

Influenza A Viruses: Combinations of Hemagglutinin and Neuraminidase Subtypes Isolated from Animals and Other Sources

Brief Review

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Introduction

The present system for the nomenclature of influenza viruses is based on recommendations by the participants in a World Health Organization meeting in 1971 (59). The influenza viruses were divided into types A, B and C on the basis of the antigenic character of the internal nucleoprotein (NP) antigen. The other elements of the nomenclature included: the host from which the strain was isolated, the geographical location, the strain number, and the year of isolation. Influenza A viruses were further divided into subtypes on the basis of the character of the hemagglutinin (H) and neuraminidase (N) antigens, e. g., A/Swine/Wisconsin/1/30 (Hsw1N1). A uniform system of nomenclature was recommended for influenza viruses from human and non-human (swine, equine, avian) sources.

In this system of nomenclature, influenza A viruses are divided into 16 hemagglutinin and 10 neuraminidase subtypes (12, 56, 57, 59). There are four H and two N subtypes of influenza A viruses from man (H0N1, H1N1, H2N2, and H3N2), one H and N subtype from swine (Hsw1N1) and two from horses (Heq1Neq1; Heq2Neq2). The largest number of different antigens exists in the avian viruses which include 9H and 6N subtypes, as well as, many of the subtypes present in mammalian viruses. Since the current system of nomenclature was adopted in 1971, it has become apparent that several subtypes can be grouped together and based on new information, consideration is now being given by the World Health Organization to reducing the number of subtypes (60, 42).

The increased interest in the ecology of influenza viruses (14) and in the possibility that influenza viruses from lower animals and birds may play a role in the origin of some pandemic strains for man (54) has resulted in the isolation of many influenza A viruses. The number of different antigenic combinations of influenza virus isolates, especially from avian species, has increased dramatically over the past few years and these viruses have also been isolated from ponds, lakes, and from fresh fecal material. In order to establish which combinations of H and N have been isolated—and from which species, a computer search of the literature was done. Novel combinations of H and N viruses from different sources in our own repository and of those submitted by collaborating investigators (see acknowledgements) were also entered into the computer.

Combinations of Hemagglutinin and Neuraminidase Subtypes of Influenza A Viruses That Have Been Detected

One problem that became apparent from the literature survey was that many influenza viruses isolated before 1971 were not classified according to the current nomenclature. Therefore, in the following tables the computer may have listed a reference, other than the original report, for a particular strain. We apologize in advance to authors whose work has been omitted and request that they notify us so that the computer data can be corrected.

When the compiled data were tabulated according to the currently accepted nomenclature system for influenza viruses, there were many gaps in the tables. We have, therefore, taken the prerogative of using the revised groupings currently under consideration by the World Health Organization (60). In this system the hemagglutinins of H0, H1 and Hsw1 are grouped together as are H3, Heq2 and Hav7, and also Heq1 and Hav1 (Table 1). Similarly, the neuraminidases Nav2 and Nav3 are placed into one subtype; we have elected not to include Nav6 along with Nav2 and Nav3 since subsequent genetic homology studies suggest that this neuraminidase is distinct from the other two (SCHOLTISSEK, personal communication). When the influenza A viruses are grouped in this way, it is apparent that most of the possible combinations of H and N have already been described (Table 1). The majority of hemagglutinin subtypes have been found in combination with several neuraminidase molecules. Influenza viruses possessing Hav4 have been found in combination with each of the possible neuraminidase subtypes. The striking exception is Hav8 which has been detected only in combination with Nav4.

The above compilation of data also shows that despite more intensive studies on surveillance for influenza viruses in both man and lower animals fostered by the World Health Organization, that only a limited number of new subtypes have been described in recent years. Since 1971 when the present system of nomenclature was adopted, only one new hemagglutinin subtype has been established—Hav9 (57) which was previously grouped with Hav6. Another avian subtype has recently been isolated in our laboratory and has been proposed as the prototype of Hav10 (unpublished data). Similarly, only two new neuraminidase subtypes have been characterized since 1971, these include Nav5 (12) and Nav6 (56) (Table 1).

