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Review article

Transmission and pathogenesis of vesicular stomatitis viruses

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Abstract

Vesicular Stomatitis (VS) is caused by Vesicular stomatitis viruses (VSV), negative single stranded RNA arthropod-borne members of the Family Rhabdoviridae. The VSV virion is composed of the host derived plasma membrane, the envelope, and an internal ribonucleoprotein core. The envelope contains a transmembrane glycoprotein, the G protein, which mediates viral entry and exit from the cell. The ribonucleoprotein core contains the viral genome encased within the nucleocapsid protein, the N protein. The large protein (L), the nucleocapsid (N) and the phosphoprotein (P) have key roles in viral replication. The matrix protein (M protein), located between the envelope and the nucleocapsid core, participates in viral assembly, and particle budding. The VSV serotypes involved with disease in livestock are New Jersey and Indiana 1, 2 and 3. Serotypes New Jersey and Indiana 1 occur from USA through Central America to much of South America. Serotype Indiana 3 (or Alagoas) occurs in the North, Northeast and Central Brazil. The serotype Indiana 2 (or Cocal), occurs in Southern Brazil and in Argentina. Outbreaks of VS in Brazil in recent years have resulted in severe economic losses. The clinical disease in horses, cattle, and pigs is characterized by vesicles in tongue, planum nasale, planum rostrale, coronary bands (CB) of the feet, prepuce, and teats. Subclinical disease, with seroconversion and lack of vesicle formation is common under natural conditions and can be induced experimentally depending on the site of inoculation. VSV infection typically involves cytolytic infection of mammalian host cells at specific sites of inoculation. Transmission can occur via infected insect bite but animal-to-animal contact could also be important in within-herd spread. There is some evidence to suggest that biting insects may play a role in the pathogenesis of VSV infection, although mechanisms of pathogenesis are not well understood. Viral spread seems to stop at the draining lymph nodes with no viremia. As a well-known *in vitro* producer of interferon, it is hypothesized that the host immune response to VSV infection may limit viral spread. A better understanding of pathogenic aspects could allow development of prevention and disease control strategies.

Key Words: VSV, vesicular stomatitis, transmission, biting insects, pathogenesis.

Introduction

Vesicular stomatitis viruses (VSV), the causative agent of vesicular stomatitis (VS), cause clinical disease in multiple livestock species. The viruses can spread quickly and have an important economic impact due to the high morbidity rates resulting in quarantine, animal movement restrictions, and decreases in production of meat and milk. Another important aspect of the disease is the fact that VS in cows and swine is clinically indistinguishable from foot-and-

mouth disease, and so all cases need to be investigated thoroughly. This is particularly important in South America where programs to eradicate foot-and-mouth disease have been implemented. The presence of VS in a region can interfere with the international trade of animals and their products, such as meat, milk, semen, embryos and biotechnological products. Vesicular stomatitis is restricted to the Americas with specific serotypes usually occurring in defined regions. Vesicular stomatitis was previously considered a List A OIE disease, which carried with it mandatory international reporting requirements and severe trade restrictions, but now it has been reclassified as one of the more than 100 "listed diseases" according to the new OIE scheme. Nevertheless, countries continue to monitor the presence of VS, and its presence can result in severe economic damage due to quarantines or trade embargoes. The purpose of this paper is to provide a review of the literature on vesicular stomatitis focusing on the transmission and pathogenetic mechanisms.

Etiology

Vesicular stomatitis viruses are enveloped, nonsegmented, single negative-stranded RNA arthropod-borne viruses (arboviruses) in the Genus Vesiculovirus, Family Rhabdoviridae (49). They have a large bullet-shaped (65-185nm) virion, and are the prototype virus for the family. The viruses have been extensively studied in vitro in numerous laboratories, largely as a tool to investigate the production of interferon. However, the natural cycles and pathogenesis of the disease caused by the various serotypes in livestock have not been as well characterized (47). There are two major serotypes of VSV: New Jersey (VSNJV) and Indiana (VSIV). The serotype Indiana has been subdivided into three distinct serological groups. Indiana type 1 represents the classical Indiana strains (13). Cocal virus (COCV) is the prototype virus of the Indiana 2 subtype and was originally isolated from mites collected from rice rats in Trinidad in 1961 and in northern Brazil in 1962 (21). Alagoas virus (VSAV) is the prototype virus of the Indiana 3 subtype and was first isolated from a mule in Alagoas, Brazil, in 1964 (3). There are other vesiculoviruses that infect humans and that will cause lesions when experimentally inoculated into domestic animals, but with no importance to date in natural outbreaks in livestock. These include Piry virus originally isolated from an opossum (*Didelphis albiventris*) in Brazil, Chandipura virus first isolated from a human in India, and Isfahan virus isolated from sandflies and humans in Iran (36, 48, 58). These three viruses will not be discussed further in this review.

The virion structure of VSV (Fig. 1), like all rhabdoviruses, is composed of an external phospholipid bilayer membrane (envelope) derived from the host cell and an internal ribonucleoprotein core. The envelope contains the viral glycoprotein or G protein, an important transmembrane protein which forms an array of 400 trimeric spikes. G protein is synthesized by membrane-bound ribosomes, associates with the chaperones BiP and calnexin that assist in correct folding, and eventually undergoes glycosylation and acylation as it moves to the Golgi apparatus. Once correctly folded and glycosylated, G protein migrates to the cell membrane (22, 49). G protein mediates cell recognition and fusion (7, 30). It is also important in determining specificity in induction of neutralizing antibodies according to serotype (29) and virulence among serotypes (30), where New Jersey is more virulent than Indiana, purportedly due to differences in pH dependent infectivity (31). The nucleocapsid core is composed of the viral genome tightly encased within the nucleocapsid protein (N). N proteins are arranged as beads on a string along the viral RNA (Fig. 1), which form an RNase-resistant core environment. Because the VSV genome is negative stranded RNA, its replication relies on a viral RNA-dependent RNA polymerase, composed of the large (L) and phosphoprotein (P) protein molecules. The N-protein RNA complex interacts with P-L complex during viral transcription and replication. P protein in combination with the L protein forms the viral transcriptase-replicase complex. When P protein undergoes polymerization, it forms trimers that are required for binding of L and N-RNA complex to form the active transcriptase. The matrix protein (M) is located between the internal surface of the envelope and the nucleocapsid core. It has numerous functions, such as condensation of the nucleocapsid during assembly and viral particle budding. The viral N, L, P and M proteins do not change their composition among particles, whereas the transmembrane G protein can vary greatly among and within serotypes (49).

