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Influenza virus infection in marine mammals

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Disease in marine mammals, major cause of mass mortalities of marine mammals not only gives the loss of natural resources but also affects human public health. Influenza virus is one of the viruses, which have been shown to be involved in these mass moratlities. Influenza virus belongs to the *orthomyxoviridae* family, and causes epidemic or occasionally pandemic diseases in humans. In three type of influenza viruses, A, B and C, influenza A virus infects a variety of avian and mammalian species including marine mammals. Several influenza virus strains have been isolated from seals and cetaceans. Antigenic and genetic studies showed that all of these influenza viruses from marine mammals originated from birds. Among them, one virus strain seemed to be more adapted to mammalian than to avian hosts. On the other hand, influenza B virus had been thought to infect only humans until the virus was recently isolated from a seal. Because interspecies transmission of the influenza viruses plays a crucial role not only in their ecology but also in the introduction of a pandemic influenza disease in humans, it is important to monitor the virus distribution in wild animals including marine mammals. However, little is known for infection of this virus in marine mammals. This review focuses on the current findings of influenza virus infection in marine mammals, and emphasizes the importance of surveillance of infectious disease in marine mammals.

Key words: influenza virus, mass mortality, seal, cetacean, marine mammals

INTRODUCTION

Humans have suffered from a highly contagious, acute respiratory disease known as "flu" since ancient times. Influenza virus, a member of the *orthomyxoviridae* family, is a major causative agent of influenza. It is divided into three types; A, B, and C. Type A virus is the most common influenza virus and shares many biological characteristics with type B virus. However, the nature of C type virus whose infection is limited to humans, is different from those of the other two types of the virus.

Influenza A virus infects a variety of avian and mammalian species including humans and marine mammals such as seals and cetaceans (Webster et al. 1992). On the other hand, influenza B virus had been believed to be a pathogen only for humans until the virus was recently isolated from a seal (Osterhaus et al. 2000).

It has been established that waterfowls are the primary host for all of the influenza A virus strains that have been introduced into mammalians including humans as pandemic strains. It has been experimentally demonstrated that pigs serve as intermediate hosts to generate human pandemic strains (Kida et al. 1994). Thus, interspecies transmission plays a crucial role in the evolution and ecology of influenza virus. It is important to monitor the distribution of influenza virus in wild animals.

Mass mortality of seals associated with severe pneumonia occurred in Cape Cod, U.S.A., in 1979-1980. Some strains of influenza A virus have been isolated from the dead seals at this mass mortality and from animals in the following stranding at the same site (Geraci et al. 1982, Webster et al. 1981b, Lang et al. 1981, Hinshaw et al. 1984, Callan et al. 1995).

As reports of the isolation of influenza virus in marine mammals have accumulated, they are attracting attention as possible new candidates for an important reservoir of the virus. Excellent review articles have been published on influenza virus infection in terrestrial animals including humans (Webster et al, 1992, Murphy and Webster 1996, Lamb and Krug 1996). However, few review articles on the influenza virus in marine mammals are available. In this review, I summarize recent reports on the infection of influenza A and B viruses in marine mammals, and consider the possibility of marine mammals as a reservoir of these viruses.

NATURE OF INFLUENZA VIRUS

(1) Influenza A virus

(i) Structure of influenza A virus

A schematic structure of influenza A virus is shown in Fig. 1. The virus forms a spherical particle with a diameter of 80–120 nm, and contains a genome of eight negative-stranded RNA segments. Each of the 1st to 6th RNA segments encodes one viral protein, while each of the 7th and 8th RNA segments encodes two proteins (Lamb and Krug 1996). Each particle consists of a host-derived lipid bilayer envelope in which the viral glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are embedded. HA protein is a major surface antigen, and is responsible for the binding of the virus to the host cell receptor, a sialylsugar chain. Susceptibility of the host animal to the virus is dependent of the surface receptor of the host cell. Avian influenza virus preferentially binds the terminal sialic acid SA2-3Gal linkage, while human influenza viruses preferentially bind the SA2-6Gal linkage (Rogers and D'Souza 1989, Conner et al. 1994). The NA protein is the second major surface antigen, and cleaves terminal sialic acid from glycoprotein. Other viral proteins are three kinds of RNA dependent RNA polymerase (PB1, PB2, and PA), nucleoprotein (NP) encapsidating viral RNA, matrix protein (M1), and mem-