Table 1. *Tabulation of antigenic subtypes of influenza A viruses isolated from mammals and birds^a*

Hemagglutinin subtype	Neuraminidase subtype		
	N 1	N 2	Neq 1
H 0 H 1 Hsw 1	Sw/Ia/15/30 (20, 45)		
H 2	Dk/Can/76 (38)	Sing/57 (10)	
H 3 Heq 2 Hav 7	Dk/Alb/25/76 (38)	HK/1/68 (9)	Dk/Can/1516/77 (38)
Heq 1 Hav 1	Ck/Brescia/1902 (17, 18)	Dk/HK/47/76 (38)	Ck/FPV/Dutch/27 (34, 40)
Hav 2	Dk/HK/35/76 (46)	Dk/It/574/66 (38)	Ck/Ger/49 (11, 35)
Hav 3		Dk/S.D./1/75 (38)	
Hav 4	Dk/Ger/210/67 (18)	Dk/Ont/4134/67 (61)	Dk/HK/174/77 (38)
Hav 5	Ck/Scot/59 (35)	Tk/Ont/5265/66 (37)	
Hav 6	Dk/Ger/1868/68 (41) ^b Tk/Ont/4689/67 (61)	Tk/Mass/65 (36) ^b Tk/Ont/5050/64 (37)	
Hav 8			
Hav 9		Tk/Wis/1/66 (30, 57)	
Hemagglutinin subtype	Neuraminidase subtype		
	Neq 2	Nav 1	Nav 2—Nav 3
H 0 H 1 Hsw 1	Dk/Alb/97/77 (38)	Dk/Alb/42/77 (38)	Whale/P. O./76 (33)
H 2			Dk/Ger/1215/73 (55)
H 3 Heq 2 Hav 7	Dk/Ukr/2/60 (50) Dk/Ukr/1/63 (30) ^b Eq/Miami/1/63 (51) ^b	Dk/Mem/928/74 (56)	Dk/Chabarovsk/ 1574/72 (53)
Heq 1 Hav 1			Tk/Eng/63 (35, 38)
Hav 2	Quail/It/1117/65 (36)		Dk/Alb/778/78 (38)
Hav 3		Dk/Eng/1/56 (4, 35)	Dk/HK/44/76 (38)
Hav 4	Mynah/Ma/71 (47)	Dk/Czech/1/56 (25, 35)	Dk/Alb/300/77 (38)
Hav 5			Tern/S.A./61 (6, 35)
Hav 6	Tk/Can/63 (27, 35)	Dk/Mem/346/74 (56)	
Hav 8			
Hav 9		Dk/HK/147/77 (38)	
Hemagglutinin subtype	Neuraminidase subtype		
	Nav 4	Nav 5	Nav 6
H 0 H 1 Hsw 1		Dk/NY/6861/78 (38)	
H 2			Dk/GDR/72 (56)
H 3 Heq 2 Hav 7	Dk/Wi/12/74 (38)	Dk/Wi/22/74 (38)	Ck/HK/1/76 (46) ^b Dk/Mn/74 (38)
Heq 1 Hav 1		Dk/Alb/224/77 (38)	
Hav 2		Dk/HK/15/76 (46)	
Hav 3		Dk/Mn/75 (38)	Dk/Ukr/1/60 (50, 56)
Hav 4	Dk/Alb/56/76 (38)	Dk/HK/191/77 (38)	Dk/Ont/52/76 (38)
Hav 5			Tk/Ont/7732/66 (28, 56)
Hav 6	Dk/Wi/6/74 (38)	Shearwater/Aust/ 1/72 (12) ^b Tk/Ca/186/64 (5, 19)	Dk/Mn/75 (38)
Hav 8	Tk/Ont/6118/68 (30)		
Hav 9			

Abbreviations used in virus name: Sw = Swine; Dk = Duck; Tk = Turkey; Ck = Chicken; Eq = Horse

^a The earliest recorded viruses with the designated subtypes isolated from mammals or birds are presented

^b The earliest characterized virus with the designated subtype

Host Range of Influenza Viruses with a Particular Combination of Hemagglutinin and Neuraminidase Molecules

Influenza A viruses with particular combinations of H and N molecules have been detected in isolates from many different species (Table 2). For example, influenza viruses possessing Hsw1N1 antigenic determinants have been isolated from people, pigs, birds, and from lake water and fecal samples. Similarly, viruses in the H3-Heq2-Hav7 subtypes have been isolated in combination with all of the different neuraminidase subtypes from a very wide range of mammalian and avian species. In view of these data, the species designation of the surface antigens may be of historical interest but does not truly reflect the circulation of a particular subtype of viruses in nature.

Other problems with regard to the host of origin include: i) the use of common names for animals, e.g., duck, does not specify the actual species. The specific Latin binominal designation, as recommended by the World Health Organization, would be much more accurate and informative. ii) The reported isolations of influenza A viruses from some species remains in doubt, for they have not been confirmed in independent laboratories. iii) The isolation of infectious virus from other sources such as lake water and fecal material poses 2 problems: a) the present and proposed system provides no category for these isolates; and b) the isolation of influenza viruses from water increases the possibility of cross-contamination in field studies, thus viruses could be isolated from species which had recently drunk this contaminated water and erroneously been recorded as an infected host.