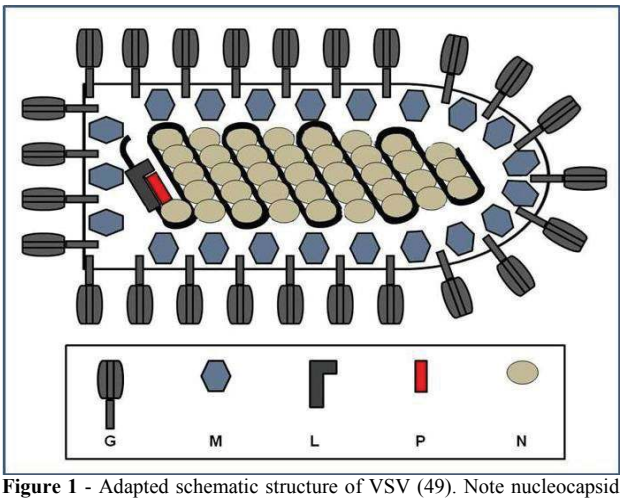

Figure 1 - Adapted schematic structure of VSV (49). Note nucleocapsid core containing the single-stranded RNA, the N protein and the complex L and P protein. The envelope contains the transmembrane the G protein and the M protein in its inner surface.

The replication cycle of VSV is typical for most of the negative-stranded RNA viruses (26) (Fig. 2). Following attachment, penetration, and uncoating the viral nucleocapsid is released within the cytoplasm. The viral genome, which is encased with the N protein, serves as a

template for initial transcription by the virion RNA-dependent RNA polymerase, resulting in synthesis of leader RNA and all five viral mRNAs for the N, P, M, G, and L genes. Once viral proteins are synthesized from primary transcripts, viral genome is replicated with synthesis of full-length positive strand RNA (antigenome), which serves as a template for synthesis of negative-strand RNA (genome). Genome encapsidation occurs at the same time as its replication. The early events of the replication cycle (attachment, penetration, uncoating, and primary transcription) take place within the first few hours postinfection. The remaining steps of the replication cycle (genome replication, secondary transcription and assembly) take 12 to 18 hours (26). It has been proposed by some investigators that VSV uses a phosphatidyl serine as a cellular receptor (52). However others suggest that VSV does not use phosphatidyl serine, because in most of the cells these molecules are found in inner portions of the plasma membrane and consequently are not available to act as a receptor for viral entry (9). VSV attachment to host cells may use nonspecific electrostatic and hydrophobic interactions (4). Lower pH also plays an important role in VSV attachment as well as viral membrane fusion (26). Lower pH alters G protein conformation which is required for fusion. As for many other viruses, VSV penetration uses clathrin-dependent endocytosis into coated vesicles. The vesicle loses its clathrin coat and becomes an endosome, subsequently the pH drops below 6.5 and G protein mediates fusion of the endosome membrane with the viral envelope. This fusion leads to the release of the nucleocapsid into the cytoplasm where M protein dissociates from the nucleocapsid, which is necessary for viral RNA synthesis to occur (26). The primary transcription mediated by the virion-associated RNA-dependent RNA polymerase occurs in the absence of protein synthesis. For transcription viral genome associated with N protein is used as a template and requires L and P proteins. When P is phosphorylated, it forms P protein trimers that bind to L protein resulting in polymerase activity (49). Transcription begins at the 3' end of the genome, where a 47-nucleotide RNA called leader is first synthesized (49).

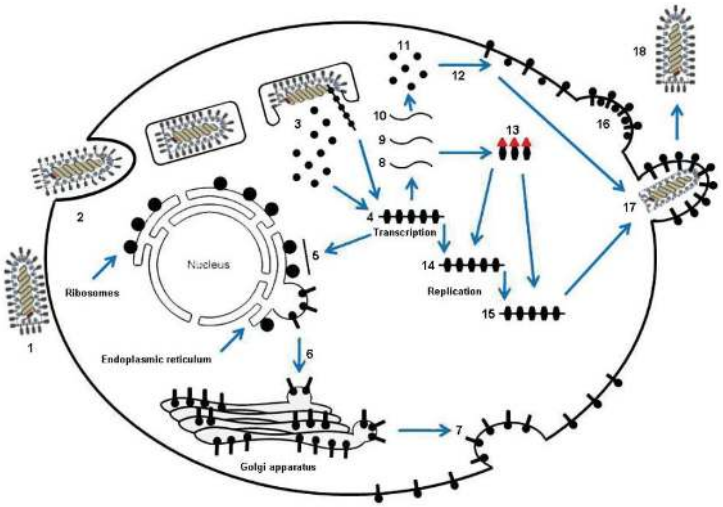

Figure 2 - Adapted diagram of the life cycle of VSV (49). 1 – Binding to cell surface; 2 – Endocytosis; 3 – Fusion and uncoating; 4 – Transcription from (-) genomic RNA; 5 – G mRNA; 6 - Synthesis and glycosylation of G protein; 7 – Delivery of G protein to plasma membrane; 8 – N mRNA; 9 – P mRNA; 10 - M mRNA; 11 – M protein; 12 – M protein migration to the inner plasmatic membrane; 13 – N:P complex; 14 – (+) Replicate intermediate; 15 – (-) Progeny genome; 16 – Formation of bud site; 17 – Budding, and 18 – Progeny virion.

