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Caliciviruses of Animals

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Caliciviruses of animals in the US first began to receive attention approximately 70 years ago. Since then, numerous caliciviruses have been isolated from a variety of animal species. The epizootics of rabbit hemorrhagic disease in the US in 2000 and 2001, and the reported isolation of a "vesicular exanthema of swine-like calicivirus" from an aborted bovine fetus in 2002 have heightened concerns about the roles of caliciviruses in diseases of animals. This paper provides the reader with an introduction to the caliciviruses of animals. The current taxonomy, natural history, epidemiology, clinical signs, zoonotic aspects, and the significance of caliciviruses in animal health are discussed. The diseases caused by different caliciviruses will not be discussed in depth in this paper, with the possible exception of vesicular exanthema of swine. Details about specific diseases are available elsewhere.

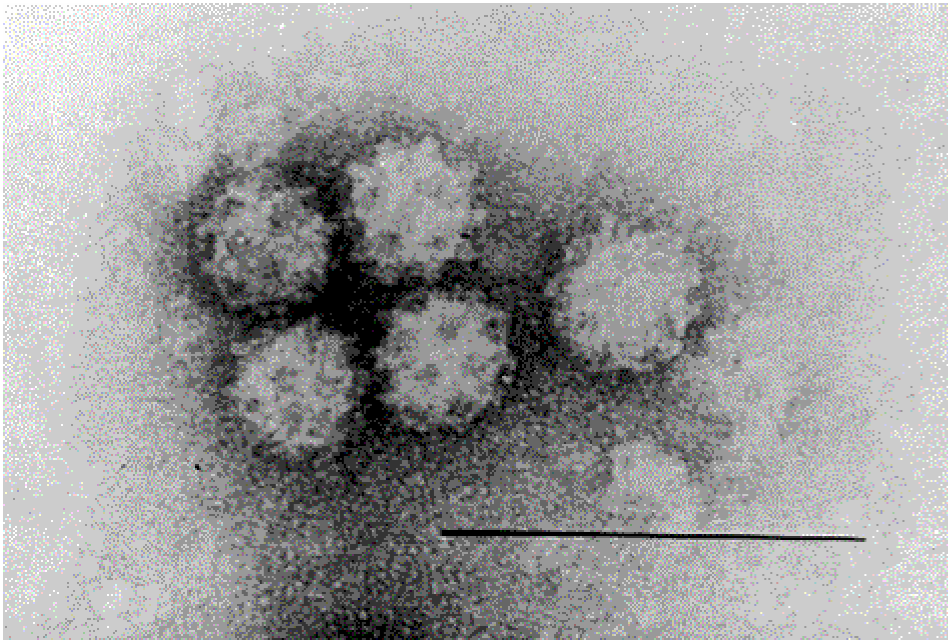
Table 1. Partial list of abbreviations that have been included in this paper.

BCV	bovine calicivirus
BECV	bovine enteric calici-like virus
CaCV	canine calicivirus
CCV	cetacean calicivirus
CSG	*Caliciviridae* Study Group
EBHV	European brown hare syndrome virus
FCV	feline calicivirus
ICTV	International Committee on Taxonomy of Viruses
NLV	"Norwalk-like" viruses
NV	Norwalk virus
PECV	porcine enteric calicivirus
PCV	primate calicivirus
RHDV	rabbit hemorrhagic disease virus
SLV	"Sapporo-like" viruses
SV	Sapporo virus
SMSV	San Miguel sea lion virus
VESV	vesicular exanthema of swine virus

What is the taxonomical classification of caliciviruses?

Shortly after being discovered, several caliciviruses (e.g., feline calicivirus, Norwalk virus) were assigned originally to the family Picornaviridae on the basis of electron microscopy. In 1999, the International Committee on Taxonomy of Viruses (ICTV) approved several proposals that had been submitted by the Caliciviridae Study Group in 1998 (Green et al., 2000). Now, caliciviruses are members of the family Caliciviridae. The name Caliciviridae, derived from the Latin word "calix", means "cup" or "chalice", and refers to the 32 cup-shaped depressions on the surface of the virion **(Figure 1)** [Prasad et al., 1994]. Within this single family, there are four genera. These genera are Vesivirus, Lagovirus, Norovirus (formerly "Norwalk-like viruses") and Sapovirus (formerly "Sapporo-like viruses"). The latter-two genera, originally assigned temporary names, now have been assigned permanent names by the scientific community.

