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Review Article

Epidemiology of Bovine Viral Diarrhea Virus (BVDV) Infection in Dairy Cattle Herds- Iran from 2000 to 2020

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Abstract

Bovine Viral Diarrhea Virus (BVDV), which is prevalent in cattle, is the causative agent of one of the most economically important animal diseases. This infection poses a significant challenge to the cattle industry. Several studies have indicated the high prevalence of BVD virus in Iran. As there is no specific treatment for this infection, the best way to overcome the disease is the use of control and prevention strategies such as vaccination. Due to the high prevalence of BVDV in Iran, there is always the question of how to implement a program to address this challenge in order to reduce economic losses. This study aimed to present the analysis of BVDV epidemiological studies in Iran.

Keywords: Bovine viral diarrhea virus, BVDV, Cattle, Vaccine, Iran

Introduction

Bovine viral diarrhea virus (BVDV), the etiological agent of bovine viral diarrhea/ mucosal disease (BVD-MD), is widespread in cattle as one of the most economically significant bovine diseases (1). BVD virus was first identified in the United States in 1946 during an epidemic, which caused diarrhea, erosive injuries, and mortality (2). A deadly infection called Mucosal Disease (MD) was also caused by the same virus in 1956 (3). Serological and immunological studies on the cattle contaminated with BVD-MD have shown that different strains of similar virus were the causative agents (4). Identifying the prevalence of an infection in a population is the most important phase in designing a control plan. This study aimed to collect reports on the incidence of BVDV infection over the tow past decades to determine the disease prevalence rate in dairy cattle in different provinces of Iran.

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Viral structure

Bovine viral diarrhea virus (BVDV), along with classical swine fever virus (CSFV), border disease virus (BDV) of sheep, HoBi-like viruses, and wild ungulate pestiviruses belong to the genus Pestivirus of the *Flaviviridae* family (5). All members of the genus Pestivirus are closely related in terms of antigenicity, but there is no significant relationship between different genera of the family (6,7,8). BVDV is a small enveloped virus with a positive-sense single-stranded RNA genome of approximately 12.5 kb in length, consisting of a 5'-untranslated region (5'-UTR), a single long open reading frame (ORF), and a 3'-untranslated region (3'-UTR) (9). The single open reading frame of the virus encodes a long polypeptide of 3,897 amino acids. This polypeptide is then processed by viral and cellular (host) proteases into the individual viral proteins (10). The virus encodes twelve proteins, including four structural (Capsid, E^{erns}, E1 and E2) and eight nonstructural (Npro, p7, NS2, NS3, NS4a, NS4b, NS5a and NS5b) proteins, at the 5' and 3' ends, respectively (11).

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To date BVDV isolates have been divided into two species (BVDV-1 and BVDV-2). BVDV-2 has been classified into 4 subgenotypes according to the 5'-UTR, Npro, and E2 sequences (12).

Bovine viral diarrhea infection

BVDV infection poses a significant challenge to the cattle industry. The disease was called BVD when occurred in the cattle over 2 years old (13). The clinical symptoms associated with BVDV infections could vary from clinically inapparent to severe, including diarrhea, respiratory problems, reduced fertility, abortion, congenital defects, and growth retardation, which could eventually lead to the cattle fatality. Also, 70-90% of BVD infections have been reported to be subclinical (14). According to their ability to induce cytopathogenicity in cell culture, BVD virus has been divided to 3 biotypes: non-cytopathic (NCP) and cytopathic (CP) and the 3rd biotype can effect on Lymphadentic tissue.

The major molecular difference between CP and NCP biotypes is the differential expression of NS3, formerly named as p80 (15). Both NS2-3 and NS3 are expressed by cp BVDVs, while NCP BVDVs express only NS2-3 (or p125) polypeptide (16). Several mechanisms have been suggested for the expression of NS3 by cp BVDVs, including insertion of cellular RNA sequences in NS2-3 near the boundary between NS2 and NS3, downstream duplication of the NS3 gene, expression of NS3 from a defective RNA genome, point mutations in the NS2-3 gene, and insertion of cellular sequences plus viral gene duplications in the N-terminus of the polyprotein (17). The fatal mucosal disease (MD) in persistently infected (PI) animals is caused by NCP biotype. The vast majority of BVDV field isolates do not induce cytopathogenicity in cell culture.