Conclusion

This compilation of data underlines the widespread zoonotic nature of influenza A viruses and reflects the need for a more unifying approach for the nomenclature of these viruses.

The many different combinations of hemagglutinin and neuraminidase subtypes found on influenza A viruses in nature probably results from genetic reassortment between influenza A viruses in mixedly infected hosts. This phenomenon has recently been demonstrated in nature with viruses infecting feral ducks in Canada (unpublished data), indicating that genetic reassortment constitutes a plausible explanation for the occurrence of the many combinations in the avian viruses. Genetic interaction between influenza A viruses in nature provides a method for the evolution of influenza viruses including some of the pandemic viruses for humans (31, 44). It seems probable that all of the possible combinations of H and N subtypes will eventually be detected. However, there may be some genetic restrictions on the compatibility of some combinations. Hav8 has only been isolated in combination with Nav4 and it is not known whether this is due to limited sampling or to some unexplained genetic restriction.

The limited number of new subtypes of influenza A viruses isolated since 1971 suggests that there may be a finite number of different influenza A viruses in nature. The limited number of new subtypes suggests that influenza A viruses are not evolving rapidly.

The detection of many antigenically and genetically related viruses in many different hosts indicates that there is no definite correlation between host range

Table 2. Tabulation of antigenic subtypes of influenza A viruses isolated from different species^a

Hemagglutinin subtype	Neuraminidase subtype		
	N 1	N 2	Neq 1
H 0 H 1 Hsw 1	Sw/Ia/15/30 (20, 45) Human/PR/8/34 (3, 15) Dk/Alb/35/76 (21) Dk/Feces/Alb/77 (38)		
H 2	Dk/Can/76 (38)	Human/Sing/57 (10) Dk/604/78 (38)	
H 3 Heq 2 Hav 7	Dk/Alb/25/76 (38)	Human/HK/1/68 (9) Tk/Eng/69 (16) Sw/Taiwan/70 (26) Ck/Kamchatka/12/ 71 (32) Calf/Duschanbe/ 55/71 (8) Dk/Wis/10/74 (38) Crow/Kazan/20/72 (53) Common Murre/ Sakhalin/1/74 (39)	Dk/Can/1516/77 (38)
Heq 1 Hav 1	Ck/"FPV"/Brescia/ 1902 (17) Human/U.S.A./67 (7) Dk/Ca/72 (48) Parrot/Ulster/1/73 (61) Pond/HK/78 (38)	Dk/HK/47/76 (38) Pond/HK/298/78 (38)	Ck/Dutch/27 (34, 40) Eq/Pr/1/56 (49) Tk/Aust/75 (2)
Hav 2	Dk/HK/35/76 (46)	Dk/It/574/66 (36)	Ck/"N" Ger/49 (11, 35) Dk/Manitoba/53 (52, 61)
Hav 3		Dk/S. D./1/75 (38)	
Hav 4	Dk/Ger/210/67 (18)	Dk/Ont/4134/67 (61)	Dk/HK/174/77 (38)
Hav 5	Ck/Scot/59 (35) Tk/Ont/6213/66 (29) Dk/Pa/69 (23)	Tk/Ont/5265/66 (37) Pheasant/Quebec/ 643/74 (61) Dk/S. D./2/75 (38)	
Hav 6	Tk/Ont/4689/67 (61) Dk/Ger/1868/68 (41) Goose/Tx/2/75 (38)	Tk/Ont/5050/64 (37) Dk/HK/110/69 (18) Tern/Pechora/105/72 (62) Goose/Tx/1/75 (38) Lake/Alb/1/78 (38) Feces/Alb/1/78 (38)	
Hav 8			
Hav 9		Tk/Wi/1/66 (30, 57) ^b Dk/HK/86/76 (38)	
H 0 H 1 Hsw 1	Dk/Alb/97/77 (38)	Dk/Alb/42/77 (38)	Whale/P. O./76 (33) Dk/Mi/77 (38)
H 2			Dk/Ger/1215/73 (55) Gull/Md/77 (38)

Table 2 (continued)

