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Review Article

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Infectious bovine rhinotracheitis – A review

Nagaro Damena*

School of Veterinary Medicine, Wollega University, P.O.Box 395, Nekemte, Ethiopia

*Corresponding author; e-mail: harawwee@gmail.com

Article Info	Abstract
Keywords:	In many parts of the world, domestic as well as wild cattle are affected by infectious bovine
Cattle disease	rhinotracheitis. The causative organism is Varicellovirus in the subfamily Alphaherpesvirinae of the
Etiology	family Herpesviridae. This review is mainly concerned with the etiology, epidemiology, economic
Varicellovirus	importance, clinical presentation of infectious bovine rhinotracheitis, diagnosis, treatment, prevention
Viral infection	and control apart from its status in Ethiopia.
Wild cattle	
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Introduction

Infectious Bovine Rhinotracheitis (IBR) is a disease of domestic and wild cattle; causing serious threat to reproductive health and productivity of cattle. The virus belongs to genus *Varicellovirus* in the subfamily Alphaherpesvirinae of the family Herpesviridae (Muylkens et al., 2007).

The disease caused by BoHV-1 can also cause vulvovaginitis infectious pustular (IPV), encephalomyelitis and mastitis. BoHV-1 affects respiratory, reproductive, ocular. alimentary, integumentary and central nervous systems besides causing neonatal infections. Infections with this agent can also manifest as ocular, neonatal, gastro-intestinal, and neurologic disease as well as reproductive failure due to abortion and other genital symptoms IPV and Infectious Pustular Balanoposthitis (IPB) (Gould et al., 2013). The disease is essentially a herd problem which occurs mostly in animals over 6 months of age.

Transmission occurs normally by contact with infected animals, aerosol route and virus-contaminated semen from BoHV-1 infected bulls (Fulton et al., 2013).

After an incubation period of 2-4 days, serous nasal discharge, salivation, fever, in appetence, and depression become evident. Within a few days the nasal and ocular discharges change to muco-purulent. Where natural mating is practiced, genital infection can lead to pustular vulvovaginitis or balanoposthitis. However, most infections run a very mild or subclinical course (Van Oirschot et al., 1993). Secondary bacterial or viral agents may contribute to a multifactor disease complex resulting in severe respiratory disease of young animals ('shipping' or 'crowding fever'). However, uncomplicated cases of BoHV-1 which causes respiratory or genital disease last about 5-10 days.

Infectious bovine rhinitracheits is a disease of economic importance in cattle. Cattle greatly contribute to the economy and welfare of most Ethiopian rural

populations. Although, IBR is not a highly fatal disease, it can cause considerable economic losses due to abortion, loss of body condition, and milk yield, loss of new born calves, temporary failure of conception, insufficient feed conversion, secondary bacterial pneumonia and cost of treatment (Bekele et al., 1989). Abortion occurs as a consequence of infection of seronegative cows by BoHV-1. The virus reaches the fetus by crossing the placental-blood barrier following systemic spread through viremia in animals afflicted by IBR (Muylkens et al., 2007). It causes the death of the fetus before degeneration of the placenta occurs, hence there is a delayed expulsion resulting in in-utero autolysis of the fetus (Zewde et al., 2021) and frequent retention of fetal membranes. Abortions typically occur during 4-8 months of gestation within15-64 days post infection regardless of the stage of pregnancy (Gibbs and Rweyemamu, 1977). Other reproductive disorders associated with BoHV-1 include infertility with increased service per conception, metritis, and oophoritis (Graham, 2013).

Regarding management, higher prevalence was obtained in extensively reared cattle than semiintensively and intensively managed cattle's. The possible reason for higher prevalence in extensively reared cattle's could be the practice of natural bull mating with bulls of unknown health status that causes the rapid spread of the disease and high contact rate with unknown herds of the neighbors reported that herds with high stock density are associated with high odds for BoHV-1 infection (Zewde et al., 2021).

