



Epidemiology of Bovine Pestiviruses Circulating in Italy

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OPEN ACCESS

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Specialty section:

This article was submitted to
Veterinary Epidemiology and
Economics,
a section of the journal
Frontiers in Veterinary Science

Received: 19 February 2021

Accepted: 22 April 2021

Published: 02 June 2021

Citation:

Luzzago C and Decaro N (2021)
Epidemiology of Bovine Pestiviruses
Circulating in Italy.
Front. Vet. Sci. 8:669942.
doi: 10.3389/fvets.2021.669942

Pestiviruses are widespread and economically important pathogens of cattle and other animals. *Pestivirus A* (formerly known as Bovine viral diarrhea virus 1, BVDV-1), *Pestivirus B* (Bovine viral diarrhea virus 2, BVDV-2), and *Pestivirus H* (HoBi-like pestivirus, HoBiPeV) species are infecting primarily cattle. Like other RNA viruses, pestiviruses are characterized by a high degree of genetic variability. This high rate of variability is revealed by the existence of a number of viral subgenotypes within each species. In cattle, the highest number of pestivirus subgenotypes has been documented in European countries, particularly in Italy. The aim of this review is to report an up-to-date overview about the genetic diversity of pestiviruses in Italian cattle herds. All three bovine pestiviruses species have been identified in cattle population with variable frequency and geographical distribution. The genetic diversity of Italian pestiviral strains may have diagnostic and immunological implications, affecting the performance of diagnostic tools and the full cross-protection elicited by commercially available vaccines. Implementation and strengthening of coordinated approaches for bovine pestivirus control in Italy are recommended. Therefore, it would be extremely important to increase control and restriction measures to the trade of cattle and biological products of bovine origin, including those containing fetal bovine serum.

Keywords: Italy, cattle, Bovine viral diarrhea virus 1, Bovine viral diarrhea virus 2, HoBi-like pestivirus, epidemiology, genetic diversity

INTRODUCTION

Pestiviruses are widespread and economically important pathogens of cattle (1). Pestivirus infections are associated with a wide range of clinical forms, including subclinical form, gastroenteritis, reproductive failures, and hemorrhagic systemic disease, and with profound immunosuppression that increases the susceptibility of infected cattle to secondary infections (2–4).

Genus *Pestivirus* in the family *Flaviviridae* is composed of 11 recognized species, *Pestivirus A* (formerly known as Bovine viral diarrhea virus 1, BVDV-1), *Pestivirus B* (Bovine viral diarrhea virus 2, BVDV-2), *Pestivirus C* (Classical swine fever virus, CSFV), *Pestivirus D* (Border disease virus, BDV), *Pestivirus E* (pronghorn pestivirus), *Pestivirus F* (Bungowannah virus), *Pestivirus G* (giraffe pestivirus), *Pestivirus H* (HoBi-like pestivirus, HoBiPeV), *Pestivirus I* (Aydin-like pestivirus), *Pestivirus J* (rat pestivirus), and *Pestivirus K* (atypical porcine pestivirus) (5).

Pestivirus A, *B*, and *H* species are infecting primarily cattle. To date, *Pestivirus A*, *B*, and *H* are classified into at least 21 (1a–1u), three (2a–2c), and four (a–d) (6, 7) subgenotypes, respectively.

The highest pestivirus prevalences were identified in cattle-producing countries where no control measures have been implemented, and their epidemiology in cattle is related to the pathogenetic mechanisms through which these viruses can cause both transient and persistent infections. Persistently infected (PI) animals, originating from a transient infection of pregnant cows or born from PI cows, shed large amounts of virus throughout their lives, thus ensuring viral persistence in the host population (2, 4).

In Italy, pestivirus infection has been reported in cattle all around the country since 1960 (8), with an increase of BVDV seroprevalence among dairy herds in the following years (9). Bovine viral diarrhoea (BVD) was recognized as a relevant disease in Italian cattle herds from the beginning of 1990, as reported by regional studies on the disease and few local voluntary control programs (10, 11), and several BVDV vaccines were also available with an increase of commercialized vaccines for both beef and dairy cattle. Preliminary investigations showed a wide genetic heterogeneity among pestivirus strains circulating in cattle (12–14). To date, an eradication program has been successfully applied in Bolzano province, bordering Austria. In this area, dairy herds are prevalent and the program is based on tissue tag testing to directly detect PI newborn calves without using vaccination; a PI prevalence $\leq 0.01\%$ has been reached so far. A compulsory program is also ongoing in Trentino province, whereas voluntary control programs are applied in few other northern regions (Piedmont, Veneto, Friuli-Venezia Giulia).