Host range and clinical signs

Vesicular stomatitis viruses have a wide host range in animals, causing natural vesicular disease in equidae (horse, mule and donkey), cattle and pigs. However, the host range is considerably wider and evidence of infection with the various serotypes has been detected in a number of species, including South American camelids and many wild rodents. Serological surveys have shown that the virus circulates in bats and tamarin monkeys in Bahia State, Brazil (2). Experimental infection has been successful in domestic rodents, deer, raccoons, bobcats, and primates. Sheep and goats are more resistant and have rarely been affected (47, 48). Vesicular stomatitis is a zoonotic disease, and people have become ill through both natural infection (40) with reported cases of encephalitis (43) and via laboratory accidents (40, 45). In ruminants and pigs, the clinical signs of VS resemble those of foot-and-mouth disease (FMD), and are characterized by initial vesicular formations that progress to erosions and ulcerations on the tongue, palate, gum, lips, snout (swine), teats, prepuce, interdigital space and coronary band. Humans usually do not present with vesicle formations; mild influenza-like signs are most commonly reported (60). Rodents develop systemic disease with viremia and

central nervous system lesions with no vesicle formation on the skin (6, 10, 20).

Because of the similarity to FMD in clinical and pathological presentation in cattle and pigs (22), a thorough and precise investigation must be done in all suspected VS cases, in order to rule out FMD (22). Furthermore, dual VSV and FMDV infections have been described from some herds of cattle and concomitant infection has been experimentally reproduced (36). In pigs, VS also has to be distinguished from other vesicular diseases, including swine vesicular disease (36). The latter has never been described in the Americas, but recent outbreaks in Europe have raised worldwide concern as a potential emergent threat.

The incubation period for VSV is variable but usually vesicles are visible within 24-72h after virus inoculation (19, 51, 56). Coinciding with the period of vesicle formation, infected animals are febrile and anorexic. Recovery typically occurs within two to three weeks of vesicle formation, but there can be severe secondary infections that can result in laminitis in horses, and severe mastitis and teat scarring in dairy cattle (36, 48).

Epidemiology

Infection rates are variable among outbreaks; morbidity can be as high as 96%. In cattle and horses mortality is negligible (12). However, as previously mentioned, in horses laminitis can develop as a result of VSV infection and this may lead to euthanasia.

Vesicular stomatitis is only present in the American continent (36, 47) (Fig. 3). The New Jersey serotype accounts for 80% of the outbreaks in the U.S., and Indiana 1 for the remainder (16). In the U.S., the southwest and southeast are the areas where VS has been reported most frequently, with fewer reports in other regions in this country (44). The New Jersey serotype is also the most important serotype in Central America, from southern Mexico to Panama (60) and in the northwestern part of South America, such as Bolivia, Colombia, Ecuador, Peru and Venezuela. In 2007, the disease was reported in 497 herds from these countries. Colombia reported 391 outbreaks where 364 were due to New Jersey and 27 due to Indiana 1 serotype (39).

In Brazil and Argentina, clinical disease associated with New Jersey and Indiana 1 serotypes has not been reported. Outbreaks of VS in these countries are caused by viruses serologically classified as Indiana 2 and 3 serotypes (14). VSV-IN 3 occurs in regions of Brazil at 1-2 year intervals and VSV-IN 2 outbreaks occur sporadically in southern Brazil and Argentina (14, 41). A serological survey from 112 equidae from the Brazilian States of Pernambuco, Bahia, Goais and Rio Grande do Sul revealed 2.6% reactivity for the New Jersey serotype (2). Therefore, even though no clinical disease associated with this serotype has been reported in Brazil, it is presumed that either VSNJV or a closely related and possibly undescribed vesiculovirus is circulating in those States. Vesicular stomatitis virus Indiana 2 has been isolated from outbreaks in Sao Paulo State, in 1966 in Rancheria and in 1979 in Ribeirao Preto. Other large outbreaks due to the Indiana 2 serotype were reported in 1998 in Santa Catarina and Parana States, in southern Brazil (http://www.panaftosa.org.br). The Indiana 3 serotype outbreaks are more frequently reported in northeast Brazil (1) and for a long time it was believed that this serotype was restricted in geographic distribution to this particular region. A virus related to Indiana 3 was isolated from naturally infected phebotomine sand flies in Colombia in 1986 (59) with serological evidence of viral circulation among livestock, but no clinical disease caused by Indiana 3 has been reported outside Brazil.

Outbreaks of VS occurred in Europe during the First World War and in South Africa from 1884 to 1943 from horses exported from the U.S.(22). Vesicular stomatitis no longer occurs in these areas.

Transmission and pathogenesis

Knowledge concerning the natural cycle and pathogenesis of VSV remains incomplete. Vesicular stomatitis virus transmission can occur in a number of ways and these are depicted in Fig. 4. Under natural conditions, insect vector transmission and direct contact have been described. Experimentally, various routes have been tried with success, including intranasal, intradermal, intravenous (19), scarification of the skin (51) or oral mucosa (56), animal-to-animal contact (56) and biological and mechanical insect vector transmission (33). However, studies with VSNJV have demonstrated that the clinical outcome of these routes of inoculation varies considerably. Livestock can be experimentally infected with subsequent clinical disease (vesicle formation) when injection is intradermal at the coronary bands, planum nasale or oral cavity (8, 18, 19, 51). Intranasal instillation, intravenous or intradermal injection at the ear (19), scarification of the flank skin (51) or insect bite at the flank skin (42) results in subclinical (lack of vesicle formation) infection, with serocorversion. Viral shedding from tonsils is known to occur in pigs (19, 56). Also, virus inoculation via insect bite at sites where lesions are not observed in cattle result in subclinical infection (41).

