved veterinary problems in certain breeds of sheep and in North American white-tailed deer(Hoff, 2009),But there is very little information is available about the epidemiology of Bluetongue Virus in the East Africa including Ethiopia. In light with the above facts the objectives of this seminar paper are.

- ✓ To review history, spread, routes of transmission and species effect economic impact, as well as the causative agent and pathogenesis and diagnosis of bluetongue, relevant preventive and control measures of bluetongue.

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2. LITERATURE REVIEW

2.1. History of Bluetongue

Bluetongue was first recorded at the end of the 18th century in South Africa after an import of fine wool sheep from Europe. It was first referred to as fever, malarial catarrhal fever of sheep or epizootic malignant catarrhal fever of sheep (Maclachlan, 2009).The name‘‘bluetongue’’is the Anglicized form of the Afrikaans, ‘‘bloutong’’, which was coined by Boer farmers to describe the distinctive cyanotic tongue of some severely affected sheep. Although the original written descriptionsof BT were published in the late 19th and early 20th centuries, the disease was likely recognizedas soon as fine-wool European sheep breeds, particularly Merino sheep, were introduced to southern Africa(Drew,2010) the 1940s, BT was thought to be confined to southern Africa.

The first well-documented epizooticof BT outside of Africa occurred amongst sheep on Cyprusin 1943 (Worwa, 2009) although the disease had likely occurred there since at least 1924 (Rodriguez-Sanchez *et al*., 2008). BT was recognized thereafter in the United States, the Iberian Peninsula and Middle East, Asia and southern Europe. The increased recognition of BT in widely separated regions of the world in the middle of the 20th century was interpreted at the time to reflect the emergence of BT from its presumed ancestral origin in Africa (Verwoerd and Erasmus, 2004).

It is now clearly apparent that BTV infection occurs throughout tropical, sub-tropicaland some temperate regions of the world. The global distribution of BTV infection very recently has drastically altered (Purse *et a*l., 2008). It has been proposed that climate change is in part responsible for this profound change in the global distribution of BTV, presumably by its impact on the vectorial capacity of resident Culicoides insect populationsin previously virus-free regions such as much of the Mediterranean Basin (Gould and Higgs, 2009).

BTV has recently spread North America and China the disease has been detected up to 50 °N. Since 1998 there has been a dramatic change in the distribution of BT, with the disease having spread into countries of north-western Europe and Scandinavia (Saegerman *et al*., 2008). It recently spread northward from the Caribbean Basin to invade the southeastern United States, where they previously did not occur and to northern Australia (Johnson *et al*., 2007).The appearance rapid spread of BTV serotype 8 that began in northern Europe fro2006-2007 in Germany (Elbers *et al*., 2008).

2.2. Etiology

BTV is the etiological agent of BT, an insect transmitted disease of ruminants. Bluetongue virus with closely related species African Horse Sickness virus (AHSV) and Epizootic Hemorrhagic Disease virus (EHDV) belongs to the genus Orbivirus in the family Reoviridae (Eschbaumer *et al.*, 2009; Maan *et al*., 2012). The virion has a diameter of 90 nm (Eschbaumer *et al*., 2009; Schwartz-Cornil *et al.*, 2008).

The virus is a non- enveloped composed of ten linear double-stranded RNA (dsRNA), it segments are packaged within a triple layered icosahedral protein capsid (90 nm in diameter) (Maan *et al*., 2012). The genome encodes seven structural and four non-structural proteins (Eschbaumer *et al*., 2009).This genetic diversity of BTV is consequence of both drift (point mutation) and shift (reasortement of BTV gene segments) (Maan *et al.,* 2012).

Outer shell composed of two structural proteins VP2 and VP5, on the outer layer VP2 is responsible for receptor binding, haemagglutination and eliciting serotype-specific neutralizing antibodies and strong affinity for BTV binding to erythrocytes (Dahiya *et al*., 2004; Schwartz-Cornil *et al.,* 2008), and the major determinant of BTV serotype and also revealed significant variations between strains of the same serotype that were derived from different geographical areas (Dahiya *et al.,* 2004; Maan *et al.,* 2007; Maan *et al*., 2012).VP5 is significantly more conserved but shows some degree of variations that reflects the geographic origin (Singh, 2005). It has a membrane penetration protein that mediates release of viral particles from endosomal compartments into the cytoplasm (Forzan *et al*., 2004).

The middle shell is composed VP7 and to a lesser extent VP3 are conserved proteins, hydrophobic in

nature and are forming major core protein. They play an important role in the structural integrity of the virus core (Anthony *et al*., 2007). VP7 can mediate attachment and penetration of insect cells in the absence of either VP2 orVP5. The VP3/VP7 complex protects the viral dsRNA genome from intracellular, thus preventing activation of type I interferon (IFN) production (Schwartz-Cornil *et al.,* 2008).

The inner shell is composed of VP3 and contains minor amounts of 3 enzymatic proteins involved in transcription and replication, namely the RNA-dependent RNA polymerase VP1, the RNA capping enzyme VP4 and the dsRNA helicase VP6 that are located at the five-fold symmetry axis of the particle (Boyce**,** 2004). VP1 has allowing efficient replication in both insect and mammalian cells, The VP6 protein has ATP binding activity and displays RNA-dependent ATPase and helicase functions (Sutton *et al*.,2007).

