An Update on Current Concepts of The Epidemiology of Bovine Pestivirus Infection in Cattle

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Summary
Bovine pestivirus is a worldwide pathogen of the cattle populations. Over 90% of pestivirus infections remain inapparent. Pestivirus infection is usually considered a disease of the alimentary tract but increasing evidence indicates involvement of the reproductive tract with significant effects on the reproductive performance of cattle. A majority of reproductive loss is associated with the non-cytopathic MCP biotype of the virus. The present review focuses on the current knowledge concerning the ways in which this pathogen may spread within the cattle population.

Key words: Flaviviridae, Cattle, Pestivirus

Introduction
Conventionally, pestivirus was considered to be a genus of the family Togaviridae. In light of new findings on the genetic composition of pestiviruses they have been recategorised as a genus of the family Flaviviridae (Horzinek 1991). The Flaviviridae have similar molecular biology to the family Togaviridae (Potgieter 1992). The genus pestivirus includes the antigenically related bovine viral diarrhoea virus (BVDV), hog cholera virus and Border disease virus. BVDV and Border disease virus have a much higher degree of antigen variation than the hog cholera virus (Baker 1987). BVDV infection is responsible for a variety of clinical syndromes including subclinical infection, immunosuppression, immunotolerance, mucosal disease syndrome, congenital defects and a variety of reproductive losses due to perinatal mortality, stillbirth, foetal mummification, abortion, embryonic death and "repeat breeding".
(Brownlie 1991). Because of this diversity of syndromes it is more appropriate to use the term "bovine pestivirus infection" rather than BVDV infection, the latter describing only one particular syndrome caused by pestivirus infection.

**Distribution of pestivirus in body tissues**

Lymphoid and certain epithelial tissues such as mucosa of the alimentary tract are the most common predilection sites of the virus in cattle (Bielefeldt, 1987). It is thought that the initial site of replication is the oronasal mucosa, particularly the palatine tonsil (Brownlie 1991). The systemic spread of the virus could occur either from free virus in serum or via circulating white blood cells (Tyler et al. 1965). Experimental infection of cattle with pestivirus was shown to decrease the B and T-cell lymphocytes population (Bolin et al. 1985a) and cause a neutrophil dysfunction (Roth et al. 1981). Taking this finding together with the role of inflammatory cells in the ovulatory process (Espey and Lipner 1994) it may explain the ovulatory failure observed in Friesian heifers that were experimentally infected with pestivirus 9 days prior to insemination (Kafi et al. 1997).

The central nervous system of the developing bovine foetus is another important target organ of bovine pestivirus. The virus has been shown to persist in the central nervous system of immunotolerant calves born with persistent infections (Fernandez et al. 1989, Brownlie 1991). Results of a German study indicate that bovine pestivirus has a strong affinity for neurons (Wohrmann et al. 1992) confirming previous reports of Cutlip et al. (1980). Further, it was shown that predilection sites of the virus in the central nervous system are the cerebral cortex and hippocampus. Interestingly, virus antigens were found in morphologically normal cells of the anterior pituitary (Wohrmann et al. 1992). In an earlier report, virus antigens had been detected by immunohistochemistry, in the granular cells of the anterior pituitary of a persistently infected (PI) bull (Barlow et al. 1986).

Testicular (Kirkland et al. 1991) and ovarian tissues of persistently (Booth et al. 1995) and transiently (Kafi et al. 1997, McGowan and Kirkland, unpublished data) infected cattle are other sites of replication of pestivirus. Pestivirus has been frequently isolated from the follicular fluid. A series of recent in vitro experiments did not show any adverse effect of pestivirus on the process of bovine oocyte maturation (Kafi 1996). Whether these apparently normal matured oocytes that were exposed to pestivirus could grow to the blastocyst stage and result in a normal calf was not examined.

**Prevalence of bovine pestivirus infection**

In an early serological study, Mirshamsi et al. (1970) demonstrated 16 to 69% of cattle tested by a serum neutralisation test were serologically positive for bovine
pestivirus. Later in a study conducted by Sedigi-Nezhad (1996) the virus was isolated from northern, western and central parts of Iran. The prevalence of bovine pestivirus infection in different countries is shown in Table 1.