Another important epidemiological feature of BoHV-1 is that infections usually produce latency. Despite the presence of colostral immunity, the virus maintains latency in trigeminal ganglion of the affected cattle and when they are stressed out due to various reasons, they shed the virus in the environment and become the source for infecting other susceptible cattle. It could be due to immune evasion mechanism and reactivation of the virus following exposure to stressors (OIE, 2010). It has been suggested that late abortions occurring up to 100 days post infection might be the result of such reactivations (Jones and Chowdhury, 2008). The virus is distributed worldwide, except the BoHV-1-free countries (OIE, 2010). Studies conducted in different countries across the world over the last 15 years reported varying sero-prevalence ranging from 35.9-77.5% in Europe and 37-60.8 % in Latin America (Raaperi et al., 2014). Recent reports from Sub-Saharan

e to stressors (OIE, 2010). It Dagalp et al., 2020). BHV-1

Africa on BoHV-1 sero-prevalence in cattle are scarce, but include 48.3% in Southern Zambia (Mweene et al., 2003), 69% in Ghana (Adu-Addai et al., 2012) and 74.5% in Gauteng province of South Africa (Njiro et al., 2011).

In Ethiopia, two preliminary surveys conducted in limited geographic areas in the mid-1970s and late 1980s demonstrated serological evidence of the presence of the virus in the country. Accordingly, the sero-prevalence of BoHV-1 was 41.8% in Harar and Sidamo provinces (Lefevre, 1975) and 67% in Gobe and Ghibe in central Ethiopia (Bekele et al., 1989) also recently in North West Ethiopia 77.6% prevalence was estimated (Zewde et al., 2021). Apart from the serological evidence in the three reports, the importance of the virus as the cause of reproductive disorder in milk shades of Central, Southern and Western Ethiopia has been investigated with a prevalence of 30.8%, 45.5% and 55.9% consecutively (Sibhat et al., 2018).

Enzyme linked immune sorbent assay has been extensively used for the assessment of seroepidemiological investigation of BoHV-1 antibodies among cattle population in the various parts of the world (Roshtkhari et al., 2012). Various intrinsic and extrinsic factors also influence the prevalence of infection among cattle population (Keneisezo et al., 2019).

Etiology of infectious bovine rhinotracheitis

Bovine herpesvirus 1 (BHV-1) is a member of the family Herpesviridae, subfamily Alphaherpesvirinae Genus: Varicellovirus (Davison et al., 2009). The virus is associated with infectious bovine rhinotracheitis (IBR) and infectious pustular balanoposthitis/ infectious pustular vulvovaginitis (IPV/IPB) (Brock et al., 2020). Restriction endonuclease analysis of DNA is a molecular technique used to identify the virus subtypes, such as, BHV1.1 and BHV1.2 (Malla et al., 2018 and Dagalp et al., 2020). BHV-1 subtype 1.1 is associated with respiratory signs and Rhinitis, while subtype 1.2 is associated with balanoposthitis pustular and vulvovaginitis.

There is a future classification on subtype 1.2 strains, namely, BHV1.2a and BHV1.2b. Some subtype1.1 and 1.2a strains are abortifacient, as shown by close connection with clinical cases of abortion and by experimental infection of pregnant heifers (Petrini et al.,

2019). Although not related with abortion, subtype 1.2b strains are commonly linked with respiratory and genital infections (Fulton et al., 2016).

Viruses isolated from buffaloes and goats and previously identified as BHV-1 by serological tests have a different restriction enzyme profile to subtypes of BHV-1, are now regarded as separate viruses and have been classified as BHV-2 and caprine herpesvirus. bovine herpesvirus respectively. The causing meningoencephalitis (previously BHV1.3) has been classified as BHV-5(Smith et al., 1993). BHV-4, which was found widespread in Israel, can cause mastitis, vaginitis, conjunctivitis, pneumonia. metritis. interdigital dermatitis and abortion in cattle (Monge et al., 2006).

