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Review Article

Review on Epidemiological Distribution of Bovine Viral Diarrhea (BVD) in Ethiopia

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Abstract

Bovine viral diarrhea virus(BVDV) is an infectious and contagious agent of cattle which cause high economic losses because of decline in production performance and it may also result in mortality. The disease is caused by Bovine viral diarrhea virus (BVDV) a member of the *Pestivirus* genus within the family *Flaviviridae* and there is no known health risk to humans from this virus. It causes diarrhea, anorexia, pyrexia, oral erosion, abortion, congenital defects, poor growth, depression, fever, immunesuppression and death in animals. Animals which persistantly infected (PI) can harbor this virus for all of their life and shed it without any clinical sign. The diagnostic approaches used to detect BVDV infections are the detection of viral components (direct tests) and detection of immune response to BVDV (indirect tests). PI animal elimination can highly mitigate the spread of the virus and control strategy which includes vaccination and strict prevention of the introduction of BVDV in previously uninfected herds. BVDV has huge impact on dairy industry by high economic losses due to decline in performance and mortality of animals and considered as a serious threat to the livestock production worldwide. The major strategies for prevention and control of this virus include isolating new animals before introducing them to the herds, culling repeat breeders, elimination of persistently infected (PI) animals, enhanced immunity through vaccination, and implementation of insecurity measures.

Keywords: Bovine Viral Diarrhea; Epidemiology; Ethiopia; Mucosal Disease; Persistantly Infected; *Pestivirus*

Abbreviations

BVDV: Bovine Viral Diarrhea Virus; PI: Persistently Infected (PI); CP: Cytopathogenic; NC: Con-Cytopathogenic; NSP: Non-Structural Protein; SP: Structural Protein; RTPCR: Real Time PCR; ELISA: Enzyme Linked Immunosorbent Assay; AGID: Agarose Gel Immune Diffusion; SNT: Serum Neutralization test; RNA: Ribonucleic Acid

Introduction

Bovine viral diarrhea virus is a contagious and infectious agent of cattle which cause high economic losses due to decline in performance and mortality of animals and considered as a serious threat to the livestock production worldwide [1]. Even if the primary host are Cattle *Pestvirus* infectionn has been reported in different animal such as: Sheep, Pigs, Goats, Giraffe and Kudu. Although there is no known health risk to humans from the BVD virus, it is one of the most significant cattle diseases because of its broad nature, transition and lack of treatment [2]. It causes diarrhea, anorexia, pyrexia, oral erosion, abortion, congenital defects, poor growth, depression, fever, immune-suppression and death [3]. Because of this virus immune-suppressive capacity, it is direct effect on respiratory system and fertility BVD infection may shows a wide variety of clinical symptoms [4]. Additionally, susceptible mother infected by BVD at the time of pregnancy may result in giving a persistently infected (PI) fetus. BVD virus is the causative agent which belongs genus *Pestivirus* the family *Flaviviridae* [5].

Animals which persistantly infected (PI) can spread by contact through nose-to-nose and harbor this virus for all of their life and shed it without any clinical sign and without showing any immune

response. The problem for transmission for BVD as a disease is recognition of these viral particles as self by host animal body and this will result in shedding of this virus by large quantities throughout life of the animal [6].

PI animal elimination can highly mitigate the spread of the virus and control strategy which includes vaccination and strict prevention of the introduction of BVDV in previously uninfected herds [8]. This virus can also transmit through indirect routes or through contaminated equipment and insemination semen infected with BVD [7].

The best way to control, prevent the transmission and reducing the effects of BVDV infection on herd and productivity is the knowledge of risks BVDV infection which are mainly environmental factors and best understanding of herd management [9]. Understanding the distribution, epidemiology, transmission and the role of PI animals in transmission of BVD is important in planning and designing appropriate disease control strategies. Therefore, the objectives of this review are to review on BVD transmission, epidemiology, prevention and control and the current status of the disease in Ethiopia.