**Table 1: The prevalence of bovine pestivirus infection in different countries.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Number tested</th>
<th>Test used</th>
<th>% Antibody positive</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>5129</td>
<td>VNT</td>
<td>60.6</td>
<td>St. George et al. (1967)</td>
</tr>
<tr>
<td>Iran</td>
<td>NA</td>
<td>VNT</td>
<td>16-69</td>
<td>Mirshamsy et al. (1970)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>922</td>
<td>VNT</td>
<td>34.0</td>
<td>Durham &amp; Faulkner (1975)</td>
</tr>
<tr>
<td>Britain</td>
<td>1593</td>
<td>VNT</td>
<td>62.2</td>
<td>Harkness et al. (1978)</td>
</tr>
<tr>
<td>Egypt</td>
<td>NA</td>
<td>VNT</td>
<td>33.4</td>
<td>EI-Dobeigy et al. (1983)</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>3157</td>
<td>VNT</td>
<td>89.0</td>
<td>Bolin et al. (1985b)</td>
</tr>
<tr>
<td>Argentina</td>
<td>1494</td>
<td>VNT</td>
<td>37.0</td>
<td>Rweyemamu et al. (1990)</td>
</tr>
<tr>
<td>Chile</td>
<td>525</td>
<td>VNT</td>
<td>77.0</td>
<td>Rweyemamu et al. (1990)</td>
</tr>
<tr>
<td>Norway</td>
<td>1133</td>
<td>VNT</td>
<td>18.5</td>
<td>Loken et al. (1991)</td>
</tr>
</tbody>
</table>

NA = not available  VNT = virus neutralisation test

The unintentional introduction of a PI animal to a herd may occur with subsequent transmission of the virus by close contact between seronegative (susceptible) animals and the PI animal. The absence of PI animals in a herd has been considered the reason for the occurrence of serologically negative herds (Blood and Radostits 1989). Before about 125 days of gestation in cattle, the foetal immunological responses are not well developed. Therefore, if the foetus becomes infected with a nCP biotype of pestivirus in this particular period of gestation, it is unable to respond to the infection and produce serum neutralising antibodies, and is thus likely to be born PI with the virus. Immunotolerance and persistent viraemia are two permanent features observed in these animals. PI calves may appear clinically healthy or illthrift. Premature birth and undersized calves may also be seen as a consequence of infection at this time (Bolin 1990). PI calves may have a mortality rate of up 50 per cent in their first two
PI calves may have a mortality rate of up to 50 per cent in their first two years of age (Duffel and Harkness 1987). The majority of deaths are due to the development of mucosal disease. PI cattle are important reservoirs of pestivirus and they appear to be efficient transmitters of the virus, shedding large amounts of virus over a long period of time (Duffel and Harkness, 1985). This could be the major mechanism maintaining pestivirus in cattle populations (Roeder and Harkness 1986). The prevalence of PI animals in the cattle population is relatively low (1-2 per cent) (Meyling 1984). Howard et al. (1990) reported a prevalence of 0.78 per cent (12 out of 1538) PI bulls in 4 artificial insemination AI centres in the USA. A sex-related prevalence of PI (in males) animals has been proposed (Littlejohns and Horner 1990) but this finding requires further investigation.

**Transmission and source of infection**
Based on available information, the possible ways of transmission and the sources of infection are discussed below:

**Contact with PI animals**
A significant number of PI carrier animals are clinically healthy. These animals can survive for years, and at the same time they may breed successfully. Those cases which have varying degrees of abnormality in growth rate or in general appearance may be discarded, or die before puberty (Meyling et al. 1990) and therefore may not contribute significantly to the spread of the virus. However, keeping the unrecognised apparently normal PI carrier animals in the herd is a major hazard to groups of susceptible animals. The progeny of these animals may in turn be apparently healthy but persistently infected (Straver et al. 1983).

Another possible route of introducing pestivirus into a herd is the purchasing of pregnant heifers that are carrying an infected foetus (Meyling et al. 1990). This highlights the significant role of national or international cattle trading as a pathway for the spread of pestivirus. The virus is most likely to be isolated from any secretion or excretion of a PI carrier animal. The faeces is not usually a common source of the virus even when there is severe damage to the gut (Brownlie et al. 1987). On the other hand, ocular and nasal discharges, saliva, urine, milk and semen are common sources of the virus (Straver et al. 1983; Radostits and Littlejohns 1988). The principal routes of infection are inhalation or ingestion of these materials (Afshar and Eaglesome, 1990). It was reported (McGowan et al. 1993) that 50 to 63 per cent of seronegative animals became infected following a 24 hour period of close contact with two PI
animals in a small concrete yard. However, the rate of transmission may depend on
the strain of the virus, stocking rate, management system (Pasture or a feedlot type
system), and also the occurrence of natural activities such as oestrus and calving
which encourage contact between cattle.

**Contact with transiently infected animals**

Those animals which undergo an acute postnatal infection with pestivirus experience
a transient viraemia and the virus may be isolated from most secretions from days 4 to
10 after exposure. The virus has been recovered until day 19 after exposure (Brownlie
et al. 1987). In these cases, which are referred to as transient infections, the amount of
virus shed in the body discharges is lower than that from PI cattle. No transmission of
the virus to susceptible animals was observed in spite of close contact between
non-infected and transiently infected animals (Meyling and Jensen 1988). Also,
animals experimentally infected by parenteral injection of an CP strain of pestivirus
did not act as a source of infection for other animals that were in contact with them
(Pritchard 1963). In contrast, transmission can occur when the transiently infected
animals return to oestrus after artificial insemination and the virus is shed in
uterocervical discharges. However, the evidence of spread of infection from
transiently infected animals suggests that it is not an efficient mode of transmission.
The mean time from exposure to serocoversion has been reported to be about 13 days
(McGowan et al. 1993). It is believed that the antibody production provide the animal
with lifelong immunity.