Figure 1. Cup-shaped morphology of calicivirus virions (From Smith et al., 1998b).



These four genera have been divided further into species (Benson et al., 2000; Wheeler et al., 2000; National Center for Biotechnology Information, 2002). Some examples of these species are: Feline calicivirus and Vesicular exanthema of swine virus (genus Vesivirus); Rabbit hemorrhagic disease virus and European brown hare syndrome virus (genus Lagovirus), Norwalk virus and Bovine enteric calici-like virus (genus Norovirus), and Sapporo virus and porcine enteric calicivirus (genus Sapovirus) **(Table 2).**

Taxonomically speaking, is hepatitis E virus of humans a calicivirus?

No. Hepatitis E virus is classified no longer as a calicivirus. There are structural similarities between hepatitis E virus and caliciviruses, when the viruses are examined by negative-stain electron microscopy. These similarities became the basis for originally assigning hepatitis E virus to the family *Caliciviridae* when hepatitis E virus was discovered. Due to the absence of phylogenetic relatedness between hepatitis E virus and caliciviruses, as well as to differences in the types of replicative enzymes used by hepatitis E virus, the *Caliciviridae* Study Group submitted a proposal to remove hepatitis E virus from *Caliciviridae*. This proposal was submitted to the ICTV in 1998, and it was accepted in 1999. Now, hepatitis E virus is in the "unassigned status" (Green et al., 2000).

What is the origin of caliciviruses in nature?

Caliciviruses can be divided broadly into two categories based their origins in nature: (1) marine caliciviruses and (2) terrestrial caliciviruses (Barlough et al., 1986a; Barlough et al., 1986b; Smith et al., 1990; Smith et al., 1998b). Marine caliciviruses are caliciviruses whose origin is thought to be the ocean. Examples of marine caliciviruses are VESV and SMSV. Terrestrial caliciviruses are caliciviruses whose origin is thought to be land. Examples of terrestrial caliciviruses are PCV and CaCV. The first recognized disease caused by a calicivirus of **marine** origin in the US was in farm swine in California in 1932. Although farm swine are terrestrial animals, it was concluded from a retrospective investigation that the calicivirus infection that was diagnosed in farm swine probably had its origin in the oceans. One of the earliest recognitions of disease caused by a calicivirus of **terrestrial** origin (FCV) was in the domesticated cat in 1957, followed by the discoveries years later of PCV and CaCV in 1978 and 1982, respectively (Smith et al., 1990).

Table 2. The four genera, an incomplete list of the species, examples of some strains of viruses in the family *Caliciviridae*, and the predominant host. These genera and species were approved in 1999 by the International Committee on Taxonomy of Viruses (ICTV) in response to proposals submitted by the *Caliciviridae* Study Group in 1998. The names of strains may vary with the source.

			Predominant Host	
Genus	**Species**	**Strain**	**Animal**	**Human**
Vesivirus	Vesicular exanthema of swine virus	VESV-A48	Yes	
	Bovine calicivirus	BCV Bos-1	Yes	
	Feline calicivirus	FCV-F9	Yes	
	Canine calicivirus	CCV	Yes	
	Mink calicivirus	MCV	Yes	
	Primate calicivirus	Primate Pan-1	Yes	
	Reptile calicivirus	RCV Cro-1	Yes	
	San Miguel sea lion virus	SMSV-1	Yes	
	Walrus calicivirus	WCV	Yes	
	Cetacean calicivirus	CCV Tur-1	Yes	
Lagovirus	Rabbit hemorrhaghic disease virus	RHDV/GH	Yes	
	European brown hare syndrome virus	EBHS/GD	Yes	
Norovirus	Norwalk virus	Southhampton		Yes
	Bovine enteric calici-like virus	BECV	Yes	
Sapovirus	Sapporo virus	Hou7-1181		Yes
	Porcine enteric calicivirus	PECV	Yes	

From: Smith et al., 1990; Green et al., 2000; National Center for Biotechnology Information. http://www.ncbi.nlm.nih.gov/taxonomy/ . 2002.

Why is it important for those involved in animal health to be aware of caliciviruses?

Caliciviruses are important to animal health for at least three reasons: (1) some caliciviruses can induce a vesicular disease that may be clinically indistinguishable from other important vesicular diseases of livestock such as foot and mouth disease[1] (FMD), vesicular stomatitis, and swine vesicular disease[2], (2) caliciviruses can induce non-vesicular diseases in some livestock, wildlife and companion animal species (e.g., reproductive failure in swine, the California sea lion, and the Northern fur seal; hemorrhagic disease in rabbits; respiratory disease in cats), and (3) at least one calicivirus is zoonotic, albeit a rare zoonosis (Smith et al., 2002).