In general lesion development is restricted to the site of inoculation. However, in some studies, pigs inoculated at the snout via intradermal injection developed vesicles at the coronary bands as well (8, 56). The authors of this study suggested a short-term viremia was present, even though it was not detected in their experiment or in any other in domestic animals to date. Because vesicles promptly developed at the site of the inoculation (snout) in those experiments, the authors alternatively suggest that virus was mechanically introduced by the snout vesicle making contact with an abraded epidermal site (coronary band) or by shedding though saliva from tonsil infection.

In animal-to-animal contact studies (19, 56), naïve pigs became infected when housed with pigs inoculated with VSNJV intradermally on the snout. Contact pigs shed virus as early as 1 day after contact with inoculated animals. Contact animals developed lesions on coronary bands or snout. In these same experiments, another group of animals was inoculated on the coronary bands with less severe vesicle formation than observed in the group inoculated at the snout. Naïve animals housed with this group (inoculated on the coronary band) failed to develop clinical disease or seroconvert (19). These studies demonstrate that the development of vesicular lesions is important for animal-to-animal contact transmission (19). They also demonstrated the importance of the site of the inoculation regarding the severity of lesion development and the fact that in order to have efficient animal-to-animal contact transmission prominent lesions (vesicles) are necessary.

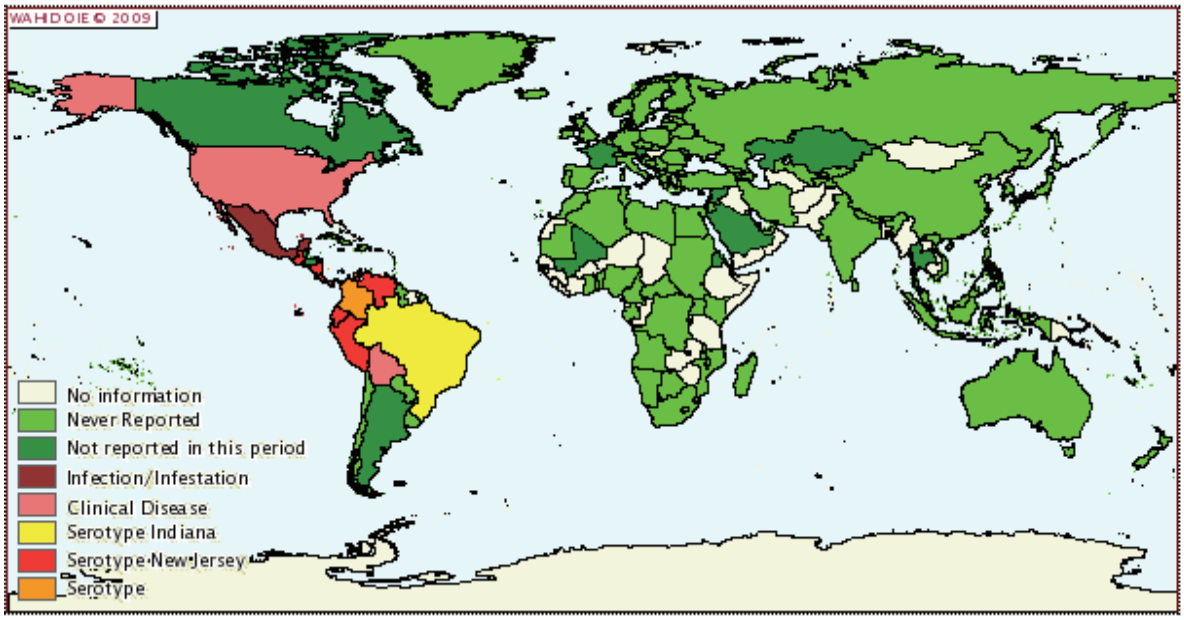

Figure 3 - Geographical distribution of vesicular stomatitis virus according to the World Organization for Animal Health (OIE) for the period of January to June of 2006 (37).

Subclinical disease is frequently reported under both natural and experimental conditions. Epidemiological data reveals that up to 90% of animals within endemic herds can be seropositive for VSV with only 10% of animals presenting the typical clinical signs (vesicles) (15, 17). One possible explanation is that insect site predilections for feeding are at the flank, ear, and periocular areas, where viral inoculation does not result in vesicle formation (33). The role of subclinical disease in transmission via insect or via animal-to-animal contact is not completely known. Some investigators suggest that it could serve as source of transmission and spread of the virus in natural conditions (42). However, it has been shown in experimental cases that it is necessary to have marked clinical disease, with evident vesicle formation, to successfully transmit the virus via animal-to-animal contact (19, 56) and also animal-to-insect (33).

As with other arbovirus transmission cycles, insects are part of the natural life cycle of VSV. In 1969, Tesh and colleagues detected VSV Indiana 1 serotype in naturally infected sand flies (Diptera: *Psychodidae*). Numerous other reports of VSV infecting hematophagous insects such as black flies (Diptera: Simuliidea) (32, 34, 35), mosquitoes (25) (Diptera: culicidae), and *Culicoides* (Diptera: Ceratopogonidae) (57) have since been published. Experimentally, only sand flies have been shown to be capable of transovarial transmission (35, 60). Studies have demonstrated that black flies are competent VSNJV vectors with transmission resulting in the development of clinical disease in mice (35) and pigs (32). In one study, cows developed specific neutralizing antibodies following the bite of VSNJV-infected midges (*Culicoides sonorensis*) feeding on flank skin (42). But in this experiment, although there was seroconversion, lesions were not observed and virus was never isolated from collected samples. In 2000, Mead and colleagues demonstrated horizontal transmission of VSNJV in black flies. This report shows that uninfected flies became infected when co-feeding with infected flies on the same non-viremic host. This finding provides a potential mechanism for maintenance of the virus in nature since viremia has not been reported in naturally or experimentally infected livestock.