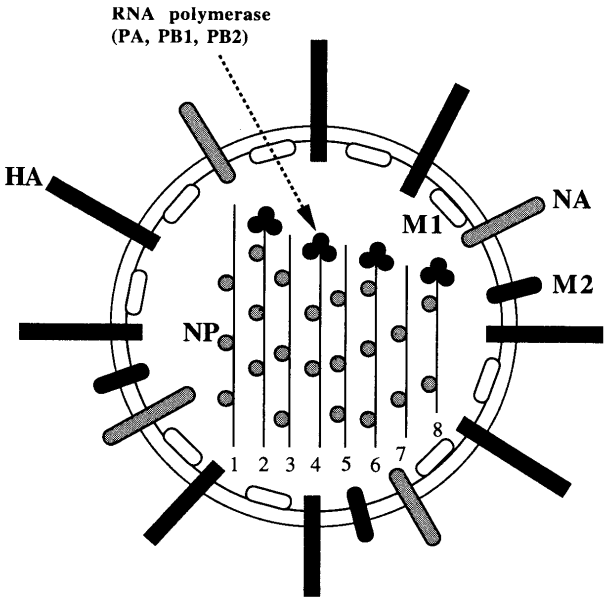

Fig. 1. Schematic structure of influenza A virus. HA: hemagglutinin, NA: neuraminidase, NP: nucleoprotein. M1, M2: matrix protein, PB1, PB2, PA: RNA dependent RNA polymerase. 1–8: genome RNA segments.

brane-embedded ion channel protein (M2) protein (Lamb and Krug 1996). Two non-structural proteins (NS1 and NS2) which are postulated to regulate a viral replication and a synthesis of viral proteins, are identified. NS1 protein is observed not in the virus particles but in the virus-infected cells, while a part of NS2 protein is found to bind to M1 protein in the virus particles.

According to serological cross-reactivity, fifteen subtypes of HA and nine subtypes of NA have been identified in influenza A virus. Therefore, subtype of the virus is designated as a combination of HA and NA subtypes, e.g., H1N1. Each virus strain is named as follows: type of virus (A, B or C)/name of host species except for humans/isolated place/strain number/isolated year. For example, A/Aichi/2/68 or A/duck/Hokkaido/5/77 mean that each influenza A virus was isolated from a patient in Aichi of Japan in 1968, or was isolated from a duck in Hokkaido in 1977, respectively.

(ii) Antigenic variation in influenza A virus

The segmental structure of the virus genome that permits a genome reassortment, gives a unique feature on the nature of influenza virus. The genome reassortment induces a complementation rescue of deficient viruses and accumulates mutations of the genes in the genome. Furthermore it produces a new chimeric virus via simultaneous multiple infections of a mammalian cell with different types of viruses or different species-originated viruses.

In ducks and pigs, genes of influenza A virus are highly conserved and their evolutional rates are slow (Kida et al., 1987, 1988). In contrast, human influenza A virus evolves rapidly by two mechanisms; "antigenic shift" and "antigenic drift" (Webster et al. 1992). "Antigenic shift" occurs by genetic reassortment of the genome RNA segments between currently circulating human influenza viruses and those of other origins, or by invasion of animal influenza viruses and by a re-emerged virus of a previously circulating virus. This is thought to be the major mechanism to cause a pandemic influenza virus strain in humans, because the host does not have a sufficient protective immunity against the newly appeared virus. "Antigenic drift" is due to an accumulation of base substitution mutations in the genes.

(iii) Infection of influenza A virus and the pathogenesis in terrestrial animals

Influenza A virus infects a variety of species of birds and mammals. When the virus infects certain animal species, replicates in them, and produces infectious particles, and the virus particles are circulated in the population, the host animal is called as reservoir.

Avian species

Many avian influenza A viruses which are non-pathogenic to the host have been isolated from wild birds, captive caged birds, and domestic ducks, chickens, and turkeys (Webster et al. 1992, Murphy and Webster 1996). Among them, aquatic birds perpetuate all known subtypes of influenza A virus (H1-15, N1-9). Infection by most strains of avian influenza A virus is asymptomatic. However, a few strains belonging to H5 and H7 subtypes called as "fowl pest", produce a systemic infection. The infected birds are accompanied by central nervous system disorder, and die within 1 week.