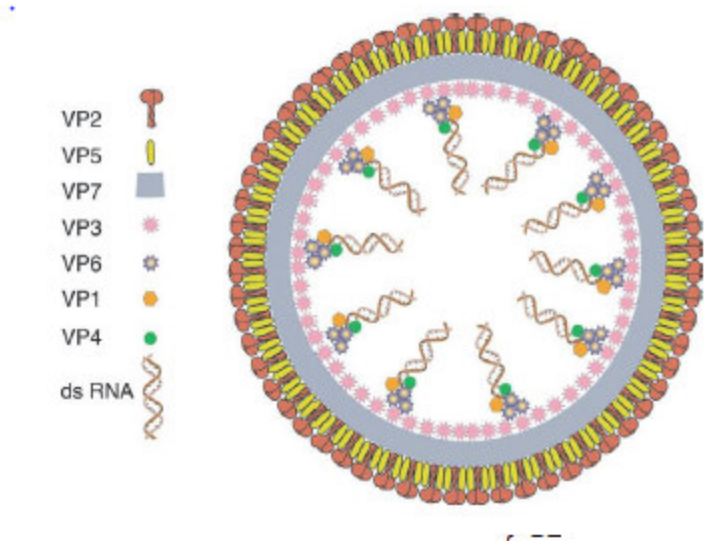

Figure 1; Representative scheme of BTV structural proteins and dsRNA segments
Source: (Schwartz-Cornil *et al*., (2008)

Non- structural proteins (NSP) the two larger BTV non- structural proteins, NS1 and NS2, minor proteins NS3 and NS3A.NS1 has a role in BTV cytopathogenesis (Owens *et al.,* 2004), NS2 is the major constituent of the viral inclusion bodies (VIB) and it is a key player in virus replication and core assembly **(**Kar *et al*., 2007). NS3 functions as a viroporin, facilitating virus release by inducing membrane permeabilization and allow BTV particles to leave host cells by a budding mechanism similarly to retroviruses (Han and Harty, 2004).NS4 has been recently identified (Ratinier *et al*., 2011).

2.3. Epidemiology

2.3.1. Species Affected

All ruminants are susceptible to infection with bluetongue, but clinical disease is most often manifested in sheep; a serious disease also develops in white-tailed deer (*Odocoileus virginianus*) (Johnson *et al*., 2006). In cattle, which play an important role in the epidemiology of BTV mainly because of prolonged viraemia and subclinical course (Tweedle and Mellor, 2002). However, in the epidemics caused by BTV-8 in Western and Central Europe, even cattle showed clinical disease (Thiry *et al*., 2006; *Darpel et al*., 2007; Elbers *et al.,* 2008). African antelopes and other wild ruminants (Howerth *et al*., 2001), but it can also affect camelids (Henrich *et al*., 2007; Meyer *et al*., 2009) and elephants (Erasmus and Mushi, 1990).It can also be transmitted to carnivores. In dogs, for instance, bluetongue has been reported following the use of a BTV-contaminated vaccine (Evermann, 2008).

It is believed that cattle and goat are natural reservoir of BTV because of their subclinical infection and prolonged viremia; only BTV infected midges remain infectious for life, with the virus replicating in salivary gland every 6-8days (Jauniaux *et al.*, 2008).

2.3.2. Geographic Distribution of Virus and Vector

Bluetongue virus can be found worldwide within tropical and subtropical climates from approximately 35° S to 40° N, and in some areas outside this region (e.g., in parts of California). Endemic areas exist in Africa, Europe, the Middle East, North and South America and Asia, as well as on numerous islands (e.g., Australia, the South Pacific, and Caribbean). Outbreaks can occur outside endemic areas, but in most cases, the virus does not persist once cold weather kills the *Culicoides* vectors. Unusually, a serotype 8 virus overwintered for multiple years in central and northern Europe (Tweedle and Mellor, 2002).

In the "Old World" the species *Culicoides imicola,* the most widely spread midge on the globe, is regarded as the major BTV vector. It shows the highest activity in the temperature range from 13 °C to 35 °C. It

reproduces in damp or wet soils fertilised with manure and feeds on cattle, sheep and horses (Mellor and Wittmann, 2002).

The *culicoides imicola* has been found in Africa, the south of Asia, Portugal, Spain, Greece, Cyprus, Corsica, Italy, Israel, Turkey, Yemen, Oman and jizan and najran, district to horn Africa such as Ethiopia, Eretria, Djubity Somalia and Sudan where the enzootic nature of BTVis larger region of Africa least five serotype (1, 2, 4,5and16) in Sudan (arabil et al 2005).

The recent study are assess the sero-prevalence and associated risk factor for small ruminants bluetongue infection in selected area agro-ecology of walayta zone, southern Ethiopia was indicate 41.17% were positive for bluetongue virus antibodies. A prevalence rate ranging from 26.53% for midland altitude to 73.47% for lowland was recorded (Yilma and Mokennen, 2015).

The species of biting midges such as *C. obsoletus, C. pulicaris* and other species, which are potential BTV vectors are found (Mehlhorn *et al.,* 2007).In the epidemic caused by BTV-8 in Germany in 2006–2007, bluetongue was transmitted by *C. obsoletus* (Mehlhorn *et al*., 2007), the species from which BTV was isolated as early as 1977 during the Cyprus epidemic and later in outbreaks in Italy (Savin *et al*., 2005),in Netherlands (Meiswinkel *et al*., 2008), and again in Germany (Hoffman *et al*., 2009). In Sicily and Germany BTV was isolated from the species *C. pulicaris* (Caracappa *et al*., 2003; Hoffmann *et al.*, 2009) and in the Netherlands from *C. dewulfi* (Meiswinkel *et al.,* 2007) and *C. chiopterus* (Dijkstra *et al.*, 2008).

The species *C. obsoletus* is one of the commonest species in Central and Northern Europe (Tweedle and Mellor, 2002) and together with *C. scoticus* is included in the *Obsoletus* complex (Savini *et al.,* 2003; Meiswinkel *et al*., 2004). The females of these two species are very similar in morphology, but species identification is possible with the use of molecular methods (Nolan *et al*., 2007; Balczun *et al.,* 2009, Stephan *et al.,* 2009).The species *C. obsoletus* midges proliferate in water-filled tree cavities or manure heaps (Anonymous, 2007).