A few studies have been done regarding pathogenesis of VSV in laboratory animals and some investigations have been done in livestock. With the limited information available, the mechanisms of the disease appear to be markedly different between rodents and livestock. As already mentioned, viremia has not been documented in naturally or experimentally infected livestock, and vesicular lesions tend to develop at the inoculation site on specific cutaneous or mucocutaneous regions (18, 19, 51, 56). In contrast, viremia with encephalitis and meningitis are expected findings in rodents (6, 10). Cornish et al (2001) infected young and adult *Peromyscus maniculatus* (deer mice), which is a natural host, via two routes - intranasal and intradermal - at the base of the tail. In this experiment, all ages of mice inoculated intranasally developed encephalitis and meningitis. However, in the group inoculated intradermally, young animals were the only ones to develop lesions in the central nervous system. No cutaneous lesions (vesicles) were observed in any of the two experimental groups.

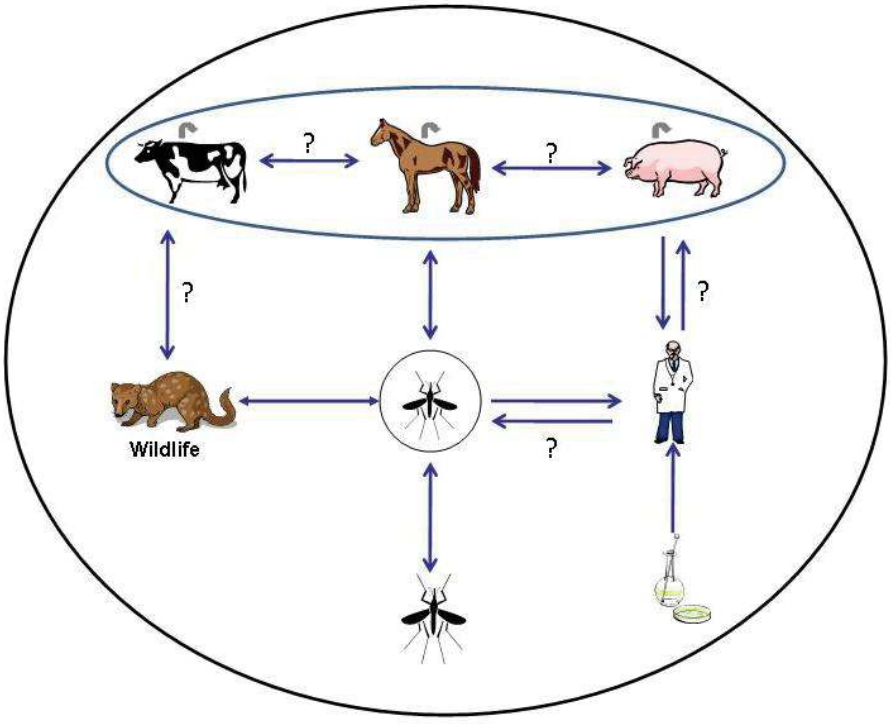

Figure 4 - Proposed natural cycle of vesicular stomatitis viruses based on current scientific information. Arrows indicate direction of virus transmission. Question marks indicate transmission routes presumed to occur but not documented in current literature.

There are no studies focusing on the early pathological and host response events of VSV infections in livestock. In experiments done with swine and horses, animals were followed past the point of seroconversion or after viral shedding had ceased. At this time point, vesicular lesions were in healing stages and so no information was gained about the microscopic events occurring during the vesicular formation stage (19, 56). Howerth et al (2006) inoculated the VSNJV and Indiana 1 serotypes independently in two groups of horses on the tongue, chin and lip, and euthanized the animals at postinoculation days 12 to 15. There was partial to full reepithelization at the primary lesion (original site of inoculation) and superficial ulceration at secondary oral lesions (commonly observed when inoculation site is the oral cavity). Histologically, there was perivascular infiltration of plasma cells and lymphocytes with lesser numbers of neutrophils. Immunophenotyping revealed a mixture of BLA36 (which recognizes B lymphocytes), CD3 (which recognizes T lymphocytes) and MAC387 (which recognizes histiocytes) positive cells. Vesicular stomatitis virus antigens were not detected at the same sites, probably because samples were collected at a late stage of the disease.

The ability of VSV to induce interferon (IFN) production has raised the attention of several investigators (5, 27, 28, 50, 61), who use VSV as a tool in various laboratory techniques for assessing interferon production. Isolates of VSV vary widely within and among serotypes in their ability to induce type I IFN production in chicken embryo cells (27). In general VSNJV serotypes tend to induce higher levels of IFN when compared with Indiana isolates (27). However, to date there are no studies assessing IFN or other cytokine production in livestock following any of the described inoculation methods, either fly bite or scarification. A question that can be raised is

whether the infected host has a different cytokine response when inoculated via fly bite as compared with scarification. A recent review of arboviral diseases describes how mosquito saliva enhances transmission and development of disease for numerous arboviral agents (53). Specifically, mosquito salivary gland extract or mosquito bites enhance transmission and infection of different arboviruses in different systems (11, 38, 54) including VSV *in vitro* (23) and *in vivo* (mice) (24). Intradermal *Aedes aegypti* salivary gland extract and Sindbis virus co-inoculation in mice downregulated IFN-gamma and IFN-beta at 24 and 72 hours postinoculation (55). This same experiment demonstrated upregulation of IL-4 and IL-10. The ability of mosquito saliva to downregulate the expression of T_H1 associated antiviral cytokines and to upregulate T_H2 associated cytokines in many arboviral diseases suggests that it would be worthwhile to determine if biting insects may be exerting similar effects in VSV-infected livestock. The generation of baseline data of host response regarding cytokine expression in cows inoculated via scarification and via fly bite could lead to a better understanding of the pathogenesis of VS in livestock.