The NCP BVDV infections between 45-125 days old could lead to PI because during this period, the fetal immune system is immature, the viral proteins act as self-antigen, and the cattle becomes PI and immunotolerant to BVDV strains, leading to viral replication in all body compartments and viral shedding throughout the whole animal life (18). Therefore, PI cattle could be considered as the most important source and the main transmission route of BVDV infection among herds (19). The interaction of BVDV with secondary pathogens is thought to be one of the factors contributing to the development of bovine respiratory disease complex (BRD) (20).

Epidemiology

In this review, only the studies investigating the prevalence of BVD in the past 20 years were reviewed with respect to the widespread distribution of BVDV infection in Iran. As shown in majority of the studies, BVDV was detected using immunoassay. Iranian cattle herds are among the most populated cattle herds in the Middle East. Iran has experienced several BVD epidemics so far because of its proximity to BVD-infected countries. In Iran, the disease was first reported in Isfahan, Kerman, and some regions of Khorasan province in 1970 (21).

The prevalence of BVDV infection among Iranian slaughterhouses has been reported between 16-69% by neutralization testing of collected blood samples (21,22). In a study by Hazrati et al., the disease causative agent was isolated from cows in two livestock units in Karaj, which were bought from the United Kingdom (23).

Holstein cows without a history of BVDV vaccination were examined in a study by Badiei and colleagues in 2010. The prevalence of the disease was determined as 52.43 % using the immunoassay method, indicating a relatively high exposure of dairy cattle herds to BVDV in the suburbs of Shiraz, Iran. A positive correlation was found between BVDV infection and age (62.5% in cows over 2 years old). The prevalence of BVDV in four geographical regions of Shiraz was determined in their study, including north (32.6%), west (26.6%), east (13.9%), and south (27%). Also, no significant association was found between the herd size and BVDV seropositivity in animals. Regarding the correlation between milk production level and BVD infection, the number of seropositive animals

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was higher in milk-producing group (44.3%) (24).

Sharifzadeh et al., found a considerable amount of BVDV genomes (18.60%) in bull semen specimens collected for the artificial insemination using RT-PCR analysis. They showed this viral agent was able to signify-cantly decrease milk production and repro-ductive efficiency as well as to increase the incidence of co-infection with other agents in cows (25).

In another study conducted by Hashemi Tabar et al., (2011), 74.17% of cows with a history of abortion were identified to be BVDV sero-positive compared to other cows with no history of abortion (66.66%); however, no significant difference was observed between the two groups in terms of seropositivity (P=0.41) (26).

In another study, 155 Holstein cows' blood samples were collected from 18 dairy cattle herds in Mashhad by Garoussi et al (4). In their study, the prevalence rate of BVD virus was estimated as 3.18% (26).

Out of 2205 blood samples collected from 59 industrial cattle farms in Qazvin province by Bahonar et al., in 2011, 1644 cases were seropositive, and 561 cases were seronegative for BVDV infection (27). In Abik, Alborz, and Buin Zahra, the prevalence rate of BVD infection was reported as 76.2, 83.2, and 59.6 %, respectively. In addition, the association between the history of abortion and BVDV seropositivity was stated to be significant (P=0.0005). Rezaeisaber et al., (2011) showed that BVDV seroprevalence in Sarabian dairy cows was 30% (28). In this study, a substan-tial difference was found between the preg-nant (17.8%) and non-pregnant animals (43.6%) regarding the prevalence of BVDV infection, which was higher in non-pregnant animals (P<0.05) (28).

In the first study investigating the prevalence of BVDV infection in 65 industrial dairy herds in Kerman as the biggest province of Iran, Khalili et al., (2012) showed that 58.4% of the industrial dairy herds were infected by BVDV (29).