C. pulicaris and *C. punctatus* midges are members of the *Pulicaris* complex (Carpenter *et al*., 2006; Dijkstra *et al.,* 2008; Hoffmann *et al*., 2009), *C. pulicaris.* They are widespread in Northern and Central Europe, but probably play only a minor role in BTV transmission (Mehlhorn *et al*., 2009)

The females of species included in the *Pulicaris* and *Obsoletus* complexes preferably attack cattle. The occurrence of *C. dewulfi* biting midges is closely related to the rearing of cattle (Bartsch *et al.*, 2009; Ninio *et al.,* 2011).

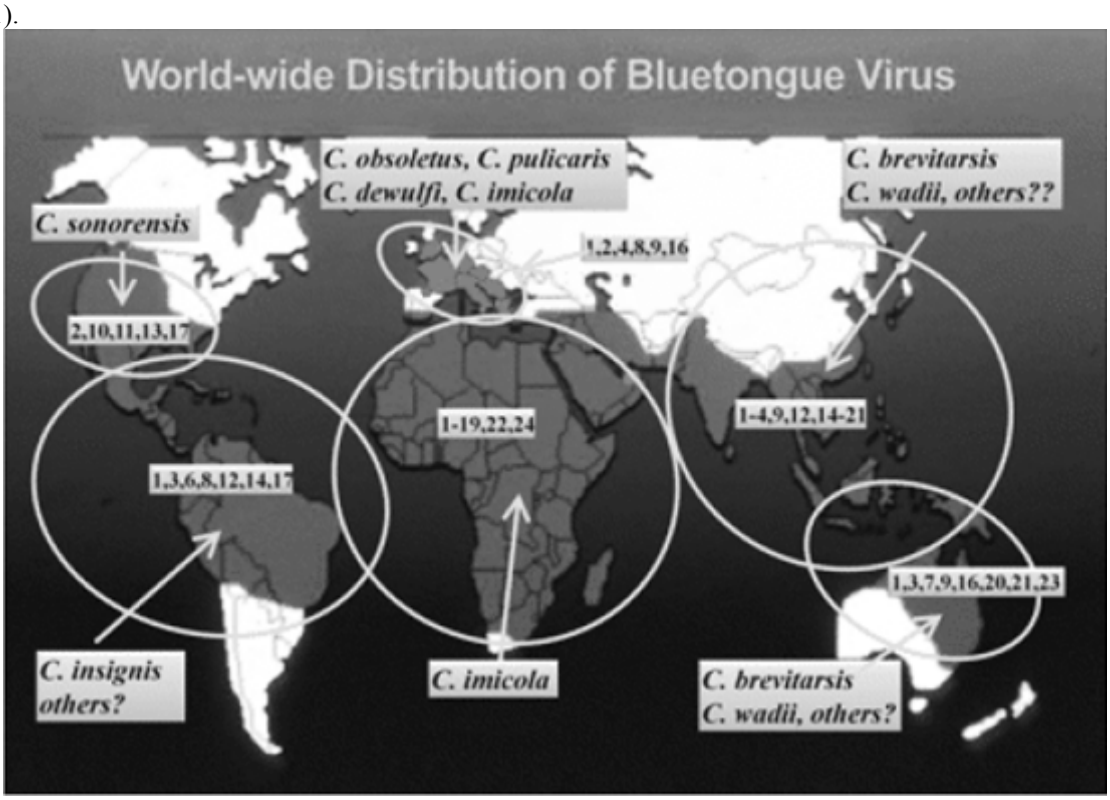

Figure 2; The (BTV) serotypes and the primary Culicoides vectors in different geographical regions denoting six predominant BTV episystems

Source**:** (Tabachnick, 2004).

2.3.3. Transmission

2.3.3.1. Culicoides biting midges

Bluetongue is almost always transmitted by biting midges of the genus *Culicoides* (*Diptera*: *Ceratopogonidae*) and therefore outbreaks depend on the competent insect vectors, virus pathogen and susceptible ruminants. The genus *Culicoides* at present includes 1300 to 1400 species, but only about 30 of them are BTV vectors (Meiswinkel, 2004), they are most frequently present in warm, damp and muddy areas which are rich in organic matter and plentiful in animal hosts they can feed on. They are most active from about one hour before sunset until one hour after sunrise (Mellor *et al*., 2000).

The genus *Culicoides* (Family Ceratopogonidae) consists of very small flies, which 'biting midges' and haematophagous insects. Female *Culicoides* feed also on mammals (including humans) and birds. These insects ingest blood at intervals of three to four days, if available, since they need it for egg deposition. They have a painful bite and can cause irritation and annoyance to animals. The main parts of animals that they attack are the head and the neck. Their biting has been associated with a hypersensitivity reaction (Taylor *et al*., 2007 and Koenraadt e*t al*., 2014).

Virus ingested by midges replicates in the insects' mid-gut cells, spreads to its salivary glands and then can be transmitted to another ruminant. The spread of *Bluetongue virus* thus coincides with the distribution of the vector species.There are over 1500 *Culicoides* species, most significant of which are *C. imicola*, *C. obsoletus*, *C. variipennis*, *C. pulicaris*, *C. sonorensis*, *C. nubeculosus*, *C. dewulfi* and *C. chiopterus*. However, only a small number of these have been shown to act as biological vectors (Mellor *et al.*, 2000, Carpenter *et al*., 200; Mehlhorn *et al.*, 2007).