The nature of the bovine viral diarrhea disease

This disease is of a disease of ruminants mainly cattle and it is caused by the virus called bovine viral diarrhea virus. These viruses are very small infectious agent. Persistently Infected (PI) cattle shed high levels of the virus continually through all their life. The infective dose for calves much is less than 500 virus particles [10].

BVDV infection is globally distributed and considered as endemic in many countries in the world. Infections of BVDV can expressed as immune suppression, fertility problem in both sex of cattle and other different types of signs which include respiratory related problems, fever and diarrhea were also observed. This leads to serious financial losses in the livestock production because of lower reproductive performance, decrease milk production and weigh, increased death rate, early culling and different cost for treatment [11].

Biology and structure of the virus

BVDV RNA virus which is a member of family *Flaviviridae*, belonging to the genus Pestvirus. The viruses of *Pestivirus* genus are spherical, single stranded, positive sense, small and enveloped RNA virus [49]. Persistent infection in cells can induced by Non cytopathogenic viruses and has an intact NS2/3 protein. Either NS2/3 protein is cleaved to NS2 and NS3 or there is a duplication of viral RNA containing an additional NS3 region in the case of cytopathogenic viruses [12].

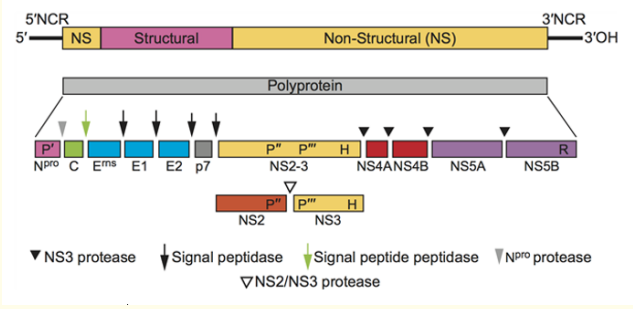

Figure 1: Genome of pestivirus. The genome has a single open reading frame (ORF) flanked by two un-translated regions (UTR): 5'-Npro, C, Erns, E1, E2, p7, NS2-3, NS4A, NS4B, NS5A and NS5B-3 [18].

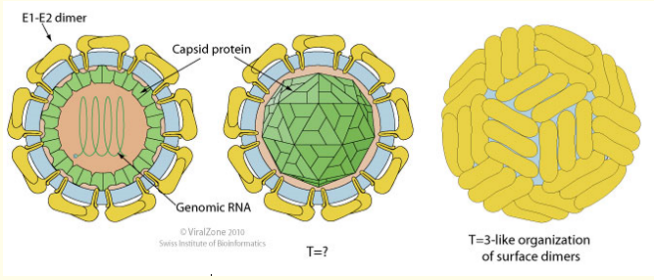

Figure 2: In addition to the enveloped capsid protein, mature virions contain three virus-encoded membrane proteins (Erns, E1 and E2) [13].

BVDV-1 and BVDV-2 are two different genotypes with several sub-genotypes. There are considerable antigenic differences in the two genotypes from each other and within species. Depending on their effect on tissue culture cells biotypes of BVDV are cytopathogenic (CP) and non-cytopathogenic (NCP) strains. The cytopathogenic strains will cause vacuolization and cell death [14]. There are two BVDV genotypes according to nucleotide sequence of the 5'untranslated (UTR) region. Isolates of BVDV-1 grouped into 16 subtypes (a-p) and BVDV-2 grouped into 3 subtypes (a-c) [15]. The

majority infection causes by BVDV are due to non-cytopathogenic (NCP) biotype.

Host range

Bovine viral diarrhea is endemic and widely distributed in all parts of the world in the wide range of host. *Pestiviruses* are a group of viruses of veterinary importance infecting livestock animals like pigs, cattle, and sheep, and also wildlife animals like wild boar and different deer species (15). The natural host for the type species of *Pestiviruses are* Cattle, but infection by BVDV has been demonstrated innumerous other species of animals [16]. Persistent infection with BVDV is demonstrated in alpacas, mouse deer, mountain goats, sheep, and goats. In persistently infected sheep and mountain goats Virus distribution among tissues is similar to that seen in cattle [17].