**Use of semen from PI or transiently infected bulls**

The semen produced by PI bulls can be an important mode of virus transmission.
These bulls may shed the virus in semen over a long period of time (Stober, 1984).
The immediate consequence of using this semen in a susceptible herd may be a
decrease in conception rate (Kirkland et al. 1994). On the contrary, satisfactory
conception rates have been achieved with semen from PI bulls (Meyling and Jensen
1988, Wentink et al. 1989). Kirkland et al. (1997) found that the use of semen from a
transiently infected bull has the potential to infect susceptible cattle. They reported a
low initial incidence of infection after AI (3 out of 60) but observed a secondary cycle
of infection apparently associated with an originally infected animal expelling an
infected conceptus and uterine fluids approximately 21 days after AI.
Transfer of infected embryos

Foetal calf serum (FCS) which is normally utilised in embryo transfer (ET) procedures and embryo research has been reported to be contaminated with pestivirus (Abraham 1993). Improper handling and poor sanitization of embryos could result in spread of the virus. A high frequency of persistent infections among ET calves have been reported (Anderson et al. 1988). The contamination of oestrus cow serum (Zurovac et al. 1994) and/or FCS (Kafi, 1996) with pestivirus antibody has been observed during studies on the effect of pestivirus on bovine in vitro derived embryos. It is also possible that bovine serum albumin as the serum component of in vitro fertilisation media or synthetic oviductal fluid contains immunoglobulin against pestivirus. Neither standard washing nor trypsin treatment was effective for removal of bovine pestivirus from zona pellucidae intact in vitro derived embryos following in vitro exposure to the virus (Trachte et al. 1997).

Transmission through the use of live vaccines

Contamination of FCS with pestivirus is frequently observed in cell culture work and this could be the cause of pestivirus contamination of biological products, such as vaccines and pharmaceuticals (Radostits and Littlejohns 1988).

Vaccination of susceptible cows, pregnant between 51 and 190 days of gestation, with a commercial modified live bovine pestivirus resulted in transplacental infection (Liess et al. 1984). The outcomes of vaccination were reported to be abortion, congenital abnormalities of the CNS, perinatal deaths, body growth retardation and persistent viral infection (Liess et al. 1984, Trautwein et al. 1986). Transmission has also been reported following the use of other live vaccines contaminated with pestivirus (Lohr et al. 1983).

Transmission via fomites and flies

The role of pestivirus contaminated-hypodermic needles in producing infection in susceptible cattle was recently demonstrated (Gunn, 1993). Also, the use of shared cattle nose tongs was shown be a way of transmitting the virus amongst susceptible animals (Gunn 1993). Lang-Ree et al. (1994). investigated the possibility of the transmission of bovine pestivirus from a PI animal to other susceptible heifers via use of a shared glove used for rectal palpation. Bovine pestivirus was isolated from five of eight heifers that were palpated per rectum in this experiment. Further, all eight heifers produced neutralising antibodies against bovine pestivirus within 13 days. Under experimental conditions, biting flies (such as Haematopota pluviialis) and
non-biting flies (Hydrotaea irritans, Musca autumnalis) were unable to transmit pestivirus to cattle and sheep (Tarry et al. 1991, Gunn 1993). Further studies are required to clarify whether flies can infect animals by feeding around their eyes or on abrasions of the body surface.

Transmission through contact with other species of animals
Pestivirus infections occur in a large number of different species of animals (Nettleton 1990). Experimentally, other animals such as sheep, goats, buffalo, deer and pigs have become infected with bovine pestivirus (Stewart 1980, Nettleton 1990). It is believed that interspecies transmission may occur (Harkness and Roeder 1988). The transmission of Border disease virus from PI sheep to cattle has been reported (Barlow et al. 1980) and also the foetopathogenicity of border disease virus in cattle has been described (Gibbons et al. 1974). The mechanisms involved in the dissemination of the virus among these different species is worthy of investigation.

Conclusions
There is now overwhelming evidence that reproductive losses are the main consequence of pestivirus infection in cattle. Reproductive and lymphoid tissues are two main predilection sites of the virus. The non-cytopathic biotype is the type that causes majority of pestivirus infections and thus the greatest economic impact. PI animals are the primary source of infection in cattle populations. Gametes, serum and somatic cells are potential sources for introduction of bovine pestivirus into bovine in vitro embryo production systems. Recent findings emphasize the significance of (IVF) and embryo transfer activities as potential means of pestivirus transmission among cattle populations.

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