The life cycle of adult *Culicoides* spp. Egg lyingtakes place in damp marshy ground or in decaying vegetable matter, in a variety of breeding sites. Egg hatching occurs after two to nine days, depending on the species and temperature, larvae in warm climates, larval development is completed in 14–25 days, the pupae are less active; they can be found on the surface or at the edges of water collections and adult midges emerge from the pupae in 3–10 days (Mehlhorn *et al*., 2007).

In general, lifespan of adult *Culicoide*s differs across the various species and ranges from one to 3.5 months; the preceding development, from egg until maturity, takes, depending on environmental conditions, at least three weeks. In moderate or cold regions, the larval stages overwinter at protected places in their habitat (Mellor *et al.*, 2000 and Mehlhorn *et al*., 2007)

The Culicoidesspp are not strong fliers and flying activity can be affected by temperature, light intensity, lunar cycles, relative humidity, wind velocity and other weather conditions. Adult females feed especially in dull, humid weather and tend to be nocturnal. Females are attracted to the smell and warmth of their hosts and different species may be host specific to varying degrees (Purse *et al.*, 2005 and Guis *et al.*, 2012).

Transmission of replicating *Bluetongue virus* is possible during subsequent meal(s) after an initial infection, as an interval of 10–15 days is required in 25 °C to produce a sufficiently large number of transmittable viruses.Progeny virus is then released into the haemocoel from where the secondary target organs, including the salivary glands, are infected Subsequent to virus replication in the salivary glands inside a female midges and intensive chance for virus transmission (Danyk, 2007).

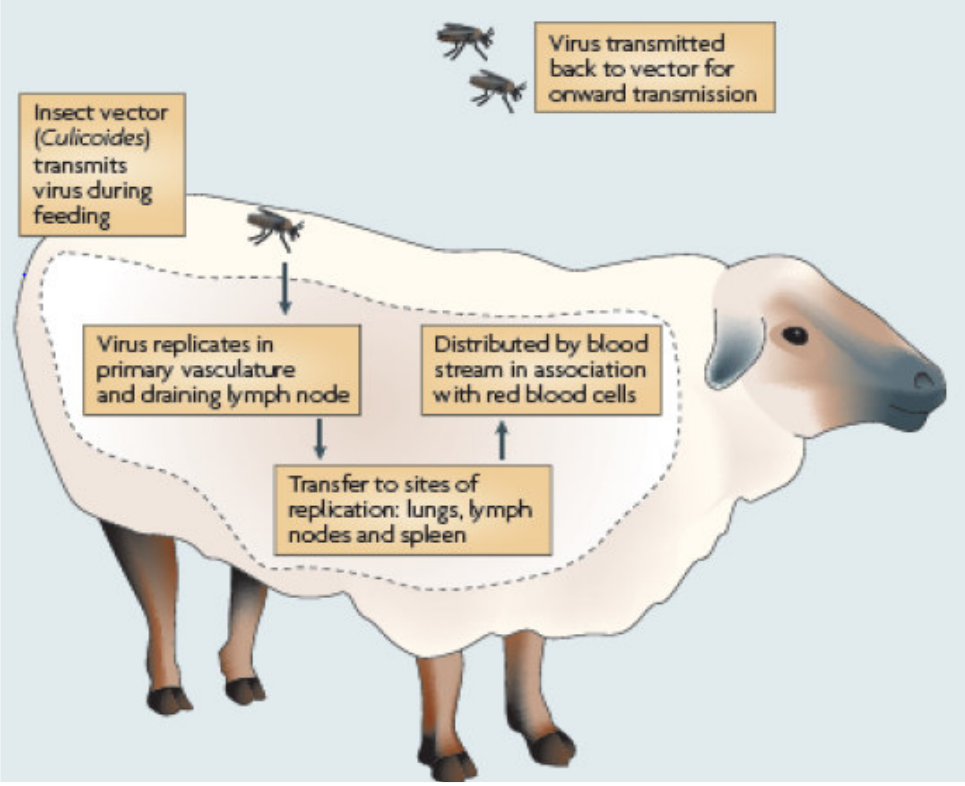

Figure 3; Transmission and replication of bluetongue virus.
Source: (Roy *et al*., 2009)

The ability of biting midges to transmit BTV is markedly influenced by ambient temperature, air humidity and total seasonal rainfall. The recent "global warming" has allowed for longer activity of biting midges and thus longer periods during which they are capable of BTV transmission. In the temperate zone the adults of biting midges with peaks of activity in spring and autumn (Gale *et al.,* 2009; MacLachlan, 2010).

Biting midges are regarded as exophagic and exophilic insects (i.e., feeding on animals outdoors and remaining outside, respectively), but some species, such as *C. dewulfi* and *C. obsoletus*, have shown endophagic,behavior (i.e., feeding inside) which increases in intensity with decreasing ambient temperatures (Baldet *et al.,* 2008).Biting midges can fly over a maximum distance of two km, but because of their small size (one mm to three mm) they can easily be carried on the wind; their passive transport up to a distance of 700 km has been reported (Ducheyne *et al.,* 2007).

2.3.3.2 .Other Ways of Transmission

In addition to biting midges, BTV has been isolated from some arthropods, e.g., sheep ked (*Melophagusovinus*) or some species of ticks (Bouwknegt *et al*., 2010) and mosquitoes However, these are mechanical vectors with only a negligible role in disease epidemiology.Bull semen can also transfer the virus, but it can be infected only when the bull is Viraemia and when semen contains red or white blood cells with which the virus is associated (Wilson *et al.,* 2008).The passage of BTV across the placenta is another mode of transmission. It has been recorded in cattle (Lewerin *et al*., 2010; Santman-Berends *et al*., 2010), sheep and in dogs (Saegerman *et al*., 2011).