Transmission

BVDV transmission occurs both vertically and horizontally with both transiently and persistently infected animals excreting infectious virus. This virus can being able to persist in the environment for more than two weeks and transmitted through contact, secretions and fomites which are contaminated [6].

Persistently infected animals shed virus in all excretions and secretions such as dung, urine, milk and colostrum, saliva and discharges from the eyes, nose and reproductive tract. Movement of these substances between farms or equipment contaminated by the virus is another potential source of transferring and introducing the virus. Cleaning and disinfecting all such items should be thoroughly to minimize the risk of transmission [18].

Prevalence of PI animals, animal-to-animal contact rates, virulence of the virus strain(s), and the susceptibility of cattle to new and indigenous strains in the herd are the four determinants that are thought to be important for the BVD is transmission [19] either through a congenital infection of the fetus or after birth. Stillbirth, or live-birth, abortion and resorption may caused by congenital infections. Fetuses may be born as BVDV infected calves if congenitally infected and survived in utero infection. Infection in this case will occur through the all life of calves and shedding this virus in environment of the farm is continuous [20].

As shown on the this figure BVDV transmission in susceptible dam is principally maintained by persistently infected (PI) calves, but also transiently infected animals can spread the virus. PI calves are congenitally infected (vertical transmission) with BVDV and continuously shed the virus. Transiently infected animals result from acute, postnatal BVDV infections (horizontal transmission). Transiently infected animals in early gestation can give birth to new PI animals [50].

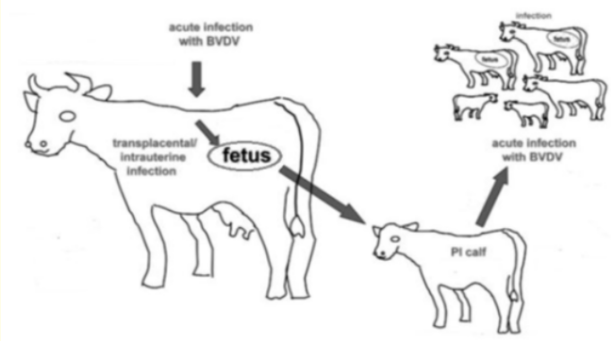

Figure 3: Vertical and horizontal transmission BVDV transmission.

Host-pathogen interaction

BVDV type 1 and BVDV type 2 are identified as distinct species within this genus, with further classifications CP and NCP based genetic differences and *in vitro* cell culture characteristics [21]. Genotype 1 is reportedly the most prevalent genotype and considered the *Pestivirus*-type species. Among some strains of BVDV there is evidence of immunologic cross-protection, including different genotypes. Between isolates and genotypes of BVDV there is also incomplete immunologic cross-protection. There is no difference in the frequency of respiratory or enteric disease (or both) between genotypes 1 and 2 as demonstrated by studies [22].

Infection of fetal by BVDV may result in immune tolerance and lifelong persistent infection [21]. PI cattle with BVDV were considered immune tolerant based on the fact they were sero-negative for BVDV. It has been shown that persistent infection does not result from cytopathogenic BVDV infection; rather, infection with non-cytopathogenic BVDV in early gestation will cause persistent infection. With widespread lesions of the alimentary mucosal surfaces and lymphoid tissues, referred to as mucosal disease (MD) persistently infected animals can develop severe disease. Mucosal disease is the result of persistent infection with a non-cytopathogenic strain of BVDV followed by subsequent postnatal infection

with a cytopathogenic strain of homologous virus. Homologous cytopathogenic BVDV in an animal persistently infected with NCP BVDV is thought to be the result of mutation of that non-cytopathogenic BVDV [23].

At the time of BVDV transplacental infection there is no well developed immunity in persistently infected animals. The virus considered as self after entered the fetal cells during immunity cell growth. The virus load remains in cell of animal's body in it is entire life and shedding continues. Even if they can look normal, persistently infected animals are usually ill-thrifty and smaller than others [24].

