Memoranda
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Memoranda are statements concerning the conclusions or recommendations of certain WHO scientific meetings; they are signed by the participants in the meeting.

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A revision of the system of nomenclature for influenza viruses: a WHO Memorandum*

In February 1980, the World Health Organization convened a meeting to consider information relevant to the nomenclature of influenza viruses and to make definitive proposals for the revision of the system which has been in use since 1971. The WHO recommendations are based on data derived from double immunodiffusion reactions involving haemagglutinin and neuraminidase antigens. The revised system of nomenclature is similar to the 1971 system in that it consists of two parts: (a) a type and strain designation, and (b) for influenza A viruses, a description of the antigenic specificity (subtype) of the surface antigens (H and N). The strain designation for influenza virus types A, B, and C contains information on the antigenic type of the virus (based on the antigenic specificity of the nucleoprotein), the host of origin (for strains isolated from non-human sources), geographical origin, strain number, and year of isolation. For influenza A viruses, the antigenic description, in parentheses, follows the strain designation and comprises two indices describing the antigenic subtype of the haemagglutinin and of the neuraminidase antigens. For the influenza A viruses from all species, the H antigens are grouped into 12 subtypes, H1–H12, while the N antigens are divided into 9 subtypes, N1–N9. Reference strains of influenza viruses are maintained by the WHO Collaborating Centres for Reference and Research on Influenza and the WHO Centres for the Study of Influenza Ecology in Animals, and are made available upon request.

There is no provision for describing distinct subtypes of influenza B and C viruses. The existence of antigenic variation among influenza B strains is well established but the available information shows that a division into subtypes is not warranted.

This revised system of nomenclature should be used universally from the date of publication of this Memorandum.

A WHO Memorandum published in 1979 (*1*) described the conclusions of a group convened to reconsider the system of nomenclature for influenza viruses decided upon in 1971 (*2*). The group reviewed the extensive information that had accumulated in the eight years since the system had been introduced, on the immunology, biology, biochemistry, genetics, epidemiology, and ecology of influenza viruses. The participants felt that the 1971 system of nomenclature had provided a valuable framework for the antigenic description of influenza viruses, but that recent immunological and biochemical findings indicated a need to reconsider the subtype designation of the haemagglutinin (H) and neuraminidase (N) antigens of some influenza A viruses. The group proposed that several subtypes be merged and that designations indicating the species of origin of the antigen be omitted. The 1979 Memorandum also encouraged laboratory studies on antigenic relationships and invited comments on the proposed changes.

* This Memorandum was drafted by the signatories listed on page 590 on the occasion of a meeting held in Geneva in February 1980. A French translation will appear in a future edition of the *Bulletin*. Requests for reprints should be addressed to Chief, Virus Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

In February 1980, the World Health Organization convened a meeting to consider further information and to make definitive proposals for influenza virus nomenclature. The present Memorandum describes the conclusions and recommendations arising from this meeting.

The proposed revision of nomenclature described herein meets the requirement for a simple system that can be used by all countries, and it is proposed that it should be used from the date of publication of this Memorandum. It is based on data derived from double immunodiffusion (DID) reactions involving H and N antigens (*3*). The DID test, when performed using hyperimmune sera specific to one or other of the antigens, provides a valuable method for comparing antigenic relationships. Similarities between antigens are detected as lines of common precipitin, whereas the existence of variation between antigens is revealed by spurs of precipitin when different antigens are permitted to diffuse radially inwards toward a single serum. Based on the results of DID tests on influenza A viruses from all species, the H antigens can be grouped into 12 subtypes, while the N antigens can be divided into 9 subtypes as indicated in Tables 1 and 2 (*1*, *3*).

Immunological cross-reactions between the surface antigens (H or N) of influenza A viruses of different subtypes have been observed even in the absence of demonstrable cross-reactions in DID tests. However, evidence of relationships, based on cross-protection (*4*) or cell-mediated immunity (*5*, *6*) in the absence of DID cross-reactions, was not considered useful for the subtyping of virus strains since such phenomena may be mediated by viral proteins other than the surface antigens. Nevertheless, cross-reactions, mediated by antibody, defined principally by haemagglutination-inhibition (HI) tests, have been observed between some subtypes, as designated previously, for example between Hswl and H2 or H3, H1 and H2, H0 and H2, and H3 and H2 viruses (*7–9*) even when possible cross-reactions due to common N antigens were excluded. Antigenic relationships between the H antigens of a human (H3) and an animal virus (Heql) have also been noted (*10*). The taxonomy of influenza viruses will require continuing re-evaluation as more is learned about the antigenic relationships among the H and the N subtypes. Although studies employing DID tests have shown some antigenic differences between the nucleoprotein (NP) antigens of influenza A viruses isolated from different hosts (*11*), it was decided that this feature should not be taken into account in the influenza nomenclature system.