Recently, until now unique route of transmission was described in ruminants. This involved ingestion of the placenta of a BTV-infected bovine fetus (Menzies *et al*., 2008).Transmission with colostrum's has also been reported by (Mayo *et al*. 2010).Bluetongue can also be spread by live attenuated vaccines against BTV, or even by vaccines against other antigens contaminated with BTV (Evermann, 2008).

2.3.3. Overwintering

The survival of virus from one "vector season" to the next is called "overwintering", BTV can survive in the absence of adult vectors for nine to 12 months of cold weather in an infected host with no detectable viraemia, disease or sero-conversion. One way in which overwintering may be achieved is by the infection of adult vectors. Although the average life span of these is usually ten to 20 days(Wilson *et al*., 2008), they can occasionally live for up to three months. This suggests that under favorable conditions some biting midges can live long enough to survive the period between two vector seasons (Lysyk and Danyk, 2007).

BTV to survive at different stages of the *Culicoides* life cycle and overwinter in cattle owing to prolonged BTV viraemia, which can occasionally last up to 100 days, Another mechanism suggested for BTV

overwintering is trans placental infection (Backx *et al.*, 2009; *Darpel et al*., 2009; Lewerin *et al.,* 2010; Santman-Berends *et al.,* 2010).

Mechanical vectors may also be involved in virus overwintering; BTV has been isolated from the sheep ked and some tick species, which are arthropod species living much longer than *Culicoides* midges. Mechanical vectors should therefore be regarded as potential reservoirs for BTV (Wilson *et al.,* 2008; Bouwknegt *et al*., 2010).

2.4. Economic Importance

The economic losses due to bluetongue is around 3 billion US$ per year in the world. The direct losses are death, abortions, weight loss and reduced milk and meat productions and indirect losses are export restrictions of live animals, semen and foetal calf serum (Bitew *et al*., 2013). Major production losses in clinical young lamb are more apparent and mortality is high up 30-70% this include death unthrifteness during prolonged covalence, wool break and reproductive losses. Indirect losses associated with decrease body weight and condition,drop milk production and poor subsequent reproduction performance where thought to have greater economic effect than occasional over disease (Marech, 2014),in addition there is restriction international trade livestock and associated gramplasm from BTV endemic countries unless the animal are certified free infection by convectional virus isolation or serology such restriction could lead economic loss for BTV endemic countries(Maclochlon and Obsum *et al*.,2006).

At present 26 serotypes have been reported throughout the world (Maan *et al*., 2012), with recent additions of the 25th serotype ("Toggenburgorbivirus") from Switzerland in goat and 26th serotype from Kuwait in sheep and goat. There is only low level of cross-protection among the BT virus serotypes and making vaccination strategies and control programmer a daunting task (Hofmann *et al*., 2008; Eschbaumer *et al*., 2009; Bitew *et al*., 2013). BT is multiple species disease to the OIE, World Organization for Animal Health and to veterinary authorities in many countries. BTV is almost exclusively spread by *Culicoides* spp. biting midges (*Diptera*) and occurs, worldwide (OIE, 2009; Maclachlan, 2011).

In the countries historically affected by bluetongue, the control strategy was based on the vaccination of exposed sheep and on clinical and serological surveillance. All international movements of animals of susceptible species and, their potentially infectious products from infected countries and zones were strictly forbidden unless they were demonstrated as non-infected, after a specified period of protection by vector attacks in an insect-proof environment, as required by the World Organization for Animal Health (OIE) standards that included bluetongue in former 'List A' diseases. Animal movements from infected countries or zones were possible, however, towards countries/zones where the absence of *Culicoides* spp. likely to be competent BTV vector was proven (OIL, 2004; Caporale, 2004).

All the serotypes can cause blue-tongue disease (BT), a non-contagious hemorrhagic disease of domestic and wild ruminants and camelids with no known zoonotic potential. Although a galaxy of serological and molecular diagnostic tools are available for the prompt, reliable and precise detection and characterization of BTV strains/-serotypes and large number immune prophylactic agents have been developed for the control of the disease however, it is still endemic in many countries with substantial economic losses (Eschbaumer *et al*., 2009).

2.5. Pathogenesis

After introduction through the bite of an infected midge, the virus is transported by the host dendritic cells from the skin to the local lymph nodes, the sites of initial virus replication, Subsequently (Hemati *et al.,* 2009), it spreads to the blood circulation inducing a primary viraemia which seeds secondary organs, that is, lymph nodes, spleen and lungs (Sanchez-Cordon *et al*., 2010). The virus replicates in vascular endothelial cells, macrophages and lymphocytes (Drew *et al*., 2010a). In early viraemia virus is associated with all blood elements, while at later stages of viraemia it exclusively associates with erythrocytes. Virus particles appear to be sequestered in invaginations of the erythrocyte membrane (MacLachlan, 2009).

Infection with BTV results in cell necrosis and apoptosis. In addition, it induces the production of TNFα, IL-1, IL-8, IL-6, IFN-I and cyclooxygenase-2, and enhances plasma concentration of prostacyclin and thromboxane, which frequently leads to an excessive inflammatory response and subsequent damage to the cells and tissues of the infected animal (Chiang *et al*., 2006; Schwartz-Cornil *et al*., 2008).

The pathogenesis of bluetongue is characterized by injury to small blood vessels in target tissue, resulting in vascular occlusion and tissue infarction. Virus-induced vasoactive mediators produced by thrombocytes, dendritic cells, macrophages and BTV-infected endothelial cells increase damage to the endothelium, interfere with its function and increase vascular permeability; this leads to the development of edema and effusions (MacLachlan *et al*., 2009; Drew *et al*., 2010).

2.5.1. Viraemia and Immune Response

Viraemia in infected animals has a prolonged course, but is not persistent, Its duration depends on the longevity of erythrocytes to which virus is bound. It is also related to the species and breed of the infected animal.