The aim of this review is to report an up-to-date overview about the genetic diversity of pestiviruses circulating in Italian cattle herds.

Pestivirus A

BVDV-1 is the most prevalent pestivirus species in cattle population in Italy, reaching a percentage equal or higher than 96.9% of the detected strains according to the available data (7, 15). Several genotyping studies were carried out to characterize the pestivirus strains circulating in Italian cattle population (6, 12, 13, 15–24).

Recently, evidence of fourth subgenotypes, namely, BVDV-1r, BVDV-1s, BVDV-1t (6), and BVDV-1u (22), has increased the number of circulating subtypes previously reported (15), accounting for 15 out of 21 BVDV-1 subgenotypes recognized worldwide (7), circulating in Italy. A conflict of designation for BVDV subgenotypes has been reported, since indeed identical letter codes have been used for different BVDV-1 subgenotypes, namely, BVDV-1l and 1r, which were first described in two countries at close intervals (7).

The probability of detection of sporadic and low prevalent subgenotypes was likely increased due to the analysis of extensive collections of BVDV isolates; nevertheless, it has to be noticed that multiple BVDV-1 subgenotypes in cattle have been detected since the preliminary studies on a small sample size (12, 16) were carried out on 26 and 38 isolates, respectively. On the whole, four frequency and distribution patterns of BVDV-1 subgenotypes were identified in Italy (15) and updated by additional genotyping studies (6, 20, 23, 24): (1) high prevalent

subgenotypes with a wide temporal–spatial distribution (BVDV-1b and 1e); (2) low prevalent subgenotypes with a widespread geographic distribution (BVDV-1a, 1d, 1h, and 1k); (3) low prevalent subgenotypes in restricted geographic areas (BVDV-1f); and (4) sporadic subgenotypes detected in few herds (≤ 5) (BVDV-1c, 1g 1j, 1l, 1r, 1s, 1t, 1u) in restricted areas (**Table 1**).

The BVDV-1 subgenotypes circulating in Italy have been reported in other countries (7), with exception of BVDV-1r, 1s, and 1t which were first and sporadically detected only in Italy (6) and BVDV-1u (22) which has been identified so far exclusively in China in different ruminant species, including cattle, water buffalo, and yak (25).

The relationships between the genetic diversity and geographic distribution of the BVDV-1 subgenotypes were investigated through phylogenetic analysis that includes spatiotemporal information in the tree inference, namely, phylogeographic analysis, in order to reconstruct the origin and viral dispersal routes. The largest virus dispersion occurred between the middle 1990s and the early 2000s; northern Italy was estimated to be a significant source area to other parts of the country of the most subgenotypes that are widespread at national level, namely, BVDV-1a, 1b, 1e, 1d, and 1h (19, 24) and also BVDV-1f (20). Considering that northern Italy is the area with the largest cattle population as well as one of the main cattle importing areas from other European countries, a possible gravity-like dynamic of the infection, originating in larger animal populations then diffusing to smaller ones following patterns of national commercial flow, has been hypothesized (19). The most prevalent subgenotypes (BVDV-1b and 1e) showed a common viral dispersal pattern with a continuous BVDV-1b and 1e interspersions from multiple areas, including other European countries until the end of the last century and with no evidence of significant geographical structure, while local circulation was prevalent in recent years with significant regional clusters (24). Accordingly, southern areas of the country concurred mainly to a restricted geographical circulation of BVDV-1b and 1e, as demonstrated by significant local transmission networks, suggesting a local maintenance of BVDV infection (24).

Molecular epidemiology and evolutionary phylodynamics allowed reconstructing the spatiotemporal westward dispersal of BVDV-1f in northern Italy and its introduction in Aosta Valley from Piedmont. Moreover, the combined approach of traditional and molecular epidemiology showed that BVDV-1f in Aosta Valley can be controlled only by monitoring the introduction of cattle from the Piedmont region (20).