In 2012, Roshtkhari et al., estimated a sero-positivity rate of 57.1% among 42 blood samples collected from cattle with no history of BVDV vaccination in Mashhad, Khorasan Razavi province. Also, no significant associa-tion was found between the size of the herd and BVDV infection (30).

Shirvani et al., (2012) surveyed a total of 642 cows blood samples collected from industrial (48.9%) and semi-industrial (53.3%) cattle in Esfahan province, Iran. They identified age as a risk factor for BVDV infection and showed that the prevalence of BVDV was higher in older cows (>4 years old) (56.1%) compared to the younger cows (<1 year old) (49.1%). The epidemiological analysis of mixed viral infections in these herds showed the possibi-lity of co-occurrence of BVDV infection with BAV-3 and BRSV (4.4%), and BPI-3V and BAV-3 (1.9%), but not BPI-3V and BRSV (0.0%) (31).

In 2013, Farjani Kish and colleagues perform-ed a seroepidemiological analysis on BVDV infection in dairy herds in Fars province. According to the results, 4% (16 out of 400 samples tested) were found to be positive. The most positive cases were less than 2 years old (P=0.3) (32).

Ghaemmaghami et al., (2013) conducted a serological study on 803 serum samples collected from 12 non-vaccinated herds in Arak, using indirect ELISA. The estimated infection prevalence rate was 54.3% (436 out of 803 samples tested). They also showed that all the herds were BVDV seropositive. This high level of BVDV infection in the herds showed that this infection was widespread in dairy herds in this area (33).

In 2014, Mokhtari reported a prevalence rate of 1.06% for BVDV infection in cattle in industrial dairy farms of Isfahan and Chahar-mahal and Bakhtiari provinces. The serolo-gical tests showed that BVD coexisted with viral Infection Bovine Rhinotracheitis so that out of 1800 blood samples, 19 (1.06%) were BVDV positive, and 10 (0.55%) were BIV positive, of which 9 (9 of 10, 0.5%) were BVDV-BIV positive (34).

The anti-BVDV IgG prevalence of 50.7 % in Chaharmahal and Bakhtiari, 55.3% in Khora-san, 74% in Semnan, and 89% in Sistan and Baluchestan was reported by Nikbakht et al.,

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(2015). This study indicated a positive association between BVDV and Bovine Herpes Virus seropositivity (P<0.01), highlighting the significance of co-infection of BVDV and BoHV1 (26.2%) as an epidemiological factor, compared to BVDV and Bovine Leukosis Virus (12.1%) (35).

In an investigation on dairy population in Fars province, Khodakaram et al., reported BVDV infection at least 4% in 2016 (36).

The seroprevalence of BVDV was estimated as 62.6% in Holstein, 66% in Sistani, and 72.85% in Afghani breeds in a research carried out by Abbasi et al., (2016) in Sistan and Baluchistan province. No noticeable association was found between the prevalence of BVDV and animals sex or breed. Similar to Badiei study, a positive relationship was found between the age and BVDV seropositivity in animals (74.1% in > 2 years old compared to 48.78% in < 2 years old) (37).

Erfani et al., (2019) collected 562 blood samples in Zanjan through a random selection of 10 dairy herds in 2018. The prevalence of antibodies against BVDV was registered as 28.6%. This study results also showed a high-level of seroprevalence for BVDV in the herds (90%), which is consistent with those reported by Ghaemmaghami in 2013. Also, a significant association was found between BVDV infection and breed (P<0.001), sex (P<0.05), and age (P<0.05); the disease was more prevalent in the cattle over 2 years old (54.45%) compared to the younger ones (27.12%), as well as in the crossbreeds (48.32%) compared to the exotic breeds (16.50%) (38). Garoussi et al. (2019) reported an estimated rate of 98.57 % (138 out of 140 tested samples) for BVD seropositivity in 11 industrial dairy herds in Mashhad (39).

Also, the seroprevalence of BVDV in a total of 216 blood samples collected from dairy cattle in Esfahan by Noaman and Nabinejad (2020) was reported as 52.8% using ELISA (40). Figure 1 demonstrates the prevalence of BVDV infection, reported in different studies conducted in various parts of Iran. This figure was provided by the analysis conducted by the authors.