Viraemia lasts 14 to 54 days in sheep and 19 to 54 days in goat, In cattle, viraemia may last as long as 60 or, even 100 days , which makes this animal an important host, from the epidemiological point of view (MacLachlan *et al.,* 2009).

The infected animals react to BTV with interferon production. Serotype-specific neutralizing antibodies against the VP2 protein confer protection against homologous strain reinfection. The sera of infected ruminants also contain serogroup-specific antibodies induced by the VP7 protein, as well as antibodies against other structural and non-structural proteins (Schwartz-Cornil *et al*., 2008). The cell-mediated immune response to BTV can probably reduce the spread of virus in the organism early after infection, but cannot eliminate the virus completely. By producing a cytotoxic effect in infected cells, CD8+ T-lymphocytes play the most important role (MacLachlan, 2006).

2.6.Clinical Signs

Bluetongue in sheep is manifested as an acute, chronic or subclinical condition; fine wool breeds are most susceptible. An incubation period of four to eight daysis followed by fever, apathy, tachypnea, and hyperemia of the lips and nostrils with excessive salivation and serous nasal discharge that is initially clear, then becomes mucopurulent and upon drying may form a crust around the nostrils. Oedema of the tongue, lips, submandibulum and sometimes ears appears, petechiae develop on the conjunctiva and ulcers on the oral mucosa. Cyanotic tongues in severe cases. In some cases, dyspnoe, profuse haemorrhagic diarrhoea or vomiting that can cause aspiration pneumonia is recorded (Tweedle and Mellor, 2002).

At the end of the pyrexia stage, affected sheep may have coronitis, laminitis or paresis and necrosis of striated muscles and, as a result, stand with an arched back and are reluctant to move. Torticollis, dermatitis and breaks in the wool may also develop (Elbers *et al*., 2009; Darpel *et al*., 2009). Infection in pregnant ewes may lead to abortion, foetal mummification and the birth of weak calves with potential congenital defects (hydrocephalus, cerebral cysts, retinal dysplasia, etc. Chronically affected sheep may succumb to other diseases such as bacterial pneumonia (MacLachlan and Gard, 2009: Saegerman *et al.,* 2011)).

The goats are less frequently infected with BTV, and rarely show any signs of clinical disease. If they do, the signs are similar to but less severe than in sheep. In the 2006 epidemic in the Netherlands, the diseased goats showed a sudden drop in milk production, high temperature, oedema of the lips and head, nasal discharge and scabs on the nose and lips, erythema of the skin of the udder and small subcutaneous hemorrhagic lesions (Dercksen *et al.*, 2007).

In cattleclinical disease is rare with the exception of BTV-8 infection in which clinical signs are manifested in large numbers of animals. Clinical infection is considered a hypersensitivity reaction mediated by the IgE antibody (Elbers *et al*., 2008). The early stages are characterized by fever, apathy and depression followed by erosion and necrosis of the oral and nasal mucosa, nasal discharge, excessive salivation, conjunctivitis, lameness and stiffness, ulcerative dermatitis, coronitis, occasional bloody diarrhea, oedema and hyperaemia. The skin of teats is often inflamed and may crack and peel. Milking cows show reduced milk production (Thiry *et al.,* 2006; Mehlhorn *et al*., 2008; Williamson *et al*., 2008; Elbers *et al*., 2009). Infection of dams in early stages of pregnancy can result in early death and resorption of the embryo; other consequences involve abortion or the birth of malformed and weak calves (Elbers *et al*., 2008).

2.7. Post Mortem Lesion

Necropsy findings in affected animals reveal subcutaneous tissues infiltrated with gelatinous fluid in the head, haemorrhages in the tunica media of the pulmonary artery or even aorta, hyperaemia, or occasionally cyanosis, of the oral mucosa with petechiae and ecchymosis. Erosions with coats of necrotic tissue may be present in the lips, tongue and cheeks. There may be hyperaemia of the ruminal pillars and reticular folds. The spleen, lymphatic nodes and tonsils are enlarged and haemorrhagic, occasionally with petechiae. The tongue root, peri-cardial sac, kidney, gut (particularly at the iliocaecal junction) and subcutaneous tissues may have petechiae. The skeletal and heart musculature shows light necrotic areas. In addition, inflammation of the upper respiratory tract, pulmonary oedema, pleuritis, pericarditis or enteritis may be present (Mauroy *et al*., 2008; MacLachlan *et al.*, 2009).

2.8. Diagnostic Approaches

A preliminary diagnosis based on clinical signs, post-mortem findings and epidemiological assessment should be confirmed by laboratory examination. Samples to be examined in the laboratory should include non-coagulated blood (use of EDTA or heparin is preferred), serum, post-mortem tissue samples such as spleen, lymph nodes, lungs2are collected. For transport, serum samples should be frozen at -20° (Sukbed and Chintun. 2013).

2.8.1. Bluetongue Virus Isolation

BTV can be isolated from blood, semen and various other tissue samples including liver, spleen, brain, lymph nodes and mucosal epithelium. Bluetongue virus can be propagated in embryonated chicken eggs (ECE), cell

cultures or in sheep. Embryonated eggs, 9 to 12 days old are inoculated with the materials by intravenous route for BTV isolation. This method is 100- 1000 fold more sensitive than yolk sac inoculation. The material obtained from ECE can either be further propagated in cell culture or directly examined using molecular methods (PCR) (Dadhich, 2004; Biswas *et al*., 2010).