Preliminary results from a recent comparative study suggest that black flies have a facilitating component for viral replication (46). In this experiment two Holstein steers were inoculated at the coronary bands with VSNJV, one was inoculated via scarification and the other via infected black fly bite. Euthanasia and tissue collection were performed at 24 hours post-inoculation with coronary bands and local draining lymph nodes processed by *in situ* hybridization using an anti-sense riboprobe for VSV. Intense cytoplasmic staining of keratinocytes from the stratum spinosum as well as in scattered inflammatory cells in the superficial dermis was observed in the coronary bands from both animals. However, the draining lymph nodes of the steer inoculated with black flies revealed markedly higher number of positive cells when compared with the scarified animal, which presented scant positively staining cells. Positive *in situ* hybridization cells were mainly distributed within capsular and cortical sinuses in both animals. This study has shown for the first time *in situ* viral transcription and/or replication in livestock tissues at the inoculation site and most importantly at distant organs, draining lymph nodes (popliteal). This may be an indication that black flies have a component that enhances viral replication.

Conclusion

Although much is known about the VSV in cell culture, and in laboratory animals, and its abilities to produce IFN *in vitro*, the disease in livestock is much less well understood. Further exploration of transmission and pathogenesis in the natural host could improve our abilities to control this economically important disease of livestock in this hemisphere.

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References

1. ALONSO, A., M. A. MARTINS, P. GOMES MDA, R. ALLENDE, M. S. SONDAHL. Development and evaluation of an enzyme-linked immunosorbent assay for detection, typing, and subtyping of vesicular stomatitis virus. J Vet Diagn Invest., 1991.3:287-92.
2. ANDRADE, C., I. MATTOS, A. DA SILVA, C. ROSAS, M. LAGROTA, J. GUIMARAES. Vesicular stomatitis in Brazil. II - Epidemiological survey in equidae, Bats and Tamarins. Anais de Microbiologia., 1981.26:47-51.
3. ANDRADE, C., C. E. ROSAS, L. AMORIM LDE, J. P. MOTA, E. N. TEIXEIRA, N. F. DOS SANTOS. Vesicular stomatitis in Brazil I--Isolation and identification of Alagoas strain. An Microbiol (Rio J)., 1980. 25:81-7.
4. BAILEY, C. A., D. K. MILLER, J. LENARD. Effects of DEAE-dextran on infection and hemolysis by VSV. Evidence that nonspecific electrostatic interactions mediate effective binding of VSV to cells. Virology., 1984. 133:111-8.
5. BASU, M., R. K. MAITRA, Y. XIANG, X. MENG, A. K. BANERJEE, S. BOSE. Inhibition of vesicular stomatitis virus infection in epithelial cells by alpha interferon-induced soluble secreted proteins. J Gen Virol., 2006. 87:2653-62.
6. BI, Z., M. BARNA, T. KOMATSU, C. S. REISS. Vesicular stomatitis virus infection of the central nervous system activates both innate and acquired immunity. J Virol., 1995. 69:6466-72.
7. CARNEIRO, F. A., F. STAUFFER, C. S. LIMA, M. A. JULIANO, L. JULIANO, A. T. DA POIAN. Membrane fusion induced by vesicular stomatitis virus depends on histidine protonation. J Biol Chem., 2003. 278:13789-94.
8. CLARKE, G. R., D. E. STALLKNECHT, E. W. HOWERTH. Experimental infection of swine with a sandfly (Lutzomyia shannoni) isolate of vesicular stomatitis virus, New Jersey serotype. J Vet Diagn Invest ., 1996. 8:105-8.
9. COIL, D. A., A. D. MILLER. Phosphatidylserine is not the cell surface receptor for vesicular stomatitis virus. J Virol., 2004. 78:10920-6.
10. CORNISH, T. E., D. E. STALLKNECHT, C. C. BROWN, B. S. SEAL, E. W. HOWERTH. Pathogenesis of experimental vesicular stomatitis virus (New Jersey serotype) infection in the deer mouse (Peromyscus maniculatus). Vet Pathol., 2001. 38:396-406.
11. EDWARDS, J. F., S. HIGGS, B. J. BEATY. Mosquito feeding-induced enhancement of Cache Valley Virus