[1] Foot and mouth disease (FMD) has not been diagnosed in the US since 1929.

[2] Swine vesicular disease has never been diagnosed in the US.

When was a calicivirus infection first diagnosed in livestock in the US, and when was the last reported epizootic?

The first evidence of a calicivirus infection in livestock was during an epizootic of vesicular disease in a swine herd in California in 1932 (Barlough et al., 1986a; Smith et al., 1998b). The source of the outbreak of vesicular disease was the feeding of raw food waste of marine origin that had been collected from restaurants. The outbreak, initially suspected to be foot and mouth disease, was contained by quarantine and slaughter of affected herds. A second outbreak of vesicular disease occurred in a swine herd in California in 1933. This outbreak of vesicular disease was excluded as an outbreak of FMD because cattle were not susceptible to the disease, horses were susceptible, and the pathogen was immunologically distinct from all three FMD virus serotypes that had been recognized in Europe. A third outbreak of vesicular disease occurred in a swine herd in California in 1934. Thus, this presumably new disease entity was named vesicular exanthema of swine (VES). The last reported outbreak of VES in the US was in 1956.

When was the first calicivirus isolated from marine mammals, and why was the isolation of this calicivirus a significant event?

Regarding marine mammals, the calicivirus SMSV-1 was isolated first from the California sea lion and the Northern fur seal on San Miguel Island, California in 1972 (Barlough et al., 1986a; Barlough et al., 1986b; Smith et al., 1990; Smith et al., 1998b). The isolation of this calicivirus from marine mammals that were experiencing reproductive failure was significant in that the virus was morphologically and physico-chemically indistinguishable from VESV, a calicivirus that had been declared "eradicated" from the US in 1959. Experimental infection of pigs with the SMSV induced a disease similar to the disease that already had been associated with VESV. Regarding the origin of VESV, the isolation of a calicivirus from the California sea lion was a significant event in that it provided an early plausible link between VESV and the ocean.

What is the prevalence of calicivirus infections in animal species?

One of the challenges to diagnosing calicivirus infections in animal species has been the absence of reliable diagnostic reagents that have undergone a rigorous process of validation (Smith et al., 1998b). Thus, while calicivirus research in animals spans several decades, epidemiological studies of the prevalence of calicivirus infections in animals are limited, both in number and in scope. There are some indications that progress is being made in developing reagents for diagnostic purposes. In a report that was published in 2002, reference was made to a " . . . full complement of diagnostic reagents. . . ." that was developed by the Laboratory for Calicivirus Studies at Oregon State University (Smith et al., 2002). These reagents are not available yet commercially. It is anticipated that, after having undergone validation, the reagents will be used to investigate livestock diseases to determine which diseases can be linked causally to calicivirus infections, if any.

How frequently were naturally-acquired calicivirus infections reported in the more common livestock and companion animal species, after VES had been eradicated from the US in 1959?

Prior to the last reported outbreak of VES in 1956, and the official eradication of VESV in the US in 1959, VESV infections in swine had become widespread. Since the eradication of VESV from domesticated swine herds in the US, there have been only sporadic reports of other calicivirus infections in livestock species **(Table 3)**. Prior to 2002, there was one report (1983) of a naturally acquired calicivirus infection in calves. Most recently, there has been one report of naturally-acquired calicivirus infection in an aborted bovine fetus (2002). There has been one report (1992) of naturally-acquired calicivirus infection in pigs during two different outbreaks of porcine reproductive and respiratory syndrome (formerly swine infertility and respiratory syndrome). There have been three reports (1981, 1985, 1988) of naturally-acquired calicivirus infection in dogs. While only a few reports of naturally-acquired calicivirus infection were found in the medical literature, the list of reports in Table 3 is not intended to be all-inclusive.

It was written in a peer-reviewed scientific publication in 2002 that caliciviruses are "endemic" in livestock populations in the U.S. What evidence is there of the endemicity of caliciviruses in US livestock?