The Bluetongue virus can also be isolated in cell lines of different animal origin. The mammalian cell lines for BTV isolation like calf pulmonary artery endothelium (CPAE) (Mecham, 2006).The cytopathic effect produced by BTV is observed only on cell lines of mammalian origin at 3 to 5 days after inoculation and appears as foci of rounded and retractile cells. If cytopathic effect (CPE) does not appear, a second passage is made in cell culture. The isolation of virus in cell culture is usually preceded by its passage in ECE which are more susceptible to BTV than cell lines. The identity of BTV in the culture medium of cells manifesting a CPE may be confirmed by antigen-capture ELISA and VNTs (Sperlova and Zendulkova, 2011).

2.8.2. Antigen Identification

Sandwich ELISAs have been described for the detectionof BTV antigens in infected cell cultures or adult Culicoides midges. Although antigen ELISAs are specific, to give a positive result and in addition to ELISA, molecular assay can be used to detect and identify the viral RNA of BTV or related viruses (Batten *et al.,* 2008).

A direct identification of BTV in blood or tissue samples is possible with use of the reverse transcription-polymerase chain reaction (RT-PCR) method that allows for sero typing and can detect BTV RNA in samples as late as 6 months after infection (Vanbinst *et al*., 2010; De Leeuw *et al*., 2013). RNA polyacrylamide gel electrophoresis (PAGE) has been used as a diagnostic tool for the identification BTV 10 segments. RNA PAGE has also been used to identify different genotypes of the same serotype, as well as to indicate different serotypes of BTV (Maan *et al*., 2008; Mertens *et al*., 2007).

2.8.3. Antibody Identification

Serogroup-specific antibodies against BTV can be detected by, competitive ELISAs test targeted to the VP7 protein. This is a rapid method permitting determination of serum or plasma antibody as early as the 6th day of post-infection (PI) (Mars *et al*., 2010; Kramps *et al*., 2008). Again an indirect ELISA based on VP 7 protein has been developed at Indian veterinary research institute (IVRI), In addition, serogroup-specific antibodies can be identified by an agar-gel immune diffusion test (AGID), a complement-fixation test and a haemagglutination-inhibition test (Mukteswar and Chand *et al*., 2009).

Agar gel immuno-diffusion (AGID) tests, for the detection of group-specific antibodies against BTV. The AGID test relies on the availability of purified soluble antigens, derived from BTV-infected cell cultures and positive control serum from hyper-immunised animals. However, AGID may produce cross-reactions with other orbiviruses like African Horse Sickness virus (AHSV) and Epizootic Hemorrhagic Disease virus (EHDV) (Sperlova and Zendulkova, 2011).

A complement fixation tests (CFT) have been used to identify BTV or to detect a rise in BTV-specific antibody titre following infection. These assays that primarily detect early antibodies, IgM, depend on inhibition of the complement-mediated lysis of activated erythrocytes by BTV antigen/antibody complexes that can also fix the available complement. However, they may only be effective for a relatively short period of time following infection and have largely been superseded by the use of the ELISA (OIE, 2009). A new indirect ELISA for the detection of BTV-specific antibodies in bulk milk (Kramps *et al*., 2008) and other samples (Chand *et al*., 2009; Gandhale *et al.,* 2010)

2.8.4. Differential Diagnosis

The clinical signs of bluetongue can easily be mistaken for those of other ruminant diseases such as Orf (contagious pustular dermatitis), foot and mouth disease, acute photo sensitization, acute haemonchosis (with depression and submandibular oedema), facial eczema, *Oestrus ovis* infestation, pneumonia, plant poisoning, salmonellosis, sheep pox, Peste des Petits Ruminants (PPR) (Williamson *et al.,* 2008), malignant catarrhal fever, pododermatitis, rinderpest, and epizootic haemorrhagic disease of deer (Mehlhorn *et al*., 2008; Williamson *et al*., 2008; Savini *et al*., 2011).

2.9. Prevention and Control

There is no specific therapy for animals with bluetongue. Symptomatic therapy includes gentle handling of affected animals, their stabling and, if indicated, administration of non-steroidal ant-inflammatory drugs.An immediate ban on animal import from countries with bluetongue is the priority measure, Prophylactic immunisation and the removal of vectors or prevention of vector attacks can also be used (Tweedle and Mellor, 2002).

2.9.1. Prophylactic Immunisation

Vaccination can prevent clinical bluetongue or at least mitigate its course by interrupting the BTV cycle in the environment; it thus reduces the economic losses due to animal infection and makes transfer and trading of animals from BTV enzootic regions possible. Bluetongue vaccines are serotype-specific and therefore, before use in a given area, the serotypes present in the environment should be taken into account. Two types of vaccines,

inactivated and live attenuated, are currently available (Savini *et al*., 2008; Bhanuprakash *et al*., 2009; Caporale and Giovannini, 2010).

2.9.1.1. Live Attenuated Vaccines

Live attenuated vaccines were until recently the only bluetongue vaccines commercially available and were originally used in endemic situations where multiple serotypes of virus are common (e.g., South Africa). In these regions multivalent live attenuated vaccines against the serotypes present there are still used (Caporale and Giovannini, 2010). One dose of attenuated vaccine is enough to provide good protection for at least one year. Their production is inexpensive, which is another advantage (Savini *et al*., 2008; Bhanuprakash *et al.,* 2009), but they may lose efficiency at temperatures over 35 °C and may provide poor protection against infection with a heterologous BTV serotype.

However, there are growing concerns about the use of BTV attenuated commercial vaccines (Veronesi *et al.,* 2005) which can result in clinical signs of bluetongue, abortion, reduced milk production, temporary poor semen quality in rams and foetal malformation if pregnant ewes are,(Breard *et al*., 2007; Savini *et al*., 2008) For these reasons it is recommended to vaccinate ewes nine to 15 weeks before mating, and rams after the matingperiod, but at least six weeks before the beginning of the following period (Savini *et al.,* 2008;Bhanuprakash *et al*., 2009).