Epidemiology of infectious bovine rhinotracheitis

BoHV-1 is a worldwide disseminated pathogen displaying significant differences in regional incidence and prevalence with regards to the geographical positions and the breeding managements of the considered regions (Ackermann and Engels, 2006). Based on serological surveys, several studies have been aimed at identifying the risk factors for BoHV-1 seropositivity. Some of them are well characterized such as the following: age, sex (males are more frequently positive than females) and herd size (Boelaert et al., 2005 and Solis-Calderon et al., 2003). Direct animal contact, such as purchase of cattle and participation in cattle shows were also found to be important risk factors for the introduction of BoHV-1 (Van Schaik et al., 2002). Other factors such as farm density or cattle density may increase the risk of BoHV-1 introduction (Van Schaik et al., 2004). As reported for other diseases caused by herpesviruses in man and animals the latency reactivation cycle has a deep epidemiological impact since it is responsible for the maintenance of BoHV-1 in a cattle population. BoHV-1 infection of new generation cattle by latent carriers submitted to reactivation stimulus may occur at several occasions as for example at birth (Thiry et al., 1985), mating, during transport or following the introduction of heifers into the group of dairy cows. Therefore the detection of BoHV-1 latent carriers is a concern in the setting up of a BoHV-1 control program.

The identification of latently infected animals is commonly based on the detection of BoHV-1-specific antibodies. However, passively acquired colostral immunity may interfere with an active antibody response following infection (Lemaire et al., 2000). As a consequence one seronegative BoHV-1 latent carrier (SNLC) was obtained 7 months after experimental infection of passively immunized calves with a virulent BoHV-1 (Lemaire et al., 2000). It is therefore imperative to develop other diagnostic tests that can detect such latently infected animals. The direct PCR identification of BoHV-1 from tonsil samples would be a useful alternative (Winkler et al., 2000). Another concern in BoHV-1 eradication schemes rose from the capacity for BoHV-1 to cross the species barrier. Field data and experimental infections have brought evidence of possible infections of several ruminant species with BoHV-1.But there is no indication so far that non cattle ruminant species could play a role of alternative reservoir of BoHV-1. In the natural situation BoHV-1 was detected in acutely and latently infected sheep. However sheep do not play a major role in the transmission of BoHV-1 to cattle (Hage et al., 1997). Successful BoHV-1 infections were experimentally obtained in sheep and goats. Red deer exhibit a limited susceptibility to BoHV-1 (Thiry et al., 2006). Otherwise the experimental host range of BoHV-1 is rather narrow. Rabbits can be infected via the intra conjunctival or the intranasal route (Meyer et al., 1996). Mice are not susceptible to the infection. Fully susceptible mice to BoHV-1infection were obtained by introducing combined genetic deficiencies in the ability to produce IFN- α/β receptor or IFN- γ receptor in a genetic background unable to produce mature B and T lymphocytes (Abril et al., 2004).

In Ethiopia, two preliminary surveys conducted in limited geographic areas in the mid-1970s and late 1980s demonstrated serological evidence of the presence of the virus in the country. Accordingly, the sero-prevalence of BoHV-1 was 41.8% in Harar and Sidamo provinces (Lefevre, 1975) and 67% in Gobe and Ghibe in central Ethiopia (Bekele et al., 1989). Apart from the serological evidence in the two reports, the importance of the virus as the cause of reproductive disorder in milk shades of Central, Southern and Western Ethiopia has been investigated with a prevalence of 30.8%, 45.5% and 55.9% consecutively (Sibhat et al., 2018).

Economic importance

Infectious bovine rhinotracheitis causes significant economic impact in both beef and dairy cattle reproduction and production feedlots. The losses incurred as a result of infertilities are due to infectious pustular balanoposthitis in male cattle and infectious pustular vulvovaginitis in cows. Other losses may include; epidemic abortion, production loss, death due to respiratory disease among all ages of the cattle, death among new born calves due to highly fatal form of systemic diseases and cost of the disease management due to secondary bacterial infection of the respiratory system occurs (saravanajayam et al., 2015)

Clinical presentation of infectious bovine rhinotracheitis

The severity of the disease caused by BoHV-1 is influenced by several factors such as the virulence of the BoHV-1 strain (Kaashoek et al., 1996), resistance factors of the host, especially the age, and potential concurrent bacterial infection. Subclinical BoHVlinfections are common. Several BoHV-1 strains display a poor ability to induce clinical signs and were classified as weakly virulent strains in a comparative virulence experiment (Kaashoek et al., 1996). Otherwise, these discrete clinical pictures can also be explained by the primary infection of passively immune calves in countries where BoHV-1 is endemic. Indeed, colostral immunity is known to protect efficiently infected animals from clinical signs (Lemaire et al., 2000).