Calicivirus infections in US livestock have been reported to be endemic by one research investigator (Smith et al., 2002). The basis of this claim is unclear, however, because this same investigator has often referred to the long-standing absence of diagnostic reagents for caliciviruses in other peer-reviewed publications (". . diagnostic reagents for epidemiologic studies need to be made available…"). The reagents to which this investigator referred include antigens, monoclonal antibodies, polymerase chain reaction primer sets, cDNA probes that are based on group epitopes, and

Table 3. Case reports of naturally-acquired calicivirus infections in livestock and companion animal species. The species of origin, virus species, year published and the author of the publication are included.			
Species of Origin	**Virus Species**	**Year** [1]	**Author**
Bovine	Bovine calicivirus bos-1	1983	Smith et al.
	Bovine calicivirus bos-2	2002	Smith et al.
Porcine	Swine calicivirus	1992	Smith et al.
Canine	Feline calicivirus	1981	Evermann et al.
	Canine calicivirus	1985	Evermann et al.
	Canine calicivirus	1988	Crandall
[1]The year in which a report was published and the year in which a calicivirus was isolated were not always the same year.			

pathotype-specific reagents to differentiate pathogenic from nonpathogenic infections. These diagnostic reagents would be a prerequisite for large-scale epidemiological investigations to verify the endemicity of caliciviruses in livestock populations. In addition to the scarcity of diagnostic reagents, the number of published scientific reports that refer to the endemicity of caliciviruses are rather sparse. In fact, there is only one state in the US in which there is merely a suggestion of calicivirus endemicity in cattle and sheep (Smith et al., 1983; Smith et al., 1990).

Has any calicivirus ever been granted sufficient priority so that the virus has been included in the surveys by the USDA APHIS's national animal health monitoring system (NAHMS)?

No. No calicivirus has ever been granted sufficient priority by the livestock industries so that the virus has been included in a national study by the NAHMS. The NAHMS of USDA APHIS solicits input from various animal industries to prioritize the pathogens that should be included in its national studies. Some factors that favor the inclusion of a pathogen in a NAHMS study are **reasonable evidence** of: (1) widespread geographic distribution of infection, (2) high prevalence of infection (3) significant cost to an industry due to high morbidity, high mortality, and decreased productivity (4) a threat to international trade and the accompanying economic consequences, and (5) public health significance. One proposal was submitted in 1997 to study calicivirus serology using laboratory specimens from the NAHMS swine serum bank. This proposal was not approved by the panel of scientific reviewers, one reason being concerns about the reliability of the diagnostic test. (Personal communication, Eric J. Bush, USDA/APHIS/VS, 2002). Salmonella, *Escherichia coli* O157:H7, bovine leukosis, *Mycobacterium paratuberculosis*, porcine reproductive and respiratory syndrome virus, and cryptosporidia are some examples of pathogens that have been included in the NAHMS' national studies. Each of these pathogens met most of the five criteria, or all five of them.

What diseases are associated with calicivirus infections, and to what extent have calicivirus infections adversely affected productivity in livestock?

Vesicular exanthema, pneumonia, abortion, encephalitis, myocarditis, myositis, and hepatitis are some diseases that have been associated with calicivirus infections in animals and in humans (Smith et al., 1998b). In addition to these diseases, clinical signs including diarrhea, coagulopathy, and hemorrhage have been observed. Not all of these diseases, nor all of these clinical signs, are apparent during infection by each and every calicivirus. For example, exanthema was common in swine that were infected with VESV, but VESV has been declared an "eradicated" disease for 43 years. Coagulopathy is common in rabbits that become infected with RHDV, but only three small outbreaks of RHD have been diagnosed in the US, all in 2001 and 2002. Abortion is common in pinnipeds that become infected with SMSV. Diarrhea is common in humans that become infected with NV, but animals are not susceptible to NV.

How prevalent are naturally-occurring, calicivirus infections in livestock species in the US?

The types of epidemiological investigations that would be necessary to establish the prevalence of naturally-occurring calicivirus infections in terrestrial animals, especially livestock species, have not been undertaken. While there have been no national studies to establish the prevalence of naturally-occurring calicivirus infections in various species of livestock, the bovine calicivirus BCV Bos-1 was recovered from dairy calves in a localized geographical region in one state in 1981 (Barlough et al., 1987; Smith et al., 1990). Also, antibodies to SMSV-5 and SMSV-13 were identified in serum from cattle in that same state, and antibodies to SMSV-13 were identified in serum from sheep in that state in 1985 (Smith et al., 1990). However, neither the isolation of BCV Bos-1 nor the detection of antibodies to SMSV-5 and SMSV-13 in cattle is sufficient to establish firmly the role of these viruses in causing disease.

