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Influenza in Animals: Its Possible Public Health Significance

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The suggestion of a possible relationship between influenza in people and influenza in animals is perhaps almost as old as recognition of the disease itself. In 1759, Short, writing on an early influenza outbreak in Ireland and England, noted that epidemic human influenza was generally accompanied by an influenza-like respiratory epizootic among horses.[12] Similar observations were made by others who noted that influenza outbreaks in Scotland in the 18th Century were preceded by epizootics of a mild but highly contagious respiratory disease in horses. In recent years a number of studies have been carried out in an attempt to define the specific relationships that may exist between human and animal influenza.

In any discussion of so-called influenza in animals it is necessary to first define the etiologic agents, since a number of unrelated animal diseases are still commonly called "influenza", *e.g.* the bacterial disease known as "goose influenza".[7] In its proper usage, influenza, human or animal, refers to only the respiratory disease resulting from infection with a member of the Myxo I group, that is a true Myxovirus. The known natural host range includes, in addition to man, equines, swine, and avian species.

The influenza viruses are enveloped, pleomorphic, RNA viruses. There are three major antigens in the virion: the ribonucleoprotein or "S" antigen, and the two envelope or "V" antigens, neuraminidase and hemagglutinin.[4] On the basis of the "S" antigen characteristics, influenza viruses are classified as Type A, B, or C. All three types occur in man, but only Type A has been isolated from lower animals. Further classification into Subtypes and strains is based on differences in the two envelope antigens. See Table 1. A characteristic of the influenza viruses is the frequency with which these antigens undergo major or minor changes, the latter resulting in so-called "antigenic drift" and the appearance of new strains.[1]

TABLE 1. *Influenza virus classification.*

Host	Type	First Isolated	Subtypes
Human	A B C	Smith et al. 1933	A_0, A_1, A_2
Swine	A	Shope et al. 1931	
Equine	A	Sovinova et al. 1958	A/Equi/1, A/Equi/2
Avian	A	Centanni & Savunozzi (1901)	At least eight

The first significant demonstration of a relationship between human and animal influenza was made after the human pandemic of 1918. This the most severe pandemic in medical history, in which an estimated 20 million persons died, was accompanied by a previously unknown panzootic respiratory disease in swine. Based on clinical and epidemiologic observations, contemporary investigators suggested that the human and swine populations were afflicted with the same disease.

Some 13 years later, Shope isolated the first influenza virus, the causative agent of the new swine disease.[10] Two years later, in 1933, human influenza virus was isolated, and the two were subsequently shown to be antigenically related, though not identical. Retrospective serologic studies years later showed that a high percentage of persons who survived the human pandemic of 1918 had developed antibodies to a virus closely related to the swine influenza virus. In other studies of the human-swine influenza relationship, serologic evidence showed that swine were naturally infected with a virus at least closely related to human influenza virus,[14] and swine infected experimentally with human isolates developed typical swine influenza-like disease.[11] It is a generally accepted concept today that the pandemic and panzootic of 1918-1919 were caused by a common or closely related virus, but that man probably served as the reservoir for swine infection rather than *vice versa*. Influenza is now well established in swine and can occur independently of the disease in man.

The relationship between human and equine influenza is less well defined. Although equine influenza had been recognized as a clinical entity for years, the first definitive laboratory evidence of this was not reported until 1957, by Heller *et al.*, who in 1955 found antibodies to type A virus in the serum of 21 convalescent horses.[5] In 1956, a major epizootic began in central Europe, from which the first equine influenza virus was isolated; a new subtype now known as A/Equi/1.[13] In 1963, a new panzootic erupted, appearing first in horses stabled at racetracks in Miami, Florida. From horses involved in this epizootic, another subtype, A/Equi/2, was isolated.[16]

Numerous attempts have been made to relate the equine disease to human influenza. Since both of the recent horse panzootics involved primarily track horses, several investigators have attempted unsuccessfully, to demonstrate evidence of human infection in animal handlers and other track personnel who have most intimate contact with these horses. Although no evidence of natural infection of humans with equine virus could be found, a small group of human volunteers became infected with equine virus after having been given large doses of A/Equi/2 by intranasal instillation.[6] There is also suggestive evidence of humans' becoming naturally infected with equine virus. It has been reported that during the influenza A2 epidemic in Russia in 1958, horses were also infected, and human A2 virus was isolated from horses as well as from people.[3] This report of natural occurrence remains to be supported by other workers, but Versteeg *et al.* in 1958 infected a horse with a laboratory strain of human A2 virus.[15]

Most interesting are the serologic relationships that have been reported between human A2 Asian influenza and the A/Equi/2 virus. Versteeg *et al.* reported finding antibody to human A2 subtype in 21 of 79 horse sera examined during the 1957 A2 epidemic.[15] Several workers found serologic evidence of an A/Equi/2 - like virus in man from about 1890 to 1900.[9] Mulder and Masurel have interpreted these and their own serologic studies as suggesting that a close antigenic relationship exists between human A2 and A/Equi/2 viruses.[8] They hypothesize that the human epidemic of the 1890's was caused by an A2-related virus which spread to horses an an A/Equi/2-type virus. This, if true, would be remarkably similar to the epidemic situation 60 years later, when the human A2 epidemic was followed by an epizootic of A/Equi/2 influenza in horses.

Avian influenza includes a greater variety of antigenic and clinical types than either swine or equine influenza. Clinically, the avian disease can range from the acute fatal fowl plague, to a mild almost inapparent sinusitis.

The relationship between human and avian influenza is even less well defined than between the influenza of humans and swine or equines. One case of fowl plague-like viral infection in a person has been reported, but this has never been supported by other natural or experimental infections.[7] Several workers have demonstrated in the laboratory that common antigens, especially neuraminidase, are shared by avian and human viruses, and that recombinant viruses can be prepared in the laboratory using both human and avian viral components, which suggests that this could also occur in nature.

The role of the animal influenza viruses in the epidemiology of human influenza remains unclear. At present, there are at least two hypotheses.

First, animal populations may serve as reservoirs for human virus between epidemics, when the virus cannot be found in man. This would explain the inter-epidemic survival of a rather labile virus and would also provide, particularly through birds, an excellent mechanism for the distribution of virus to susceptible human populations. The proposition that animals serve as interepidemic reservoirs of human virus is based on the ability of animal isolates to produce infection in man and *vice versa,* on the various serologic relationships that have been established, and on the observed epidemiologic patterns of human and animal disease.

Second, animals may serve as a source for specific viral components in such a way that human and animal virus recombinations occurring in nature provide the mechanism for the spontaneous appearance of new antigenic types to which the populations are highly susceptible. Evidence for this is found in the experimental recombinations of animal and human virus produced in the laboratory, and the demonstrated sharing of common surface antigens between human and animal viruses found in nature.

It should be noted that it is equally possible that the human population serves as a reservoir for animal influenza in a similar manner.

Summary

There often appears to be an epidemiologic association between human and animal influenza outbreaks. Serologic studies have demonstrated that the influenza viruses of avian, swine, and equine species may be closely related to the influenza viruses of man. Isolation of viruses common to man and animals have been claimed. It appears certain that human and animal influenza viruses do sometimes share common antigens. The exact relationship between human and animal influenza is not yet understood and will require additional study.

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