Pestivirus B

BVDV-2 was first identified in the USA (26) and then detected in several countries (27–30). Contaminated fetal calf sera or other biological products likely contributed to BVDV-2 introduction into Europe (31), where it circulates at lower rates than BVDV-1 (7). In Italy, BVDV-2 has been reported both in cattle (12) and in small ruminants since the 1990s (32). Despite the early identification in our country, BVDV-2 showed a sporadic frequency in cattle (12, 15, 33), with BVDV-2a representing the most prevalent subgenotype in this country (21, 22) as well as at a global level (7). BVDV-2c strains have been recently detected in

TABLE 1 | Frequency of BVDV-1 subgenotypes in cattle.

Subgenotype	Sequence no.	Years	Geographic origin*	References
BVDV-1a	30	2000–2014	NCSI	(6, 15)
BVDV-1b	245	1995–2016	NCSI	(6, 15, 22–24)
BVDV-1c	3	2008–2010	CS	(6, 15)
BVDV-1d	28	1995–2010	NCS	(6, 15, 23, 24)
BVDV-1e	144	1996–2013	NCSI	(6, 15, 23, 24)
BVDV-1f	55	1999–2014	NC	(6, 15, 20)
BVDV-1g	5	2002–2010	NS	(6, 15)
BVDV-1h	28	1996–2016	NCSI	(6, 15, 22–24)
BVDV-1j	1	1995	N	(15)
BVDV-1k	8	2001–2011	NCSI	(6, 15)
BVDV-1l	2	2007	C	(6, 15)
BVDV-1r	4	2010–2012	NS	(6, 23)
BVDV-1s	1	2008	C	(6)
BVDV-1t	1	2013	I	(6)
BVDV-1u	5	2009–2015	SI	(22, 23)

*N, northern Italy; C, central Italy; S, southern Italy; I, Islands.

southern Italy in cattle and to a greater extent in small ruminants (22). It is noteworthy that this BVDV-2 subgenotype, which was responsible for a severe outbreak of BVDV-2c infection occurred in Germany and the Netherlands during 2012–2014 (34, 35), had been found to circulate in Italy since 2004 (22).

Pestivirus H

This emerging pestivirus species was first detected in South America (36) and then reported in South America, Europe, and Asia (37). Viruses circulating in South America, Europe, Thailand, and China were found to be closely related, other Asian HoBiPeV strains are highly divergent, and at least four different subgenotypes have been identified so far (6). In Europe, HoBiPeV was first detected in cattle in southern Italy in 2010 (14), although retrospective analysis of archival samples dates back its circulation in this country to 2007 (38). In Italian cattle, the virus was responsible for respiratory distress (14, 39), abortion (40), birth of PI calves (41, 42), mucosal disease (43), and gastroenteric signs (42), with severe economic losses in infected herds (42). Subsequently, an extensive collection of Italian cattle pestiviruses was analyzed to assess the frequency of this emerging virus in Italy. HoBiPeV strains were not further detected in cattle neither in southern Italy, where the virus was first detected (22, 23), nor all around the country (15).

PESTIVIRUS GENETIC VARIABILITY WITHIN HERDS

The high diversity of circulating pestiviral strains affects also the BVDV variability at the herd level. A unique genetic variant was detected in the majority of herds, but co-circulation of different genetic pestiviruses (species and subgenotypes) was also observed in both dairy and beef herds, based on analysis of different strains within a narrow collection period (≤ 3 months) (15). In addition, the genetic variability of 5'UTR of the same BVDV subgenotype

circulating within herds has been observed. This finding could indicate the introduction of a different strain or the genetic evolution of a single circulating strain, consistent with the mean evolutionary rate estimated for this genomic region, which is 9.3×10^{-3} substitutions/site/year, with a credibility interval between 4.8 and 14.7 substitutions for 1,000 nucleotides (19).

BOVINE PESTIVIRUSES CIRCULATING IN NON-BOVINE RUMINANTS

BVDV-1 was detected in water buffalo (*Bubalus bubalis*) in southern Italy (18, 22, 44). At the genetic typing, the strains were characterized as of BVDV-1b subgenotype, and a role in the etiology of abortion (44) and persistent infection in adult animals (18) in this ruminant species was suggested.