How prevalent are naturally-occurring, calicivirus infections in non-livestock species (e.g., dogs, cats)?

Calicivirus infections have been diagnosed in companion animal species including the cat and the dog (Fastier, 1957; Hoover et al., 1975; Evermann et al., 1981; Evermann et al., 1985; Smith et al., 1998b). Occasional infections have been reported in the opal eye perch, the white tern (a migratory sea bird), snakes, and one amphibian. Some caliciviruses are not highly host-specific, so some viruses may adapt to several different animal species. For example, all members of the family *Felidae* are susceptible to infection by FCV. FCV also has been diagnosed as a naturally-acquired infection in the dog, as an experimental infection in the coyote, and serological evidence of FCV infection in humans has been reported. These human infections may be due simply to occasional exposure of a human to a cat with an acute infection (J. Neill, personal communication, 2002). While the prevalence of FCV in the domesticated cat has not been established, FCV is one calicivirus for which vaccines are manufactured annually in the US. This suggests that FCV infection is at least a perceived health risk to domesticated feline populations.

How prevalent are naturally-occurring, calicivirus infections in humans?

The prevalence of calicivirus infections in humans has not been established. Calicivirus infections are thought to be a frequent cause of foodborne disease; however, the infections are rarely diagnosed due to the absence of reliable diagnostic reagents (Centers for Disease Control and Prevention, 2001a; Centers for Disease Control and Prevention, 2001b). One investigation of calicivirus infection in human blood donors showed that 19 percent of 150 patients were antibody-positive to calicivirus polyvalent antigen from several strains of SMSV (Smith et al., 1998b). However, it was not established that any of these patients already **had** developed a disease that was attributed to caliciviruses, or that they **ever** developed such a disease. Another concern about this investigation is that the blood donors represented a convenience sample (with all of its potential shortcomings) of the human population, versus some type of random sample, of which the latter generally would be expected to provide a more accurate estimate of the population prevalence of calicivirus infection in humans.

How are caliciviruses transmitted among susceptible livestock hosts?

Several livestock species are susceptible to calicivirus infections. However, much of what has been learned thus far about the transmission of caliciviruses in animals is based on what was learned from the VESV epizootics that occurred in the US during the 1930s to 1950s (Smith et al., 1990; Smith et al., 1998b). Transmission of VESV may be either direct or indirect. The most important direct route of transmission of VESV was via ingestion. The exposure was due to the feeding of raw food wastes (i.e., fish scraps) that were contaminated with VESV, thus the fish-to-swine cycle of transmission of VESV. After the initial three outbreaks of VESV, the route of transmission during subsequent outbreaks was via ingestion of raw garbage (i.e., using raw pork trimmings as a source of feed), which created the swine-to-swine cycle of transmission. Virus shedding occurs shortly before the vesicles form, and for several days afterwards. VESV was shed in feces, urine, both nasal and oral secretions, and fluids from vesicular lesions. The exact modes of transmission of the bovine caliciviruses have not been determined. However, the utilization of marine by-products as feed supplements is suspected to be a route of transmission. Calicivirus transmission by direct contact with virus-laden vesicles has been shown to be an important route of exposure in some species.

Contrary to what was thought shortly after caliciviruses were initially discovered, some caliciviruses are not highly host-specific **(Table 4)**. For example, SMSV-5 has at least 16 different hosts, and FCV-F9 is infectious to the domesticated cat, possibly the cheetah, the dog, and the coyote. Indirect transmission of caliciviruses occurs through contaminated feed, water, and fomites. The body louse of swine, *Haematopinus suis*, may have been more of a mechanical vector for transmission of VESV, rather than having been an intermediate host for transmission.

Table 4. Transmission of caliciviruses among various animal species, including the source of the virus, the recipient host, and whether the transmission occurred experimentally or naturally.			
		Type of Transmission	
Source of Virus	**Recipient Host**	**Experimental**	**Natural**
opal eye perch	swine	✝	
reptile	snakes (3 species)		✝
reptile	amphibian		✝
reptile	marine mammals		✝
seal meat	mink	✝	
sea lion	opal eye perch	✝	
opal eye perch	Northern fur seal	✝	
host-free virus	shellfish	✝	
host-free FCV	dog		✝
host-free FCV	seal		✝
piglets	sows	✝	
sea lion	human		✝
From Smith et al., 1998b. (Revised).			