(Bunyaviridae) infection in mice. J Med Entomol., 1998. 35:261-5.
12. ELLIS, E. M., H. E. KENDALL. The Public Health and Economic Effects of Vesicular Stomatitis in a Herd of Dairy Cattle. J Am Vet Med Assoc., 1964. 144:377-80.
13. FEDERER, K. E., R. BURROWS, J. B. BROOKSBY. Vesicular stomatitis virus--the relationship between some strains of the Indiana serotype. Res Vet Sci., 1967. 8:103-17.
14. FERNANDEZ, A. A., M. S. SONDAHL. Antigenic and immunogenic characterization of various strains of the Indiana serotype of vesicular stomatitis isolated in Brazil. Bol. Centro Panamericano Fiebre Aftosa., 1985. 51:27-30.
15. FRANCY, D. B., C. G. MOORE, G. C. SMITH, W. L. JAKOB, S. A. TAYLOR, C. H. CALISHER. Epizootic vesicular stomatitis in Colorado, 1982: isolation of virus from insects collected along the northern Colorado Rocky Mountain Front Range. J Med Entomol ., 1988. 25:343-7.
16. HANSON, R. P., J. ESTUPINAN, J. CASTANEDA. Vesicular stomatitis in the Americas. Bull Off Int Epizoot., 1968. 70:37-47.
17. HAYEK, A. M., B. J. MCCLUSKEY, G. T. CHAVEZ, M. D. SALMAN. Financial impact of the 1995 outbreak of vesicular stomatitis on 16 beef ranches in Colorado. J Am Vet Med Assoc., 1998. 212:820-3.
18. HOWERTH, E. W., D. G. MEAD, P. O. MUELLER, L. DUNCAN, M. D. MURPHY, D. E. STALLKNECHT. Experimental vesicular stomatitis virus infection in horses: effect of route of inoculation and virus serotype. Vet Pathol., 2006. 43:943-55.
19. HOWERTH, E. W., D. E. STALLKNECHT, M. DORMINY, T. PISELL, G. R. CLARKE. Experimental vesicular stomatitis in swine: effects of route of inoculation and steroid treatment. J Vet Diagn Invest., 1997. 9:136-42.
20. HUNEYCUTT, B. S., Z. BI, C. J. AOKI, C. S. REISS. Central neuropathogenesis of vesicular stomatitis virus infection of immunodeficient mice. J Virol., 1993. 67:6698-706.
21. JONKERS, A. H., R. E. SHOPE, T. H. AITKEN, L. SPENCE. Cocal Virus, a New Agent in Trinidad Related to Vesicular Stomatitis Virus, Type Indiana. Am J Vet Res., 1964. 25:236-42.
22. LETCHWORTH, G. J., L. L. RODRIGUEZ, J. DEL CARRERA. Vesicular stomatitis. Vet J., 1999. 157:239-60.
23. LIMESAND, K. H., S. HIGGS, L. D. PEARSON, B. J. BEATY. Effect of mosquito salivary gland treatment on vesicular stomatitis New Jersey virus replication and interferon alpha/beta expression in vitro. J Med Entomol., 2003. 40:199-205.
24. LIMESAND, K. H., S. HIGGS, L. D. PEARSON, B. J. BEATY. Potentiation of vesicular stomatitis New Jersey virus infection in mice by mosquito saliva. Parasite Immunol., 2000. 22:461-7.
25. LIU, I. K., Y. C. ZEE. The pathogenesis of vesicular stomatitis virus, serotype Indiana, in Aedes aegypti mosquitoes. I. Intrathoracic injection. Am J Trop Med Hyg., 1976. 25:177-85.
26. LYLES, D. S., C. E. RUPPRECHT. Rhabdoviridae, p. 1363-1408. *In* D. M. Knipe and P. M. Howley (ed.), Fields Virology, 5th ed, vol. 1. Lippincott Williams and Williams, Philadelphia. 2007.
27. MARCUS, P. I., L. L. RODRIGUEZ, M. J. SEKELLICK. Interferon induction as a quasispecies marker of vesicular stomatitis virus populations. J Virol., 1998. 72:542-9.
28. MARCUS, P. I., M. J. SEKELLICK, S. T. NICHOL. Interferon induction by viruses. XXI. Vesicular stomatitis virus: interferon inducibility as a phylogenetic marker. J Interferon Res., 1992. 12:297-305.
29. MARTINEZ, I., J. C. BARRERA, L. L. RODRIGUEZ, G. W. WERTZ. Recombinant vesicular stomatitis (Indiana) virus expressing New Jersey and Indiana glycoproteins induces neutralizing antibodies to each serotype in swine, a natural host. Vaccine., 2004. 22:4035-43.
30. MARTINEZ, I., L. L. RODRIGUEZ, C. JIMENEZ, S. J. PAUSZEK, G. W. WERTZ. Vesicular stomatitis virus glycoprotein is a determinant of pathogenesis in swine, a natural host. J Virol., 2003. 77:8039-47.
31. MARTINEZ, I., G. W. WERTZ. Biological differences between vesicular stomatitis virus Indiana and New Jersey serotype glycoproteins: identification of amino acid residues modulating pH-dependent infectivity. J Virol., 2005. 79:3578-85.
32. MEAD, D. G., E. W. GRAY, R. NOBLET, M. D. MURPHY, E. W. HOWERTH, D. E. STALLKNECHT. Biological transmission of vesicular stomatitis virus (New Jersey serotype) by Simulium vittatum (Diptera: Simuliidae) to domestic swine (Sus scrofa). J Med Entomol., 2004. 41:78-82.
33. MEAD, D. G., E. W. HOWERTH, M. D. MURPHY, E. W. GRAY, R. NOBLET, D. E. STALLKNECHT. Black fly involvement in the epidemic transmission of vesicular stomatitis New Jersey virus (Rhabdoviridae: Vesiculovirus). Vector Borne Zoonotic Dis., 2004. 4:351-9.
34. MEAD, D. G., C. J. MARE, E. W. CUPP. Vector competence of select black fly species for vesicular stomatitis virus (New Jersey serotype). Am J Trop Med Hyg., 1997. 57:42-8.
35. MEAD, D. G., C. J. MARE, F. B. RAMBERG. Bite transmission of vesicular stomatitis virus (New Jersey serotype) to laboratory mice by Simulium vittatum (Diptera: Simuliidae). J Med Entomol., 1999. 36:410-3.
36. OIE. 2008. Vesicular Stomatitis, p. 367-376. *In* WOAH (ed.), Manual of Diagnostic Tests and