If the fetus is infected with a non-cytopathic strain of this virus prior to 125 days of pregnancy time persistence infection may appear [25]. Mucosal disease which is invariably fatal is only developing in persistently infected animals [26]. Mucosal disease can be experimentally induced via super infection with a CP strain that is antigenically homologous to the persisting NCP strain [27] or naturally transmitted between PI animals that are PI with the same homologous NCP BVDV isolates. All CP biotypes produce the non-structural (NS) proteinNS3, whereas in NCP biotypes only the uncleaved forms NS2/3 can be detected. Prior to spreading to GIT epithelium this virus is localizes in the germinal part of lymph nodes, GIT related lymphoid tissue of Peyer's patches and tonsils [27]. Cytopathogenic BVDV inhibit Ag presentation to T cells and in opposite monocyte differentiation and activation promotion may take place. This will result in uncontrolled inflammation, increased viraemia and impairing antiviral protections [28].

Intrauterine infections

The most consequence for birth of persistently infected calves by this virus is intrauterine Infections of fetus. Stage of pregnancy at which the mother infected acutely with this virus decides the effects of infection on the fetal. Delayed conception may occur due to BVDV infection of mother before conception and in the first 18 day period of pregnancy [29]. Infection and death of embryo may happen from infection with BVDV once the embryo is attached (29 - 41 days). Immune tolerance and birth of persistently infected calves with this virus may result from infection of mother during gestation period from about day 30 - 120 can result [30].

Infection BVDV around day 80 to 150 can be teratogenic and depending on the stage of infestation of developing fetus during pregnancy abortion can happen at any time.

Birth of normal calves can result from infection of gestation period post 120 days in which the animals are antibody positive and antigen negative for BVD. This is because the immune system of the fetal has developed, after 120 day gestation, and has the ability to recognize and fight off this virus and result in producing anti-BVD antibodies [31].

HPI based on the course of the disease

Viral replication occurs in epithelial cells, after viral entered and contacted with mouth and nose mucosal lining. This virus replication has a predilection for the lymphoid tissues, tonsils and oropharynx epithelium [32]. After taking up this virus or cells infected with this virus, phagocytes transport them to peripheral lymphoid tissues and the virus can also spread with the bloodstream. Since viraemia may happen about days 2 - 4 after infection, isolation of virus from serum or leukocytes is possible between from between day 3 and 10 days [33].

Diagnosis of BVDV

For the diagnosis of active infection with virus or previous evidence for infection there are various diagnostic tests. Depending upon whether investigation is for individual or herd different types of diagnosis method can be used. Diagnostic testing is important for producers to identify persistently infected animals and cull them from the herd, because persistently infected animal look normal. The highly sensitive diagnostic method for timely identification of persistently infected animals is PCR, so producers can remove these animals as early as possible. Since calves may have high amount of maternal antibody titers to this virus, due to ingestion of colostrum identification of BVDV in calves depending only on the antibody detection methods can be complex [7]. The binding of antibodies gained from dam to the virus and inhibit its identification in this type of test is called shielding. PCR methods of detection use blood samples or samples from tissue of animals and can be finished in a short time period and result can also highly accurate. In the case of screening of milk from bulk collection, diagnosis of infection of large group of animal with this virus and for strategic eradication campaign antibody detection methods can be used [34].

Detection of virus or antigen

Currently, Real time PCR and Indirect ELISA are the mostly performed tests to detect viral antigen. Testing again and again must be carried on samples which are positive to identify animals which

on course of acute and chronic dieses with the virus [7]. If the animal is persistently infected animal, positive test result must be found after three weeks since the primary test result [37]. Type I and type II of this virus can be detected by Real time PCR by primers which are specific to them [38,39].

The Antigen ELISA used for diagnosis of persistently infected animals and important for screening herd at herd level. It is one of simplest; less costly and rapid test method. Various samples, such as serum, milk and ear notches for use with, multiple BVDV Ag ELISAs now available commercially [34,36].