How can calicivirus infections be controlled in domestic livestock species? What measures were taken to minimize the risk of transmission of VESV?

With the exception of the VESV outbreaks in swine in the US from the 1930s through the 1950s, outbreaks of diseases due to caliciviruses in most terrestrial livestock species have not been apparent. Due to what appears to be very limited opportunities to study naturally-acquired calicivirus infections in livestock, anything more than brief commentary about control of caliciviruses in species other than swine would be speculative. Regarding VESV specifically, the passage of, and probably of even greater importance, the **enforcement** of, Federal legislation that made it illegal to feed raw waste to swine was of paramount importance in controlling VESV (Smith et al., 1990; Smith et al., 1998b). Domesticated rabbits in the US are not classified as livestock per se, but are reared as companion-animals, as laboratory animals, and for meat and pelts. Nonetheless, the first epizootic of rabbit hemorrhagic disease, a calicivirus infection of rabbits, occurred in a single rabbitry (n = 27 rabbits) in the US in 2000. This epizootic of RHD was controlled by euthanasia of the few surviving rabbits. The same is true for the outbreak of RHD in Flushing, NY in 2001.

Are there vaccines to prevent calicivirus infections in domestic animal species, and to what extent are these vaccines beneficial?

Epizootics due to caliciviruses are rare in the US. The percent morbidity in most terrestrial animals infected with caliciviruses has varied from low to high. The percent mortality has been low consistently, with the exception of the domesticated rabbit. The only calicivirus for which commercially-available vaccines are being manufactured consistently is FCV (Entriken, 2001) **[Table 5]**. The absence of commercially-available calicivirus vaccines for other domestic species suggests that diseases caused by caliciviruses in these species are rare, or are diagnosed only rarely. The absence of these vaccines also may indicate that the veterinary pharmaceutical and biological industries have not identified any economic benefits of manufacturing calicivirus vaccines. Regarding the efficacy of calicivirus vaccines, some demonstrable level of efficacy can be assumed for vaccines that are licensed by the USDA APHIS Centers for Veterinary Biologics; furthermore, the efficacy of these licensed vaccines can be assumed generally to be at least 12 months.

Are calicivirus diseases zoonotic (i.e., can diseases caused by caliciviruses be transmitted from animals to humans)?

Zoonotic infections due to caliciviruses seem to be rare. Antibodies to SMSV-4 and SMSV-5 in laboratory workers who had worked with marine caliciviruses were reported as far back as 1978. Although antibodies can be an indication of prior exposure and/or infection, no disease ever was recognized in these workers. SMSV-5, originally isolated from northern fur seals that had clinical signs of a vesicular disease, was recovered from a laboratory worker with a systemic illness in which there were vesicular lesions on all extremities (Smith et al., 1998a). This isolate was designated SMSV-5 Homosapien-1 (SMSV-5 Hom-1). The source of infection in this patient could not be determined with certainty; however, the patient was responsible for "processing" caliciviruses as well as isolating caliciviruses from calves that had been infected experimentally with SMSV-5. In addition to the definitive diagnosis of SMSV-5 in the laboratory worker, serum reactivity to SMSV was detected in blood donors living along the Pacific coast of North America (Smith et al., 1998b). The prevalence of serum reactivity to group SMSV antigens in this convenience sample of 300 donors was 18 percent. Again, no clinical signs of diseases associated typically with caliciviruses were recognized in these blood donors.

Table 5. Commercial production of biologicals in the US that are intended to provide protection against calicivirus infections/diseases of domestic animal species. The species, the number of different pathogens for which vaccine was manufactured, the percent of those pathogens that are caliciviruses, the total number of vaccines per species for all pathogens, and the percent of those vaccines that were advertised as providing immunity against caliciviruses are included.

	Pathogens		**Vaccines**	
Species	**Number of Pathogens**	**Percent of Pathogens that are Caliciviruses**	**Total Number of Vaccines Per Species**	**Percent of Vaccines that Provide Immunity Against a Calicivirus**
Bovine	39	0	392	0
Canine	13	0	105	0
Equine	16	0	78	0
Feline	10	10 (n = 1)	67	46 (n = 31)
Ovine	23	0	75	0
Porcine	23	0	219	0
Poultry	36	0	389	0

Source: Entriken, T.L. (Editor). *Veterinary Pharmaceuticals and Biologicals 12th Edition 2001/2002* . Veterinary Healthcare Communications. Lenexa. pp. 301-332. 2001. www.vetmedpub.com .

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