Vaccines for Terrestrial Animals, 2008, vol. 1. World Organisation for Animal Health.
37. OIE May 9 2008 2009, posting date. World Animal Health Information Database (WAHID) Interface - Disease distribution maps. OIE - World Organization for Animal Health [Online.]
38. OSORIO, J. E., M. S. GODSEY, G. R. DEFOLIART, T. M. YUILL. La Crosse viremias in white-tailed deer and chipmunks exposed by injection or mosquito bite. Am J Trop Med Hyg., 1996. 54:338-42.
39. PANAFTOSA 2007, posting date. Informe anual 2007. PANAFTOSA - Foot-and-Mouth Disease Center. [Online.]
40. PATTERSON, W. C., L. O. MOTT, E. W. JENNEY. A study of vesicular stomatitis in man. J Am Vet Med Assoc., 1958. 133:57-62.
41. PAUSZEK, S. J., R. ALLENDE, L. L. RODRIGUEZ. Characterization of the full-length genomic sequences of vesicular stomatitis Cocal and Alagoas viruses. Arch Virol., 2008. 153:1353-7.
42. PEREZ DE LEON, A. A., W. J. TABACHNICK. Transmission of vesicular stomatitis New Jersey virus to cattle by the biting midge Culicoides sonorensis (Diptera: Ceratopogonidae). J Med Entomol., 2006. 43:323-9.
43. QUIROZ, E., N. MORENO, P. H. PERALTA, R. B. TESH. A human case of encephalitis associated with vesicular stomatitis virus (Indiana serotype) infection. Am J Trop Med Hyg., 1988. 39:312-4.
44. RAINWATER-LOVETT, K., S. J. PAUSZEK, W. N. KELLEY, L. L. RODRIGUEZ. Molecular epidemiology of vesicular stomatitis New Jersey virus from the 2004-2005 US outbreak indicates a common origin with Mexican strains. J Gen Virol., 2007. 88:2042-51.
45. REIF, J. S., P. A. WEBB, T. P. MONATH, J. K. EMERSON, J. D. POLAND, G. E. KEMP, G. CHOLAS. Epizootic vesicular stomatitis in Colorado,., 1982: infection in occupational risk groups. Am J Trop Med Hyg., 1987. 36:177-82.
46. REIS, J., L. RODRIGUEZ, D. G. MEAD, G. SMOLIGA, C. BROWN. Detection of Vesicular Stomatitis New Jersey Virus in experimentally infected cattle using *in situ* hybridization and immnunohistochemisty. Veterinary Pathology., 2008. 45:767.
47. RODRIGUEZ, L. L. Emergence and re-emergence of vesicular stomatitis in the United States. Virus Res., 2002. 85:211-9.
48. RODRIGUEZ, L. L. Vesicular Stomatitis., p. 423-426. *In* C. C. Brown, Torres, A. (ed.), Foreing Animal Diseases., Seventh ed. United States Animal Health Association, Boca Raton, FL. 2008.
49. ROSE, J. K., M. A. WHITT. Rhadoviridae: The viruses and their replication, p. 1221-1244. *In* D. M. Knipe, Howley, P.M. (ed.), Fields Virology, Fourth ed, vol. 1. 2001.
50. SCHABBAUER, G., J. LUYENDYK, K. CROZAT, Z. JIANG, N. MACKMAN, S. BAHRAM, P. GEORGEL. TLR4/CD14-mediated PI3K activation is an essential component of interferon-dependent VSV resistance in macrophages. Mol Immunol., 2008. 45:2790-6.
51. SCHERER, C. F., V. O'DONNELL, W. T. GOLDE, D. GREGG, D. M. ESTES, L. L. RODRIGUEZ. Vesicular stomatitis New Jersey virus (VSNJV) infects keratinocytes and is restricted to lesion sites and local lymph nodes in the bovine, a natural host. Vet Res., 2007. 38:375-90.
52. SCHLEGEL, R., T. S. TRALKA, M. C. WILLINGHAM, I. PASTAN. Inhibition of VSV binding and infectivity by phosphatidylserine: is phosphatidylserine a VSV-binding site? Cell., 1983. 32:639-46.
53. SCHNEIDER, B. S., S. HIGGS. The enhancement of arbovirus transmission and disease by mosquito saliva is associated with modulation of the host immune response. Trans R Soc Trop Med Hyg., 2008. 102:400-8.
54. SCHNEIDER, B. S., L. SOONG, Y. A. GIRARD, G. CAMPBELL, P. MASON, S. HIGGS. Potentiation of West Nile encephalitis by mosquito feeding. Viral Immunol., 2006.., 19:74-82.
55. SCHNEIDER, B. S., L. SOONG, N. S. ZEIDNER, S. HIGGS. Aedes aegypti salivary gland extracts modulate anti-viral and TH1/TH2 cytokine responses to sindbis virus infection. Viral Immunol., 2004. 17:565-73.
56. STALLKNECHT, D. E., D. E. PERZAK, L. D. BAUER, M. D. MURPHY, E. W. HOWERTH. Contact transmission of vesicular stomatitis virus New Jersey in pigs. Am J Vet Res., 2001.62:516-20.
57. SUDIA, W. D., B. N. FIELDS, C. H. CALISHER. The isolation of vesiculay stomatitis virus (Indiana strain) and other viruses from mosquitoes in New Mexico, 1965. Am J Epidemiol., 1967. 86:598-602.
58. TESH, R., S. SAIDI, E. JAVADIAN, P. LOH, A. NADIM. Isfahan virus, a new vesiculovirus infecting humans, gerbils, and sandflies in Iran. Am J Trop Med Hyg., 1977. 26:299-306.
59. TESH, R. B., J. BOSHELL, G. B. MODI, A. MORALES, D. G. YOUNG, A. CORREDOR, C. FERRO DE CARRASQUILLA, C. DE RODRIGUEZ, L. L. WALTERS, M. O. GAITAN. Natural infection of humans, animals, and phlebotomine sand flies with the Alagoas serotype of vesicular stomatitis virus in Colombia. Am J Trop Med Hyg., 1987. 36:653-61.
60. TESH, R. B., P. H. PERALTA, K. M. JOHNSON. Ecologic studies of vesicular stomatitis virus. I. Prevalence of infection among animals and humans living in an area of endemic VSV activity. Am J Epidemiol., 1969. 90:255-61.

61. WAIBLER, Z., C. N. DETJE, J. C. BELL, U. KALINKE. Matrix protein mediated shutdown of host cell metabolism limits vesicular stomatitis virus-induced interferon-alpha responses to plasmacytoid dendritic cells. Immunobiology., 2008. 212:887-94.