Following the intranasal inoculation of seronegative calves, high fever is measured for 4 to 5 days (peak at 41 °C) and may be accompanied by apathy and anorexia. Adult dairy cows show a significant milk drop during that period (Van Schaik et al., 1999). After 2 to 3 days of incubation, respiratory and ocular signs are observed. They are consistent with the inflammatory response and the epithelium damages caused by BoHV-1 at primary replication sites. They consist of red appearance of nasal mucosa, serous to mucopurulent nasal discharge, and in severe cases heavy breathing at inspiration (tracheal stridor caused by necrotic debris in the tracheal lumen) and cough. An endoscopy examination revealed a red appearance of pharyngeal and tracheal mucosal epithelia and the presence of several necrotic foci recovered with dead mucosal epithelial cells embedded in fibrinous exudate (Muylkens et al., 2006). Ocular signs such as conjunctivitis and mucopurulent ocular shedding are not uncommon. Abortion is a consequence of a respiratory BoHV-1 infection of a seronegative cow. Naturally

occurring BoHV-1 abortions are usually observed at 4 to 8 months of gestational though experimental virus parenteral inoculation of heifers prior to 3 months induce embryonic death (Miller and Van der Maaten, 1986).

The systemic spread by viremia, BoHV-1 must cross the maternal- fetal barrier to produce lethal infection of the fetus (Owen et al., 1964). The route of BoHV-1 from the placenta to the fetus is unknown but since viral lesions are consistently observed in the fetal liver, haematogenous spread occurs most likely via the umbilical vein. The incubation period between inoculation with BoHV-1 and abortion is 15 to 64 days. Although the lesions are observed both in the placenta and in several fetal organs, it was suggested that placental degeneration would be secondary to the fetal death induced by BoHV-1 As stated above only BoHV-1.1 and BoHV-1.2astrains have been so far associated with abortigenic potential (Miller et al., 1991). Neonatal calves may experience multi- systemic infection following congenital infection prior to birth or early post- natal BoHV-1 infection (Kaashoek et al., 1996).

Excessive salivation and diarrhea are consecutive to BoHV-1 replication in the epithelium of digestive organs that are not common targets for BoHV-1. Several lesions are observed in the digestive tract such as glossitis, esophagitis and acute necrotizing rumenitis. The outcome is fatal within four to five days; calves die in a moribund state. The BoHV-1 genital form is usually transmitted at mating. The names given to the diseases affecting the cow (infectious pustular vulvovaginitis, IPV) and the bull (infectious pustular balanoposthitis, IPB) describe clearly the clinical pictures observed following the primary infection. Although the infection is restricted to the genital organs, more severe infection leading to orchitis in the bull and endometritis in the cow have occasionally been reported (Gibbs and Rweyemamu, 1977).

Diagnosis of infectious bovine rhinotracheitis

Identification of the agent

The virus can be detected from nasal or genital swabs from animals with respiratory signs, vulvovaginitis or balanoposthitis, taken during the acute phase of the infection and in severe cases, from various organs collected at post-mortem by antigen capture ELISA (Collins et al., 1988) and reverse passive Haemagglutination test (Edwards and Gitao, 1987). Following infection, BoHV-1 may persist in infected animals in a latent state in sensory neurons e.g. in the trigeminal or sacral ganglia (Ashbaugh et al., 1997).

The virus can be reactivated and this results in virus shedding (re-excretion) without exhibition of clinical disease (Grom et al., 2006). Therefore, antibody-positive animals have to be classified as infected with BoHV-1 (with two exceptions: serological responses induced by vaccination with an inactivated vaccine or by colostral antibodies). For virus isolation, various cell cultures of bovine origin are used, for example, secondary lung or kidney cells or the Madin–Darby bovine kidney cell line (MDBK) (Mehrotra et al., 1987 and Mehrotra et al., 1994).