In wild ducks, influenza A virus replicates preferentially in the cells lining the intestinal tract, cause no disease signs, and are excreted in high concentrations in the feces (Kida et al. 1980). The virus has been isolated from freshly deposited fecal material of wild ducks and from unconcentrated lake water (Hinshaw et al. 1980, Ito et al. 1995). The avirulent nature of avian influenza infection in birds may be the result of an adaptation to this host for a long time, making birds a stable reservoir that ensures perpetuation of the virus. Thus, birds, aquatic birds in particular, play a central role in the ecology of influenza viruses. In the words, birds are the source of influenza virus to other susceptible animals. Influenza viruses of avian origin have been implicated in outbreaks of influenza in humans, as well as in domestic poultry.

Pigs

Clinical signs of the disease in pigs are similar to but milder than those in humans, and include nasal discharge, coughing, fever, labored breathing, and conjunctivitis. Several different variants of H1N1 and H3N2 subtypes of avian and human influenza virus have been isolated from pigs. Pigs are thought to occupy a unique position in influenza virus infection, because they are susceptible not only to avian influenza virus but also to human virus. Two pandemic viruses, "Asian" and "Hong Kong" influenza viruses, have been shown to be genetically reassorted between strains of human and avian origin (Kawaoka et al. 1989, Scholtissek et al. 1978, Webster and Laver 1972). Genetic assortment between human and avian influenza viruses in pigs has been experimentally demonstrated (Kida et al. 1994). This unique role of pigs in virus infection has been confirmed by study of the virus receptor; the swine trachea has receptors for both avian influenza (SA2-3Gal specific) and for human influenza viruses (SA2-6Gal specific) (Ito et al. 1998). Thus, pigs play a pivotal role in the

Table 1. Disease outbreaks associated with influenza A virus in seals on Cape Cod, U.S.A.

Virus subtype	H7N7	H4N5	H3N3
Disease outbreak	1979–1980 (mass mortality)	1982–1983	1991–1992
Histopathological finding	Bronchopneumonia	Bronchopneumonia	Bronchopneumonia
Genome origin	Bird	Bird	Bird
Virus recovery from the following tissues*	Lung, brain, lymph nodes	Lung, brain, lymph nodes	Lung
Documented infection to primates	Yes (human, squirell monkey)	No	No
Virus recovery from experimentally inoculated animals			
Seals	+	+	N.T.
Ferrets	+	+	N.T.
Ducks	−	+	N.T.

* Includes the tissues from animals which were experimentally inoculated with the virus.

generation of new chimeric viruses as a "mixing vessel" and in an introduction of new pandemic strains to humans.

Horses and mink

In horses, two different subtypes of influenza A virus, H7N7 (equine 1: A/Equine/Prague/1/56) and H3N8 (equine 2: A/Equine/Miami/1/63), have been identified (Webster et al., 1992). Although the equine influenza virus was first isolated in 1956, the historical records indicate that influenza viruses have infected horses for a long time. Both virus strains cause dry hacking cough, fever, and loss of appetite, muscular soreness, and tracheobronchitis. Infection by H3N8 virus usually induces more severe disease than that by H7N7 virus, and often introduces secondary bronchial pneumonia or inflamentation of heart muscle. It has been shown that all of the gene segments of a recently isolated equine H3N8 virus in North China were from the avian influenza virus (Guo et al. 1992).

H10N4 subtype of influenza virus was isolated in farm-raised mink. It was avian in origin, and caused a systemic infection and disease in mink (Klingeborne et al. 1985).

These findings demonstrate the followings; (i) Aquatic birds are the main natural reservoirs of influenza A virus and perpetuate all subtypes of the virus in a conservative and stable manner; (ii) Interspecies transmission occurs mainly from aquatic birds to mammalian species; (iii) Pigs play a unique role as a "mixing vessel" between human and avian viruses.

(2) Influenza B and C viruses

Influenza B and C viruses basically infect only humans. Infection of both viruses has not been reported in terrestrial animals except for humans. Influenza B virus causes the similar symptoms as that caused by influenza A virus infection in humans. The frequency of serious disease caused by influenza B virus is about four-fold less than that caused by influenza A virus. Influenza C virus causes sporadic upper respiratory tract illness in humans. Both type B and C viruses have no subtypes. So their evolution involves only "antigenic drift", but do not involve "antigenic shift". This explains why type B or C virus does not cause a pandemic disease.