The RNAs of several influenza virus strains and their recombinants have been characterized by various methods including RNA-RNA (*12*) and RNA-DNA hybridization, oligonucleotide analysis (*13*), and nucleotide sequence determinations (*14*). Results obtained using RNA-RNA hybridization techniques have indicated that the genes coding for the H antigen of viruses of the previously designated Hswl, H0, and H1 subtypes are closely related (*12*). The genes coding for the H antigens of viruses previously designated H3, Hav7, and Heq2 subtypes also exhibit a high base-sequence homology, as do those coding for Heql and Havl. The gene coding for Hav5 was found not to be closely related to Hswl, H0 and H1 genes. (P. Palese and G. Scholtissek, unpublished results, 1980). The results of the analyses of genes coding for the Nav2 and Nav3 proteins support the antigenic relationships described for these antigens. Based on similar analyses Nav6 appears to constitute a separate subtype (*12*).

Genes coding for corresponding non-surface proteins of different influenza A viruses have been compared using similar methods, and it was found

Table 1. Proposed subtypes of haemagglutinin antigens of influenza A viruses

Proposed subtypes	Previous subtypes (1971 system)
H1[a]	H0, H1, Hsw1
H2	H2
H3	H3, Heq2, Hav7
H4	Hav4
H5[a]	Hav5
H6	Hav6
H7	Heq1, Hav1
H8	Hav8
H9	Hav9
H10	Hav2
H11	Hav3
H12	Hav10

[a] Minor antigenic relationships indicated by DID cross-reactions have been observed in some laboratories between the H antigens of viruses of the proposed H1 and H5 subtypes

Table 2. Proposed subtypes of neuraminidase antigens of influenza A viruses

Proposed subtypes	Previous subtypes (1971 system)
N1	N1
N2	N2
N3	Nav2, Nav3
N4	Nav4
N5	Nav5
N6	Nav1
N7	Neq1
N8	Neq2
N9	Nav6

that viruses can be separated into two groups on the basis of the genes coding for the non-structural (NS) protein (*12*). Nucleic acid hybridization analyses and oligonucleotide fingerprinting have provided evidence that viruses of the human H3N2 subtype evolved as a result of genetic recombination between a human H2N2 virus and an influenza A virus from an unidentified species. They acquired 7 of their 8 genes from the H2N2 virus and one gene, that coding for the H antigen (*12*), from the other virus. Several of the recent H1N1 isolates have also been found to be recombinants containing several genes derived from H3N2 viruses (*13*).

Knowledge of the primary structure of influenza virus proteins, obtained by tryptic peptide, nucleic acid sequence, and amino-acid sequence analyses, is at present restricted to the haemagglutinin molecule. The results of comparative tryptic peptide analyses, particularly of the HA2 components of the haemagglutinins, have been valuable in assigning viruses to subtypes. Specifically, the H antigens of the former Hswl, H0, and H1 subtypes have been shown to be related in this way. The comparative data so far obtained from sequence analyses, although less extensive, are consistent with the proposed nomenclature system. The nucleotide sequences that have been determined indicate that the haemagglutinins within a subtype are much more closely related to each other than to those of other subtypes (*14–17*).

Monoclonal antibodies, when used in addition to conventional serological reagents, have proved to be useful in antigenic analysis of influenza viruses. The monoclonal antibodies to the H or N antigens of influenza viruses are valuable for discriminating between closely related antigenic variants within a subtype (*18*), while those to the nucleoprotein (NP) may be used for typing and partial genotyping of influenza viruses. However, they are often too specific for routine serological typing and subtyping of influenza viruses.

In considering the proposal to merge the former Hswl, H0, and H1 subtypes into a single subtype (H1), the following factors were taken into account: (1) the identification of each of these former subtypes with major epidemics accompanied by replacement of the antecedent influenza A virus strains; (2) the marked antigenic differences among those viruses, demonstrable by HI and virus neutralization tests; and (3) the problems likely to arise with the abandonment of a familiar terminology. The meeting considered a suggestion that the H antigen subtypes, such as those of H1, should be qualified with designations of H1*sw* etc., to reflect the previous nomenclature. This proposal was regarded as inconsistent with the principles of the new nomenclature unless subsubtype designations were also given for antigenic variants within all other subtypes. This possibility was considered, but it was decided that the precise identity of strains within the proposed H1 subtype (e.g., whether they are "A/swine influenza virus-like" or "A/FM1/47 virus-like") should be defined, as for other subtypes, by specific reference to prototype or reference strains.

THE NOMENCLATURE SYSTEM

The revised system of nomenclature is similar to the 1971 system in that it consists of two parts: (*a*) a type and strain designation, and (*b*) for influenza A viruses, a description of the antigenic specificity of the surface antigens (H and N).