The virus produces a cytopathic effect in 2 - 4 days. It is identified by neutralisation or antigen detection methods using monospecific antisera or monoclonal antibodies (Madbouly et al., 2008). BoHV-1 isolates can be further be subtyped by DNA restriction enzyme analysis (RFLP) (Magyar et al., 1993) into subtypes 1.1 and 1.2. BoHV- 1.2 isolates can be further differentiated into 2a and 2b (Metzler et al., 1985). Development of rhinotracheitis or vulvovaginitis and balanoposthitis depends more on the route of infection than on the subtype of the virus.

The virus previously referred to as BoHV-1.3, a neuropathogenic agent, is now classified as BoHV-5. Viral DNA detection methods have been developed and the polymerase chain reaction technique is increasingly used in routine diagnosis including real-time polymerase chain reaction (PCR) (Jain et al., 2009 and Rana et al., 2011). Sachin et al., (2014) described loop-mediated isothermal amplification (LAMP) assay for rapid detection of bovine herpesvirus 1 in bovine semen. On comparison with TaqMan real-time PCR, they claimed that the LAMP assay had a diagnostic sensitivity of 97 %, specificity of 100 %, and accuracy of 99.2 % for detection of BoHV-1 in bovine semen and could be used under field condition.

Serological tests

Several serological tests are available for the detection of antibody and a rise in titre between the acute and convalescent phase of infection. The primary immune response to BHV-1 experimental inoculation of cattle is characterized by the formation of both IgM and IgG antibodies. Secondary immune responses are characterized primarily by the formation of IgG2 antibody. The VNT has been widely used and is the gold standard by which other techniques have been evaluated (Perrin et al., 1996). However, the ELISA is a specific, sensitive, and more practical test for detection of BHV-1 antibodies. A variety of ELISAs, namely indirect ELISA, c-ELISA, and AB-ELISA have been employed to screen serum samples of cattle and buffaloes in India (Nandi et al., 2004, 2007).

The IgM-ELISA is useful for the diagnosis of recent infection with BHV-1 in calves (Suman et al., 2013). Furthermore, a micro-ELISA is being used for the control program of BHV-1 infection in Switzerland. The test is simple, rapid, and convenient compared to the serum neutralization test, which requires cell culture facilities and is time consuming. The only currently available assay that differentiates antibodies against BHV-1 from BHV-5 is a BHV-1 gE blocking ELISA (Wellenberg et al., 2001). Of note, an antibody- ELISA and VNT were successfully employed in yaks and mithuns also (Rajkhowa et al., 2004; Bandyopadhyay et al., 2009)

Differential diagnosis

There are several other diseases that cause similar signs, including lungworm, bacterial and other viral pneumonia, mycoplasma bovis and sunburn (Radostits et al., 2007). Less common diseases like malignant catarrhal fever and some exotic diseases such as foot and mouth disease can also cause similar signs.

Treatment of infectious bovine rhinotracheitis

Specific treatment of the sick animal will vary on a case-by-case basis. If a diagnosis of IBR is made, the veterinary practitioner may advise immediate isolation and vaccination of the sick and 'at-risk' animals with intranasal vaccination to reduce clinical signs and control spread of infection.

There is no treatment (or vaccination) that can remove latent infection from an animal (Muylkens et al., 2007). However, regular vaccination of latently infected animals can help to reduce reactivation and transmission to other cattle. Non-steroidal anti-inflammatory drugs (NSAIDs) are perhaps the most important part of IBR treatment as they minimize the damage to the upper airways and make the affected animals feel better.

Prevention and control of infectious bovine rhinotracheitis

Since IBR does not appear to be a highly contagious disease, separation of sick animals and quarantine regulation may be used as a means to limit further spreading of the disease inside the farms and to prevent the introduction of the infection to the clean areas. However, in order to control the disease more efficiently, besides the above sanitary measures, an immune prophylactic scheme is of absolute necessity. Natural or experimental exposure of cattle to IBR virus results to a very good immunological response which appears soon after recovery and persists for a long period of time. The immunity, in addition to the humoral antibody, in some extent, is related to the "cell mediated and cellular immunity" and to the production of interferon and nasal antibody in infected animals. Immunity against IBR could also be produced by vaccination of cattle with live or killed-virus vaccines (Hazrati, 1977).