INFECTION OF INFLUENZA A VIRUS IN SEALS

(1) Mass mortality and influenza A virus in seals

A series of isolations of influenza A virus from dead seals at Cape Cod stimulated study of the virus on marine mammals (Table 1).

In December 1979 to October 1980, a mass mortality of harbor seals (*Phoca vitulina*) associated with a severe pneumonia, occurred in New England coast of Massachusetts, in the U.S.A. (Geraci et al. 1982). The acute and devastating disease first appeared within a tight grouping of seals on Billingsgate Shoal, Cape cod. It spread rapidly, and at least 130 animals died within one month. Thereafter, the mortality rate declined as the seals dispersed northward along the New England coast. Finally, approximately 600 animals, were estimated to be dead during this outbreak of the disease. Ninety percent of the dead seals was less than 3 years old (Geraci et al. 1982). The clinical signs of the disease were dramatic. They appeared weak, moved feebly without coordination, and exhibited severe respiratory distress. Their necks were swollen, and occasionally thrashed their heads to clear frothy white or bloody discharges to the air. On postmortem examination of the dead animals, pneumonia characterized by necrotizing bronchitis and bronchiolitis, and hemorrhagic alveolitis, were found (Geraci et al. 1982). H7N7 influenza A virus (A/seal/Massachusetts/1/80) was isolated from the lungs and brains of the dead animals (Webster et al. 1981b, Lang et al. 1981).

After this mass mortality, surveillance for strandings and pathological examination of dead seals on the New England coast continued. During 1981-1982, there was no increase in seal deaths or strandings compared to earlier years. However, virological study was conducted using dead seals with pathological evidence of pneumonia. H4N5 influenza A virus (A/seal/Massachusetts/133/82) was isolated from the lungs of one dead seal (Hinshaw et al. 1984). In 1983, three- to four-fold increase in the number of dead or dying seals compared to previous years was observed and approximately sixty dead seals were discovered. The dead seals showing pathological evidence of pneumonia were virologically examined. Histopathological examination of the lungs indicated necrotizing bronchopneumonia characterized by extensive degeneration, necrosis, and desquamation of the bronchial and bronchial epithelium. H4N5 virus again was

isolated from their lungs (Hinshaw et al. 1984).

In 1991–1992, the number of stranded animals increased as compared to previous years. H4N6 virus (A/seal/Massachusetts/3807/91 and A/seal/Massachusetts/3810/91) was isolated from the lung tissues of dead seals in 1991, and H3N3 virus (A/seal/Massachusetts/3911/92 and A/seal/Massachusetts/3984/92) was isolated from the lung tissues of dead seals in 1992. The pathologic lesions of these tissues were consistent with viral pneumonia and included an acute interstitial pneumonia and subcutaneous emphysema (Callan et al. 1995).

Genetic and/or antigenic studies showed that all of these seal viruses originated from birds (Webster et al. 1981b, Lang et al. 1981, Hinshaw et al. 1984, Kida et al. 1982, Callan et al. 1995).

These indicated that seals are reservoirs for influenza A viruses originated from birds.

(2) Infectivity of the seal viruses to other animals

H7N7 virus (A/seal/Massachusetts/1/80) was inoculated intranasally or intratracheally to seals. The animals developed a mild cough and mucopurulent discharge from the eyes and nose (Webster et al. 1981b). The virus was recovered from nasal washes of the sick seals. On postmortem examination, macroscopic and histopathological evidence of pneumonia was observed. The virus was isolated from lungs, bronchial lymph nodes, and conjunctiva but not from the brains of the autopsied animals. Thus, the H7N7 virus caused an only mild respiratory disease in experimentally infected seals, suggesting that other factors such as other infectious diseases or environmental factors were involved in the mass mortality. The H7N7 virus was observed to replicate in the respiratory tract of pigs, cats and ferrets. The virus was isolated from nasal washes, but no clinical signs were observed in these animals. In avian species, the H7N7 virus replicated poorly, produced no clinical signs, and was not shed in the feces. Thus, the seal virus behaved biologically more like a mammalian strain than like an avian strain. Nevertheless, the genome seems to be originated from birds (Webster et al.1981b).