The strain designation for influenza virus types A, B, and C contains the following information:

1. A description of the antigenic type of the virus based on the antigenic specificity of the NP antigen (type A, B, or C). Since 1971, a further type-specific internal antigen of the influenza A and B viruses, the matrix (M) protein, has been described (*19*). Typing of influenza A and B viruses based on the M protein is consistent with the results obtained with NP antigen (*20*).
2. The host of origin. This is not indicated for strains isolated from human sources but is indicated for all strains isolated from non-human hosts, e.g., swine, horse (equine), chicken, turkey. For viruses from non-human species, both the Latin binomial nomenclature and the common name of the host of origin should be recorded in the original publication describing the virus isolate, e.g., *Anas acuta* (pintail duck). Thereafter, the common name of the species should be used for the strain, e.g., A/duck/USSR/695/76 (H2N3). When viruses are isolated from non-living material the nature of the material should be specified, e.g., A/lake water/Wisconsin/1/79.
3. Geographical origin
4. Strain number
5. Year of isolation.

For influenza A viruses, the antigenic description, in parentheses, follows the strain designation and includes the following information.

(*a*) An index describing the antigenic character of the haemagglutinin, i.e., H1, H2, H3, H4, etc. The numbering of subtypes is a simple sequential system which applies uniformly to influenza viruses from all sources.

(*b*) An index describing the antigenic character of the neuraminidase, i.e., N1, N2, N3, N4, etc. As with the H antigen subtype, this is a simple sequential numbering system applied uniformly to all influenza A viruses.

It is implicit that a given H or N subtype designation will encompass strains exhibiting a considerable degree of antigenic variation within the subtype (antigenic "drift"). The precise antigenic position of an influenza virus within a subtype may be defined by indicating similarities to designated reference strains. Examples of reference strains for each subtype of H and N antigen are listed in Tables 3–7.

In some cases, influenza A strains isolated from different host species are of common subtype designation. This does not necessarily imply that these viruses are transmitted naturally from one species to the other.

Reference strains of influenza viruses are maintained by the WHO Collaborating Centres for Reference and Research on Influenza and the WHO Centres for the Study of Influenza Ecology in Animals, and are made available upon request. Reference strains are viruses that have noteworthy properties, and include one or more examples of each new variant within a subtype that exhibits antigenic drift from the prototype, and which is responsible for epidemiologically significant outbreaks of disease or epidemics.[a] Other examples of reference strains are (i) viruses that possess new combinations of H and N subtypes; (ii) viruses that have unusual biological properties; and (iii) viruses that have been the subject of extensive investigations reported in the scientific literature.

There is no provision for describing distinct subtypes of influenza B and C viruses. The existence of antigenic variation among influenza B strains is well established but the information shows that a division into subtypes is not warranted. The description of these viruses is therefore limited to strain designation, e.g., B/England/5/66, C/Paris/1/67.

Recombinant viruses

Recombination between influenza viruses of different types (e.g., influenza A and B viruses) has not been demonstrated. However, recombination between viruses within a type is readily accomplished in the laboratory and apparently occurs in nature, as has been recently observed with H1N1 and H3N2 subtypes (*13*). The nomenclature of recombinant viruses therefore presents special problems.

The previously recommended system (*2*) for the nomenclature of recombinant influenza A viruses applied to laboratory-derived strains that were antigenic hybrids deriving their H and N antigens from different parents. This should still be followed, but to take account of the increasing use of laboratory-derived recombinant influenza viruses, many of which are obtained by recombinations that do not involve genes coding for surface antigen, it is recommended

[a] Newly recognized human influenza reference strains are described in the *Weekly epidemiological record*.

Table 3. Examples of reference strains for the proposed subtypes of haemagglutinin and neuraminidase antigens of influenza A viruses isolated from man

H and N subtypes	Reference strains
H1N1	A/PR/8/34 (H1N1)
	A/Weiss/43 (H1N1)
	A/FM1/47 (H1N1)
	A/England/1/51 (H1N1)
	A/Denver/1/57 (H1N1)
	A/New Jersey/8/76 (H1N1)
	A/USSR/90/77 (H1N1)
H2N2	A/Singapore/1/57 (H2N2)
	A/Japan/305/57 (H2N2)
	A/England/12/64 (H2N2)
	A/Tokyo/3/67 (H2N2)
H3N2	A/Hong Kong/1/68 (H3N2)
	A/England/42/72 (H3N2)
	A/Port Chalmers/1/73 (H3N2)
	A/Victoria/3/75 (H3N2)
	A/Texas/1/77 (H3N2)

Table 4. Examples of reference strains for proposed subtypes of haemagglutinin and neuraminidase antigens of influenza A viruses isolated from swine