Prevention of IBR by modified live-virus vaccine has been outstandingly successful since it was first practiced in 1957 (Chwarz et al., 1957). Modification of the virus has been achieved through successive passaging of IBR virus in calf kidney, rabbit kidney, dog kidney, and swine kidney cell cultures by several workers (Saunders et al., 1972). Vaccine is given by intramuscular inoculation or by intranasal administration. Nasal administration of the vaccine has the advantage of stimulating the secretory immune system in the respiratory tract of cattle to produce nasal Interferon and antibody much better than the vaccine inoculated intramuscularly. The immunity following nasal administration of modified live-virus vaccine appears within 48 to 72 hours after administration of the vaccine.

Live-virus vaccine, regardless of the route of administration has the dis- advantage of causing a high rate of abortion, up to 70 percent, especially in cows from 5th through 7th month of gestation (Kahrs et al., 1973). Each kind of vaccine, however, has its own particular advantage and could be used, depending on the circumstances involves, for the control of IBR as follows (Hazrati, 1977):1) Live-virus vaccine is recommended for vaccination of calves in feed- lots. Vaccine could be administered either nasally or intramuscularly. Vaccination by intramuscular route can be carried out with much more simplicity and

accuracy, and thus it appears to be the route of choice under ordinary conditions. In some situation, e.g. during an outbreak of IBR among animals in feedlot or neighboring farms, when an early immunity is desirable, vaccination via intranasal is strongly recommended. 2) When calves have to be immunized while nursing their susceptible pregnant dams, nasal vaccination must be avoided as this may results in infection of the cows and possible abortion. On the other hand, nasally administration of the vaccine is preferable in the case of young calves of 4 to 6 monthold, whose passively acquired nasal antibody has been declined but still possess circulation antibody, as only in this way the vaccine could stimulate the production of antibody without the interference of circulating antibody. 3) In dairy farms cows must be vaccinated before pregnancy. In emergency situation, however, susceptible unvaccinated pregnant cows could be with killed-virus vaccinated а vaccine. as administration of live virus vaccines may result to a high rate of abortion.

IBR status in Ethiopia

In a study, the disease sero-status was relatively lower than the reports of Córdova-Izquierdo et al., (2007) who found 90% prevalence in humid tropics of Mexico and 93.75% in Egypt from cattle imported from Sudan. Yet, no vaccination for IBR in Ethiopia has been delivered. The wide distribution and high sero-prevalence of BoHV-1 in Ethiopia had been a strong indicator that the virus was circulating in indigenous cattle's in the areas.

Thus, there might be a large pool of latently infected cattle that could potentially serve as a source of infection for other animals, as infected cattle are considered to be infected for life (Muylkens et al., 2007)

Therefore, control and prevention of the disease were indicated through the use of vaccinations, preferably using marker vaccines until the prevalence of the disease would be decreased to the level where test and culling could be considered as an alternative (Constable et al., 2017). Based on geographical location, the study areas were significantly associated (P<0.001) with seroprevalence of BoHV-1 infection. This heterogeneity may be related to the density of cattle's in each rural district; differences in prevalence between districts and by factors such as herd size, disease control measures, type of breeding and age of the animal (McDermot et al., 1997).

Conclusions

Herpesviruses comprise the family Herpesviridae. Varicelloviruses are the causative organism of the disease IBR which infects both wild and domestic animals, Beef and dairy cattle feedlots are significantly affected by infectious bovine rhinotracheitis. A variety of ELISAs, namely indirect ELISA, c-ELISA, and AB-ELISA have been employed to screen serum samples of cattle and buffaloes in India. In Ethiopia, no vaccinations for IBR have been administered. Several studies have indicated that BoHV-1 is widely distributed and has a high sero-prevalence in Ethiopian cattle. However, serious diagnosis and preventive measures with reference to Ethiopean conditions are needed to control the IBR and the associated economic loss.

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