Immunohistochemistry is another most famous method of BVDV antigen detection in the USA and has been confirmed to detect persistently infected animals with very accurate sensitivity when used on tissue samples. But, it faces disadvantages as it is limited to sample from tissue, is sensitive to technical error, is laborious, relies on a subjective scoring method, requires experienced personnel and is unreliable for use on samples stored in formalin for more than 15 days [40].

BVD antibody detection

There are several antibody detection methods which are a simple, inexpensive, reliable and rapid including dot-blot enzyme immunoassay [41] an agarose gel immune diffusion (AGID) test [26] and a microsphere based immune assay. Serum Neutralization test (SNT) and the Ab ELISA are the most common methods for detecting specific Abs to BVD virus. Even if, it is expensive and time consuming due to a need for tissue culture, the Neutralization test is a highly specific test. SNT is based on inhibition of viral replication by Abs present in a serum sample, but it may have variable results between different laboratories because of the use of different strains or cell types [34,35]. For determining herd immunity testing Bulk Milk test can be a very important, beneficiary and less costly method [42].

Status of BVDV in Ethiopia

In Ethiopia 9.59% prevalence was reported as first serological evidence of BVD virus [43]. Later on 11.7% [44] BVDV exposure evidence was reported among dairy cattle in central and southern Ethiopia, then recently 32.9% occurrence indicated by [45] in Ethiopian dairy farm by using ELISA, 32.6% prevalence was reported by [46] and estimated individual level seroprevalence (51.7%) was the highest result yet reported in Ethiopian cattle in Jimma town [47] respectively. Table 1 elaborate prevalence status in ethiopia.

S.N	Animal Individual prevalence	Region	Source
1	51.7%	Jimma town	[47]
2	9.59%	Jimma zone	[43]
3	11.7%	Central and southern ethiopia	[44]
4	32.9%	Ethiopia	[45]
5	32.6%	Ethiopia	[46]

Table 1: Prevalence of BVD in Ethiopia.

Control and preventions

By using well integrated elimination of persistently infected animals, strategic vaccination and well practiced biosecurity control can successfully achieved. Vaccination a crucial strategy used for control and eradication of BVD virus. High-quality colostrums and strategic vaccination could also decrease the proportion of susceptible cattle to this virus. The two categories of vaccines are live and killed vaccines. Live virus vaccines require only single dose at the first immunization period. Live virus vaccines are very difficult to store and handling. Killed virus vaccines are cost and several doses are must to given for immunization. Killed vaccines are not sensitive high temperature, and they are highly inert to different chemicals. Identification and elimination of PI is the mainstay of eradication [34,48].

To minimize BVD Virus transmission, the most important thing is infected animal needs to be removed to prevent contact with other animals. Making infected cattle less infectious is one the best of strategy to minimize BVD Virus transmission and increasing antibody titer can be used achieved this strategy. Therefore, it is must for producers to remove persistently infected animals from the herd on the farm [19]. Three best options recommended are: 1) euthanize humane ways, 2) sell to a slaughter only to the market, 3) isolate and rise for slaughter [48].

Conclusion and Recommendation

Through an understanding of the epidemiology of BVDV infection, the impact of the disease decreased production, reduced reproductive rate and increased occurrence of other diseases may be

minimized or eliminated through control or eradication. Primarily, BVD control programs aim to eradicate the virus by eliminating the main source of viral spread PI individuals. Clear understanding available diagnostic methods and their Individual strengths and weaknesses allows this to be carried out, both time and cost-efficiently. Once eradication is complete, it is must to put necessary measures in place that maintain freedom from BVD virus which may includes a integrated protective strategy such as increasing well practiced biosecurity, including diagnosing of new animals before introducing in to herd and strategic vaccination. Therefore, Continuous monitoring should be practiced and important prevention and control approaches should be taken based on the findings. Farmers and owners of dairy farm need to isolate animals before introducing to their farms, eliminate repeat breeder and aged animals from herds. PI animals must be identified to control the transmission as it is the main source of infection and Vaccine must be used by introducing appropriate vaccine type in Ethiopia.

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