Hemagglutinin subtype	Neuraminidase subtype		
	Neq 2	Nav 1	Nav 2—Nav 3
H 3 Heq 2 Hav 7	Dk/Ukr/2/60 (50) Eq/Miami/2/63 (51) Tern/Pechora/112/72 (38) Heron/Chabarovsk/ 700/73 (53) Finch/Eng/76 (2) Dk Feces/Alb/2/77 (38) Lake/Alb/7/77 (22)	Dk/Mem/928/74 (56) Ck/HK/43/78 (38)	Dk/Chabarovsk/ 1574/72 (53) Tern/Turk/18/73 (53)
Heq 1 Hav 1			Tk/Eng/63 (35, 58) Dk/Ca/72 (48)
Hav 2	Quail/It/1117/65 (36) Dk/Ca/72 (48)		Dk/Alb/778/78 (38)
Hav 3		Dk/Eng/56 (4, 35)	Dk/HK/44/76 (38)
Hav 4	Mynah/Ma/71 (47) Flowerpicker/Thail/ 72/47) Hoopoe/Thail/72 (47) Green Weaver/ Thail/72 (47) Oriole/Thail/72 (47) Bluebird/Thail/72 (47) Finch/Thail/72 (47) Thrush/Thail/72 (47) Sunbird/Thail/72 (47) Pietta/Thail/72 (47) Dove/Ont-Thail/ 5805/72 (61) Tanager/Ecu/72 (47) Ck/Ala/75 (24) Lake/Alb/2/78 (38) Tk/Mn/78 (38) Parrot/Eng/70 (1) ^b Cockatoo/Eng/72 (1) ^b Parakeet/Eng/72 (1) ^b	Dk/Czech/1/56 (25, 35) Tk/Alta/6962/66 (61) Goose/HK/1/76 (46) Lake/Alb/1/77 (38)	Dk/Alb/300/77 (38)
Hav 5			Tern/S. A./61 (6, 35) Dk/HK/826/69 (18) Shearwater/Try/ 264C/75 (13)
Hav 6	Tk/Can/63 (27, 35) Dk/Wi/13/74 (38)	Dk/Mem/346/74 (56)	
Hav 8			
Hav 9		Dk/HK/147/77 (38)	
H 0 H 1 Hsw 1		Dk/NY/6861/78 (38)	
H 2			Dk/GDR/72 (56) Gull/Md/19/77 (38)

Table 2 (continued)

Hemagglutinin subtype	Neuraminidase subtype		
	Nav 4	Nav 5	Nav 6
H 3 Heq 2 Hav 7	Dk/Wi/12/74 (38)	Dk/Wi/22/74 (38)	Dk/Mn/74 (38) Ck/HK/1/76 (46)
Heq 1 Hav 1		Dk/Alb/224/77 (38)	
Hav 2		Dk/HK/15/76 (46)	
Hav 3		Dk/Mn/75 (38)	Dk/Ukr/1/60 (50, 56) Goose/Del/73 (38) Gull/Md/5/77 (38) Tern/Aust/396/75 (13)
Hav 4	Dk/Alb/56/76 (38)	Dk/HK/191/77 (38)	Dk/Ont/52/76 (38)
Hav 5			Tk/Ont/7732/66 (28, 56)
Hav 6	Dk/Wi/6/74 (38) Hawk/Md/1/77 (38) Gull/Md/77 (38)	Tk/Ca/186/64 (5, 19) Shearwater/Aust/ 1/72 (12) Dk/Del/73 (19)	Dk/Mn/75 (38)
Hav 8			Tk/Ont/6118/68 (30) Dk/Alb/283/77 (38)
Hav 9			

Abbreviations used in virus name: Sw = Swine; Dk = Duck; Tk = Turkey; Ck = Chicken; Eq = Horse

^a The earliest recorded viruses with the designated subtypes isolated from mammals and birds are presented

^b This antigenic classification differs from that given in the reference because these viruses have been reclassified

and surface antigens. In fact, the gene constellations controlling host range, as well as other biological characteristics such as virulence, are poorly understood (43). With regard to the problems in nomenclature, it is increasingly obvious that the species designation of the subtype is really unnecessary and sometimes confusing. For example, A/duck/Alb/35/67 (Hsw1N1) (21) has been referred to as an "avian swine-like virus". Dropping the species designation, as suggested by the World Health Organization, from the antigenic classification would eliminate such incongruities.

The data in this paper were assembled in part to provide investigators with a current listing of known isolates from different species, thereby enabling them to determine if their influenza viruses represented novel combinations of H and N antigens. The literature search may well have missed some viruses; in addition, some investigators may have unpublished information on influenza virus isolates from their studies. Investigators are encouraged to write to the authors so that omissions can be corrected and a complete listing of influenza viruses established. These data will most certainly be useful in understanding the ecology of influenza A viruses, as well as providing a convenient source of references on those influenza viruses that have been isolated.

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