During the studies, four people involved in the autopsies of the seals contracted purulent conjunctivitis. The replication of the virus was confined to the eyes and antibodies did not develop in the serum of the infected individuals (Webster et al. 1981a). To evaluate the replication and virulence of the virus from human conjunctiva in primates, the virus was administered into squirrel monkeys (Murphy et al. 1983). When the virus was administered intratracheally, it replicated in the lungs and nasopharynges and induced illness almost to the same extent that a human influenza A virus did. One monkey died of pneumonia and the virus was recovered from the spleen, liver, muscle, and lung, indicating that the virus had the capability of systemic spread in primates. After conjunctival administration in seals, the virus replicated in the conjunctivae, however, did not induce conjunctivitis. It is interesting that the seal virus showed systemic spread in squirrel monkeys. Some of avian H5 and H7 viruses are known to cause systemic infections in their natural hosts as "fowl pest", whereas human viruses are only rarely isolated from sites other than the respiratory tract. It should be noted that this seal virus was H7 strain virus.

H4N5 virus (A/seal/Massachusetts/133/82) was inoculated to three species of seals (harbor seal (*Phoca vitulina*), ringed seal (*Phoca hispida*) and harp seal (*Phoca groenlandica*)) and ferrets. No overt disease signs or histological evidence of pneumonia were observed in these animals (Hinshaw et al. 1984). However, the virus was recovered from nasal and corneal swabs of harbor seals, a ringed seal, and ferrets, but not from harp seals. In sacrificed seals, the virus was recovered from the lung and lymph nodes (bronchial, mesenteric, and mandibular). Thus, the pathogenecity of the H4N5 virus in seals seems to be milder than that of H7N7 virus. In contrast to H7N7 virus, the virus orally inoculated to ducks replicated to high titers in the intestinal tracks. This tropism is a common feature of avian strains. Human individuals who performed autopsies on seals and worked with the viruses showed no influenza symptoms and had no detectable antibodies to the H4N5 virus (Hinshaw et al. 1984). This suggests that, in contrast to the H7N7 seal virus, there was no transmission of the H4N5 virus to humans.

(3) Survey of antibodies against the seal influenza viruses

To determine whether there had been prior infection of H7N7 influenza virus in seals, seal serum samples were examined (Webster et al. 1981b). Antibodies against the influenza virus with faint titers were present in three out of nine sera from free-ranging harbor seals collected in Maine in September 1998. No influenza virus-specific antibodies were detected in the sera from eight harbor seals and nine gray seals collected in Icelandic waters, and from 227 northern fur seals (*Callorhinus ursinus*) collected in the Bering Sea, Pacific Ocean, and Sea of Okhotsk in 1971–1980.

Antibodies to H4N5 viruses in seals were also examined after isolation of the virus (Hinshaw et al. 1984). However, no antibodies were detected in 200 seal sera collected in 1975–1982.

INFLUENZA B VIRUS INFECTION IN SEALS

Influenza B virus had been known to infect humans until the virus was isolated from a harbor seal (Osterhaus et al. 2000). In the spring of 1999, stranded seals were found on the Dutch coast, and 12 juvenile with respiratory problems were examined. Antibodies against influenza B virus were detected in two seals, and influenza B virus was isolated from a throat swab sample of one seal (B/seal/Netherland/1/99). Sequence analyses and serological examination indicated that the virus was closely related to a strain that circulated in humans 4 to 5 years earlier. Retrospective examination of the virus-specific antibodies was conducted using the sera obtained from 580 seals before 1995 and from 391 seals during or after 1995. None of seal sera before 1995 were positive, whereas 8 (including above two animals) seal sera during and after 1995 showed positive. Among 8 seropositive seals, six animals were harbor seal pups, and two were grey seal pups. Harbor and grey seals are known to share the same habitat in Dutch coastal waters. The results indicate that seals can be infected by influenza B virus and may constitute an animal reservoir. This finding is the first report of influenza B virus infection in animals other

than humans. Further study of influenza B virus infection in seals is mandatory in order to confirm the distribution of the virus, and to reveal the mechanism of interspecies transmission of the virus between humans and seals.