H and N subtypes	Reference strains
H1N1	A/swine/Iowa/15/30 (H1N1)
	A/swine/Wisconsin/67 (H1N1)
H3N2	A/swine/Taiwan/1/70 (H3N2)

Table 5 Examples of reference strains for proposed subtypes of haemagglutinin and neuraminidase antigens of influenza A viruses isolated from horses

H and N subtypes	Reference strains
H7N7	A/equine/Prague/1/56 (H7N7)
H3N8	A/equine/Miami/1/63 (H3N8)

Table 6. Examples of reference strains for proposed subtypes of haemagglutinin antigens of influenza A viruses isolated from avian species

Proposed subtype designation	Previous subtype designation	Reference strains	Other strains with related antigens
H1	Hsw1	A/duck/Alberta/35/76 (H1N1)	A/duck/Alberta/97/77 (H1N8)
H2	H2	A/duck/Germany/1215/73 (H2N3)	A/duck/Germany/1/72 (H2N9)
H3	Hav7	A/duck/Ukraine/1/63 (H3N8)	A/duck/England/62 (H3N8) A/turkey/England/69 (H3N2)
H4	Hav4	A/duck/Czechoslovakia/56 (H4N6)	A/duck/Alberta/300/77 (H4N3)
H5	Hav5	A/tern/South Africa/61 (H5N3)	A/turkey/Ontario/7732/66 (H5N9) A/chick/Scotland/59 (H5N1)
H6	Hav6	A/turkey/Massachusetts/3740/65 (H6N2)	A/turkey/Canada/63 (H6N8) A/shearwater/Australia/72 (H6N5) A/duck/Germany/1868/68 (H6N1)
H7	Hav1	A/fowl plague virus/Dutch/27 (H7N7)	A/chick/Brescia/1902 (H7N1) A/Turkey/England/63 (H7N3) A/fowl plague virus/Rostock/34 (H7N1)
H8	Hav8	A/turkey/Ontario/6118/68 (H8N4)	—
H9	Hav9	A/turkey/Wisconsin/1/66 (H9N2)	A/duck/Hong Kong/147/77 (H9N6)
H10	Hav2	A/chick/Germany/N/49 (H10N7)	A/quail/Italy/1117/65 (H10N8)
H11	Hav3	A/duck/England/56 (H11N6)	A/duck/Memphis/546/74 (H11N9)
H12	Hav10	A/duck/Alberta/60/76 (H12N5)	—

Table 7. Examples of reference strains for proposed subtypes of neuraminidase antigens of influenza A viruses isolated from avian species

Proposed new subtype designation	Previous grouping	Reference strains	Other strains with related N antigens
N1	N1	A/chick/Scotland/59 (H5N1)	A/duck/Alberta/35/76 (H1N1) A/duck/Germany/1868/68 (H6N1)
N2	N2	A/turkey/Massachusetts/3740/65 (H6N2)	A/turkey/Wisconsin/66 (H9N2) A/turkey/England/69 (H3N2)
N3	Nav2 Nav3	A/tern/South Africa/61 (H5N3) A/turkey/England/63 (H7N3)	A/duck/Germany/1215/73 (H2N3)
N4	Nav4	A/turkey/Ontario/6118/68 (H8N4)	A/duck/Wisconsin/6/74 (H6N4)
N5	Nav5	A/shearwater/Australia/1/72 (H6N5)	A/duck/Alberta/60/76 (H12N5)
N6	Nav1	A/duck/Czechoslovakia/56 (H4N6) A/duck/England/56 (H11N6)	—
N7	Neq1	A/fowl plague virus/Dutch/27 (H7N7)	A/chick/Germany/N/49 (H10N7)
N8	Neq2	A/quail/Italy/1117/65 (H10N8)	A/turkey/Canada/63 (H6N8) A/duck/England/62 (H3N8)
N9	Nav6	A/duck/Memphis/546/74 (H11N9)	A/turkey/Ontario/7732/66 (H5N9)

that a postscript "R" be added after the strain designation to draw attention to the recombinant nature of the virus, e.g., A/Hong Kong/1/68(H3N2)R; B/Lee/40R; C/Taylor/1233/47R. In addition, the strain of origin of the H and N antigens of antigenic hybrid recombinant influenza A or B viruses should be given, e.g.,

A/BEL/42(H1)—Singapore/1/57(N2)R
B/Lee/40(H)—Singapore/222/79(N)R

The designation R in the nomenclature system should be augmented by the investigators' individual system of recombinant designation and, where possible and relevant, available information about the genotype of the virus should be provided in the form of footnotes, tables or description of materials.

It is emphasized that the above system for designating recombinants should not be used for apparently naturally occurring virus strains.

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