BVDV Vaccination

Bovine viral diarrhea is one of the most important diseases responsible for the major economic losses in the Iranian dairy industry. Since BVD infection has no specific treatment, the best way to overcome the disease is the use of control and prevention strategies. Vaccination services are important tools to reduce BVDV-associated economic losses. More than half a century has passed since the first vaccine production for this disease, but many doubts remain about its effectiveness and efficiency (19). Several studies have been conducted with the aim of confirming the efficiency of the vaccines manufactured by different companies (19).

Coggins et al., (1960) discovered the first modified live vaccine against the disease (strain Oregon C24v) (41). Two types of available vaccines are inactivated (NY-1 strain) and modified live vaccines (MLV).

In addition, further MLVs in conjunction with other agents were introduced by the other researchers (13). Most forms of MLVs are cytopathic BVDV, which induce both humoral and cellular immunities (10). The effectiveness of these vaccines depends on age, average milk production, pre-vaccination antibody titers, and different stages of pregnancy (1).

The use of MLVs during the first six months of pregnancy is not recommended due to the possibility of inducing immunosuppressive effects or intrauterine infection in pregnant animals. While it is possible to inject killed vaccines without side effects at any age and even during pregnancy, they induce weaker immune response than MLVs. Neither MLV nor inactivated vaccines provide continuous protection, and both require annual boosters (3,22).

Based on the above studies, the prevalence of BVDV infection has been high in various provinces of Iran in the last decade. Some attempts have been made in recent years to import BVD vaccines in order to avoid or reduce the disease harmful effects (22).

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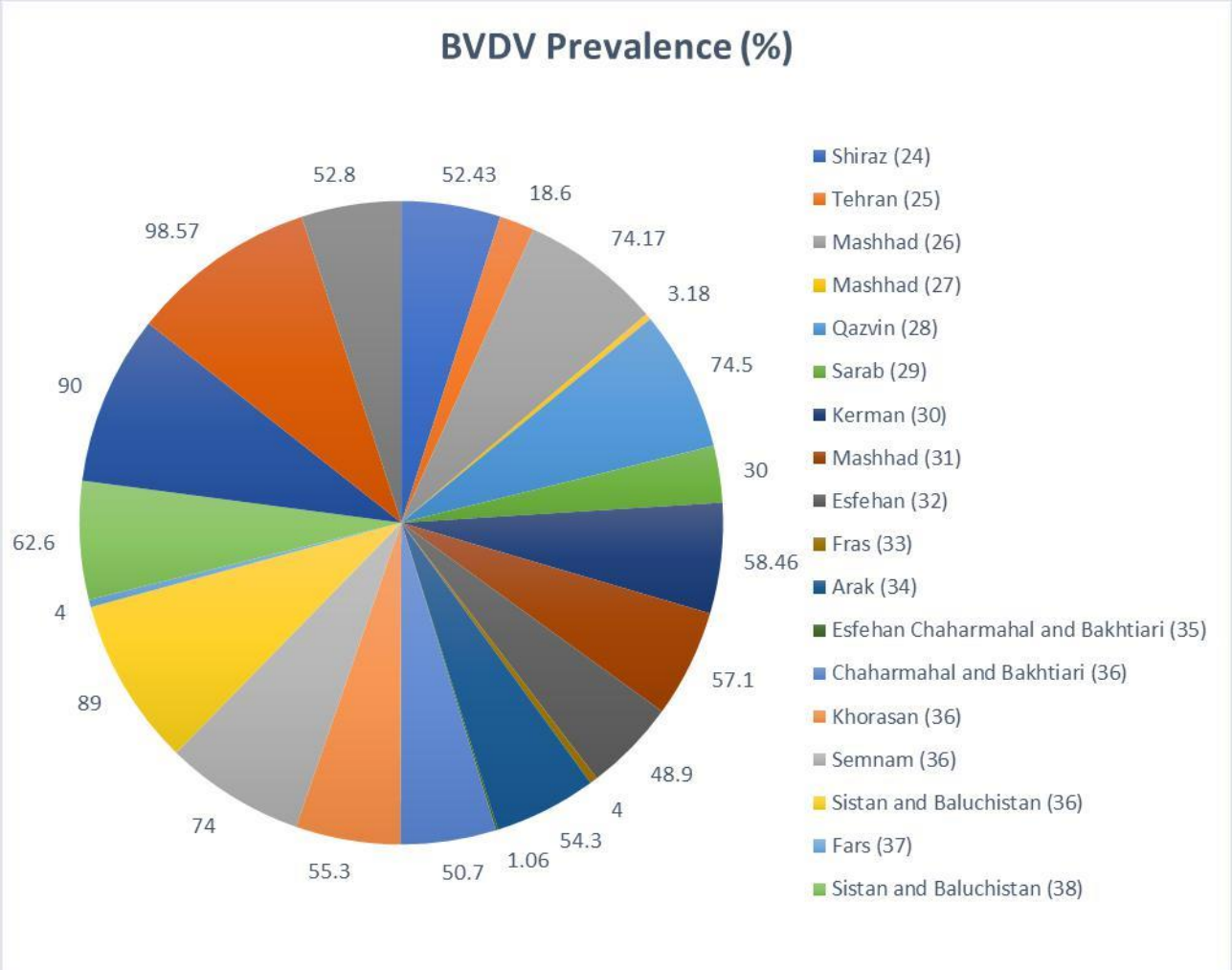