INFLUENZA A VIRUS INFECTION IN CETACEANS

Information regarding the influenza A virus infection in cetaceans is very limited. H1N3 influenza A virus (A/whale/Pacific Ocean/19/76) was isolated from whales (*Balaenopteridae*) which were caught in the South Pacific in 1975–1976 (Lvov et al. 1978). As well as seals, there were two major strandings of longfin pilot whales (*Globicephala melaena*) on Cape Cod, U.S.A., in 1984 (Hinshaw et al., 1986). The first one occurred in October at Eastham and involved 97 whales. The second one, in November at Wellfleet involved 23 animals. The animals had sloughing skin and showed extreme emaciation. Postmortem examination revealed that the hilar node was approximately five times larger than normal size. The lungs were hemorrhagic, and the liver was small and friable. Influenza A viruses of H13N2 (A/whale/Maine/2/84) and H13N9 (A/whale/Maine/1/84) subtypes were isolated from the lungs and hilar nodes of the whales. Antigenic and genetic analysis indicated that the isolated virus was closely related to the H13 influenza viruses from gulls (*Larus* species) (Hinshaw et al. 1986). The H13 gull virus is known to be biologically distinguishable from other major avian influenza viruses in that they are not enterotropic in ducks (Hinshaw et al. 1982). Ducks inoculated orally with the whale virus showed neither disease signs nor virus replication in the intestinal tract; rectal inoculation of ducks with the whale virus resulted in virus replication in the lower intestinal tract. This property was similar to that of gull virus. The replication of the virus in mammals was shown by intranasal inoculation to ferrets (Hinshaw et al. 1986). The transmission route remains to be elucidated; however, fecal-oral transmission of the virus through seawater might be likely.

DISCUSSION AND FUTURE WORKS

Interspecies transmission of influenza virus is an important factor in the evolution of the influenza A virus and in the generation of newly emerging viruses. Surveillance of the virus infection in wild animals provides useful insights not only for understanding the ecology of the virus but also for control of the disease in humans. However, the available information regarding influenza virus infection in marine mammals is very limited. As a first step, a worldwide serological monitoring of the virus is crucial in order to determine the distribution of the virus infection in marine mammals. Furthermore, virus isolation is essential for the characterization of the virus including its pathogenesis. We are now undergoing to epidemiological survey of influenza A and B viruses in Caspian seals. Caspian seals and many kinds of birds live together in the Caspian Sea. Recent expanding human activities around the Caspian Sea might give a chance of virus transmission between humans and seals.

It should be noted that experimentally introduced H7N7 virus did not induce severe disease in healthy seals. This suggests that the virus cannot induce severe illness without the simultaneous presence of other infections or environmental factors.

Thus, the monitoring of infectious diseases in marine mammals helps to provide an understanding of the cause of mass moratlities of marine mammals Furthermore, such study might help to determine the risks to the survival of these mammals.

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海棲哺乳類におけるインフルエンザウイルス感染

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海棲哺乳類における感染症の研究は，近年相次ぐ海棲哺乳類の大量死のような海洋における生物資源の損失ばかりでなく，ヒトの健康や衛生に対しても重要であることが明らかになりつつある．インフルエンザウイルスを含むいくつかのウイルス感染が，この大量死に関与することが示されている．インフルエンザウイルスはオルソミクソウイルス科に属するウイルスで，ヒトに毎年の流行や，時として世界的大流行を引き起こす．インフルエンザウイルスには抗原特異性から，A, B, Cの3型が知られている．インフルエンザA型ウイルスは多くの鳥類や哺乳類に感染し，海棲哺乳類においても複数のウイルス株が分離されている．血清学的ならびに遺伝学的解析により，これまで海棲哺乳類から分離された全てのウイルス株はトリに由来することが明らかになった．しかし，その感染性からトリよりもむしろ哺乳類に適応していると考えられるアザラシ由来のウイルス株も分離された．一方，インフルエンザB型ウイルスはヒトにのみ感染すると考えられていたが，最近アザラシからもウイルスが分離され，B型ウイルスがヒト以外にも感染することが示された．宿主の種の壁を越えたウイルス感染は，インフルエンザの新型ウイルスの出現メカニズムにおいて極めて重要なファクターであることから，海棲哺乳類を含む野生動物におけるウイルス感染のモニタリングは重要である．しかし，海棲哺乳類におけるインフルエンザウイルスに関する知見は未だ少なく，今後その重要性がますます大きくなると思われる．この総説にでは，これまでの海棲哺乳類のインフルエンザ感染の知見をまとめ，感染症の監視システムの重要性を述べる．

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