2.9.1.2. Inactivated Vaccine

If properly produced, inactivated vaccines can induce reliable and protective immunity that, for a good and lasting effect, requires re-vaccination. Although their production is rather expensive, at present they are the best compromise in terms of safety and efficiency (Schwartz-Cornil *et al*., 2008; Bhanuprakash *et al*., 2009). Well inactivated vaccines can prevent the development of clinical disease in susceptible hosts, reduce direct economic losses due to infection, facilitate safe trading in animals and prevent the development of Viraemia, or make it less severe, monovalent inactivated vaccines were first prepared against BTV-2, then against BTV-4; bivalent vaccines were made against BTV-2 and BTV-4 (Savini *et al.,* 2008). Today monovalent vaccines against BTV-1, BTV-8 and BTV-9 are available (Zientara *et al.,* 2011).

2.9.1.3. New-Generation Vaccines

At the present moment new types of vaccines are being developed; they include, for instance, recombinant vector vaccines, sub-unit vaccines and others which would offer advantages such as no risk ofvirus transmission, rapid onset of immune response or options to make them polyvalent However, they are expected to have a considerably higher price, which would be a disadvantage (Roy *et al*., 2009).

2.9.2. Vector Control

Understandably, it is impossible to completely eliminate *Culicoides* midges in the natural environment. It is possible, however, to reduce midge populations to ineffective levels, or to prevent vector attacks by stabling susceptible animals overnight since midges have nocturnal feeding habits. In addition, the protection of animals in stables can be improved by door and window screens made of a fine mesh or a coarse fabric impregnated with insecticide (Radostits *et al*., 1994; Calvete *et al.,* 2010).

Alternative approaches involve moving the animas from insect resting and breeding sites or complete elimination of such sites. The species *C. imicola*, *C. obsoletus* and *C. pulicaris* breed in wet soils rich in organic matter and such grounds should be drained and dried. The control of adult midges can be carried out by use of approved insecticides applied outside or inside (in areas with *C. dewulfi* occurrence) the stable or directly to the susceptible animals (Schmahl *et al.,* 2009).

The latter approach is allowed only with agents of low toxicity to mammals such as synthetic pyrethroids (deltamethrin, cyfluthrin, permethrin and fenvalerate); these agents provide protection for three to five weeks and can be used in the form of insecticide-impregnated ear tags. Animals can also be protected by systemic invemectins administered intradermally or subcutaneously. The larvicide Abate (5% temephos granulated with gypsum) can be applied to midge breeding grounds. Insect repellents can also be used for direct protection of animals; diethyl toluamide (DEET), for instances effective for up to four hours (Mehlhorn *et al.,* 2009; Schmahl *et al.,* 2009).

3. CONCLUSION AND RECOMMENDATIONS

Bluetongue is viral disease that effect primary sheep and very rarely cattle, goat and other domestic animal. It is non-contagious and transmission by insect vector and other mode of transmission of virus. The disease caused by an icoasohedral,non-envelope,ten segments dsRNA virus which have seven structural protean (VP1-VP7) particularly VP2 is very important for emerging new serotype due to reasortement and drift, four non-structural protean (NS1-NS3/NS3A) within the oribivirus genes of family Reoviridae.

The geographical distribution of BTV infection in the risk of intear world, where previously restricted in specific geographical area between 35° S to 40° N, but recent beyond this geographical area due to global warming and environmental degradation are the condition favorable for insect reproduction and viral replication and in legal international trade can influence the incidence, distribution particularly those transmitted by

arthropod vectors is one of the predisposing factor for sero-positivity for small ruminate BTV infection are speed up. The transport of infected vectors by the wind was also demonstrated, to be a significant determining factor in the spread of BTV over long distances.

The disease is major impact economic growth of country in the endemic area due to lethal effect health of animal, international trade restriction and disease control program. The physio-pathological mechanisms of the BTV after bite midges vector that infect by causative agent BTV induced vasoactive mediators produced by thrombocytes, dendritic cell and macrophages to thrombo-heamorrhagic disease.

The diagnosis of this disease depended host factor, molecular basis of BTV virulence and specificity of sero type the insect vector, geographical status and mammalian reservoir. This disease have not specific treatment dueto this condition the control bluetongue disease through timely and relevant vaccination are feasible,The immunization of susceptible sheep remains the most effective and practical control measure against BT. In order to protect sheep against multiple circulating serotypes, three pentavalent attenuated vaccines have been developed, however new generation vaccine are effective, which have no risk virus transmission, rapid onset immune response and the insect vector controls are bases the species, mechanism of life cycle and geographical distribution and host species related vector.

Generally this disease are the dangerous world wide occurrence disease so based on the above conclusion the following recommendation can be forwarded to responsible person, government and non-government organization

- Unlawful animal movement should be restricted.
- Inlegal transbaunder trade livestock should be controlled.
- Should be not import animal and animal products from endemic disease country unless diagnosis by gold standard.
- Disease monitoring and surveillances should be timely reported.
- Antigen related vaccine and recombinant vaccine bank should be organized the virus BTV serotypes.
- Serious analysis should be conducted before decision made in what types vaccine used and for what type of serotypes used and in particularly evaluate the effecy and safety both polevalent and monovalent vaccine.
- Consideration should be done the life cycle occurrence and distribution and taxonomy of culicoides species tocontrol vector.
- Introduction resistance breeds and free from vaccine adaptation should be, into disease endemic area.
- Education should be given for the farmer about a management control disease and insect bite animals.
- Different research and experiment should be done to find out the disease and serotypes of virus in enzootic area.
- Prophylactive vaccination should be given before outbreak disease in endemic area.
- To prevent vector attacks by stabling susceptible animals overnight since midges have nocturnal feeding habits.

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