Fig. 1. Prevalence of BVDV infection reported in different studies conducted in various parts of Iran. The numbers indicate the references.

The efficacy of an imported inactivated BVD vaccine (Bovilis) containing the cytopathic strain C86 was investigated in a study on a high-yield dairy farm cattle by Raoofi et al., (2013). Their study results showed that the use of imported vaccines was effective and could be considered as one of the key means of controlling the disease in our country (42). It is important to note that the dairy cattle breeding system in Iran is different from the conditions in Europe. The centralized herd management system in Iran is more similar to the cattle herd conditions in North America. According to the results of antibody detection in serum or milk, European countries have a higher prevalence of PI compared to the North America, which is due to the use of a pasture-dependent breeding system in Europe (43,44,45).

The use of inactivated BVD vaccine is the first choice in Europe in order to control BVDV infection. Therefore, the polyvalent nature of American vaccines is one of the points that should be considered (46,47).

Several studies have been performed to determine the efficacy of BVD vaccine (Bovilis) in inducing protection against the production of PI calves after acute virus-controlled challenges (42). It should be noted that both BVDV1 and BVDV2 genotypes have been isolated from PI cases in Iran (48). Although vaccines in the United States provide cross-protection against both genotypes, BVD vaccine (Bovilis) producers claim that in order to induce fetal protection against BVDV genotype 2, given the situation in Iran, inactivated monovalent vaccine that could be used during pregnancy, is the best option for the vaccination against BVD (42,48).

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Conclusion

The variations in the distribution pattern of BVDV infection in different countries and even in different regions of a country could be related to the mean age of herd, environmental variability, herd size, and the presence of PI animals. In addition, fast transmission, high antibody prevalence, BVDV irregular distribution patterns, the incidence of asymptomatic infections, and the presence of PI animals make the epidemiology of the virus more complex. Since cows are the primary source of the virus, identifying these cows with acceptable laboratory methods (ELISA, RT-PCR), removing them, and preventing infected animals from entering the herd are the most successful ways to combat the disease.

Moreover, infected bulls need to be identified, and the use of their semen in artificial insemination systems should be avoided. Nordic countries; Austria, and Switzerland have successfully implemented such preventive programs without vaccination.

In Iran, vaccination policy against BVDV may not have been feasible; however, other control systems should be rigorously enforced, including strict biosecurity, elimination of PI animals, movement control of the contaminated herds, serological surveillance, and comprehensive zoosanitary measures.

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Conflict of interest

The authors declare that they have no conflict of interest.

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