Circulation of BVDV-1 and BVDV-2 in sheep flocks was reported in southern Italy (22, 32). BVDV genetic typing allowed detecting BVDV-1a and 1f in sheep in central Italy (18), as well as BVDV-1e and BVDV-2c in both sheep and goat flocks in southern regions (22).

BVDV detection in wild ruminants is sporadic in Europe and analogous to BDV (45, 46), most probably dependent on a domestic source (47, 48). High mortality outbreaks caused by BDV infections were reported in Pyrenean chamois (*Rupicapra pyrenaica*) (49, 50), and introduction from sheep into the wildlife has been suggested for this virus (51).

Recently, BVDV-1 has been reported in wild ruminants in Italian central Apennines (52), with subgenotypes 1a and 1c being detected in red deer (*Cervus elaphus*), roe deer (*Capreolus capreolus*), and Apennine chamois (*Rupicapra pyrenaica ornata*), and in roe deer and Apennine chamois, respectively. No bovine pestivirus has been detected in wild ruminants in Italian Alps so far, and accordingly serological investigations suggest that pestivirus circulation either is absent or occurs at low prevalence

in roe deer and red deer (53–55). In Alpine chamois (*Rupicapra rupicapra rupicapra*), no seropositivities were detected for BVDV by the virus neutralization test (53), while seroprevalences of 18% (55) and 25.5% (54) were observed for pestiviruses by the ELISA test, with no differentiation between BVDV and BDV.

DISCUSSION

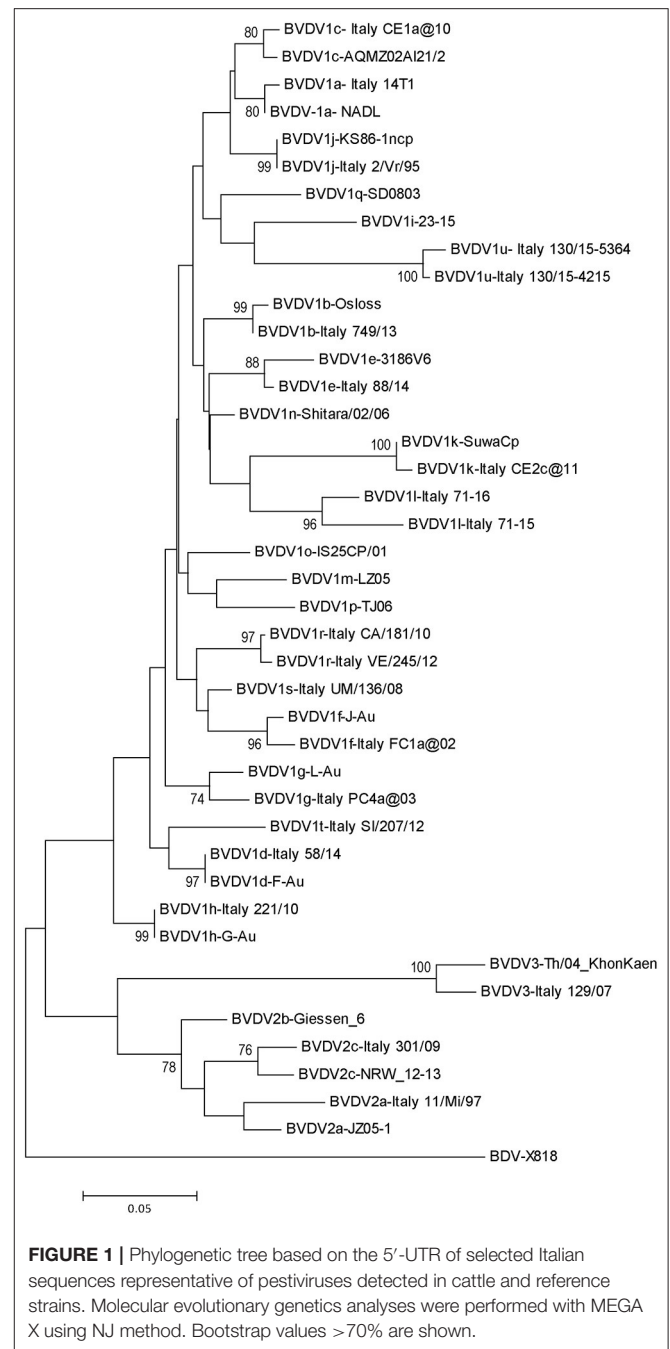
Pestivirus A, B, and H species have been identified in Italian cattle population with variable frequency and geographical distribution. Phylogenetic analysis of extensive collections of strains of the three bovine pestiviruses has allowed to detect several subgenotypes, accounting for 15 out of 21 BVDV-1 subgenotypes, two out three of BVDV-2, and one out of four HoBiPeV subgenotypes (Figure 1), recognized so far.

Based on the global distribution of BVDV subgenotypes recently reviewed (7) and integrated by other available literature (14, 22–24, 38), Italy is characterized by the highest genetic diversity of bovine pestiviruses among cattle-producing countries worldwide. Recently, a better understanding of national pestivirus distribution has been achieved, with the most prevalent subgenotypes being represented by BVDV-1b and 1-e (69.5%), having a wide distribution in all the country, including islands. Several subgenotypes (BVDV-1a, 1d, 1h, 1k) showed a wide dispersion despite the lower frequency compared to BVDV-1b and 1e. BVDV-1f is mainly restricted in northwestern Italy, namely, Piedmont and Aosta Valley, with evidence of the entry of BVDV-1f in Aosta Valley from Piedmont and transmission chains among local cattle farms (20). The remaining BVDV-1 subgenotypes were sporadically reported in Italy, but it has to be noticed that BVDV-1 heterogeneity is increasing due to the identification of novel subgenotypes (6) or emerging subgenotypes, such BVDV-1u (22), which had been previously reported exclusively in China (25).

BVDV-2 displays a very limited circulation in cattle (12, 33), whereas a higher frequency of detection has been observed in small ruminants in southern Italy (22, 32), where livestock breeding is mainly characterized by semi-intensive and extensive farming of sheep and goat flocks.

The sporadic frequency of HoBiPeV in Italy and the absence of circulation in other European countries support the hypothesis that HoBiPeV was introduced to southern Italian cattle herds through contaminated biological products, rather than infected animals (23, 36).

On the whole, the high level of BVDV-1 genetic heterogeneity and the spatial distribution of BVDV are mainly attributable to the cattle trade within the country and to introduction of viral strains from other countries, in the absence of any control measures. Northern Italy was estimated to be a source area to other parts of the country of subgenotypes that are now widespread at the national level (19, 24). In addition, biological products contaminated by fetal bovine serum have to be considered as possible source for introduction of bovine pestivirus species and subgenotypes into new areas (6, 31, 56).



A data integration of the cattle movement dataset with the pestivirus status is advisable to optimize the outcome of molecular characterization of pestiviruses, performing an accurate contact tracing among farms and investigating transmission pathways among different areas. Moreover, the genetic diversity of Italian pestiviral strains may have diagnostic and immunological implications, affecting the performance of diagnostic tools and the full cross-protection elicited by commercially available vaccines (57–59). In this respect, implementation and strengthening of coordinated approaches for bovine pestivirus control in Italy are recommended.

The current European situation of eradication and control programs for pestiviruses in cattle is rapidly evolving, with an increased number of countries applying systematic control measures at the national level (60, 61). For BVDV mitigation, it would be extremely important to regulate the cattle trade according to the disease status of a farm or a region and also to increase control and restriction of trade of biological products containing fetal bovine serum (4).

Dairy farms are recently identified as the key drivers of pestivirus persistence and dispersion in Italy, and control measures targeting these farms would lead significant reduction in the pestivirus circulation in Italian cattle to a higher extent than targeting other production compartments (62).

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AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

The authors thank Dr. Monica Giammarioli (Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche, Perugia, Italy) and Dr. Alexander Tavella (Istituto Zooprofilattico Sperimentale delle Venezie, Bolzano, Italy) for providing information on published BVDV sequences and eradication program in Bolzano province. The authors acknowledge support from the University of Milan through the APC initiative.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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