Recommended composition of influenza virus vaccines for use in the 2008–2009 influenza season

This recommendation relates to the composition of vaccines for the forthcoming influenza season in the northern hemisphere (November 2008 to April 2009). A recommendation will be made in September 2008 relating to vaccines that will be used for the influenza season in the southern hemisphere (May to October 2009). For countries in equatorial regions epidemiological considerations will influence which recommendation (February or September) individual National Authorities consider more appropriate.

Influenza activity, September 2007–January 2008

Between September 2007 and January 2008, influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. In general, activity was low compared with the same period in recent years[1]. In the southern hemisphere, mild influenza activity continued in September and declined in October. In the northern hemisphere, influenza activity began in Asia and North America in November and increased in December-January, while in Europe, activity began in December and increased in January.

Influenza A(H1N1) viruses predominated in most parts of the northern hemisphere and were associated with outbreaks in some countries. Influenza A(H3N2) was sporadic in many countries and outbreaks were reported in the United States. Influenza B viruses circulated at low levels in most countries throughout the period while outbreaks were reported in China, Hungary and the United States of America.

The extent and type of seasonal influenza activity worldwide are summarized in Table 1 hereafter.

Table 1 Extent and type of seasonal influenza activity worldwide, September 2007 - January 2008

Country, area or territory	2007				2008
	September	October	November	December	January
Africa					
Algeria			*H1	*H1	*H1, *H3
Côte d'Ivoire		*A	*A		
Egypt	*B	*H1, *B	*H1, *B	*H1, *B	
France, Réunion	*H1				
Ghana	*H1		*H1	*H1, *H3	
Kenya	*H3, *B				
Madagascar	*H1	*H1, *B	*H1, *B	**H1	**H1, *B
Mauritius	*H1				
Morocco				*H1, *B	
Senegal	*H1	*H1			
South Africa	**H1, *H3, **B	*H1, *B	*B		*A
Tunisia		*H3	*H3, *B	**H3, **B	
Uganda	*H3, *B	*B			
America					
Argentina	*H3	*H3, *B	*B		
Brazil	**H3, *B	*A, *B	*B	*B	
Canada	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	**H1, *H3, *B	***H1, *H3, *B
Chile	*H1	*A	*H1	*A, *B	*A

[1] http://www.who.int/wer/2007/wer8241/en/index.html

Country, area or territory	2007				2008
	September	October	November	December	January
Costa Rica	*A				
El Salvador	*H1, *H3				
France, French Guiana					*H1, *H3
France, Guadeloupe					***A
France, Martinique					**H1, *B
Guatemala	*H3	*H3			
Honduras		*H1, *H3	*H3		
Mauritius	*H1				
Mexico	*H1, *H3, *B	*H1, *H3, *B	**H1, *A	**A	
Panama	*A, *B	*A, *B			
Peru	*A, *B	*A, *B	*A, *B	*A, *B	
United States of America	*H1, *H3, *B	*H1, *H3, *B	**H1, *H3, *B	***H1, **H3, *B	****H1, ****H3, ***B
Uruguay	*A	*B			
Asia					
Cambodia	*H1, *H3, *B	*H1, *H3, *B	*H3, *B	*H1, *B	
China		*H3, **B	*H3, **B	**H3, **B	**H3, ***B
China (Province of Taiwan)	*H1, *H3, *B	**H1, **H3	*H1		
China, Hong Kong SAR	*H1, *H3, **B	*H1, *H3, **B	*H1, *H3, *B	*H1, *H3, *B	**H1, *H3, **B
India	*B				*H3
Indonesia	*H3,*B	*H1,*B	*B	*H1	
Iran (Islamic Republic of)	*H1	*H1, *B	*H1, *B	**H1, *B	*H1, *B
Japan	*H1, *H3	**H1, *H3, *B	***H1, *H3, *B	***H1, *H3, *B	**H1, *H3, *B
Malaysia	*B	**H1, **H3, *B	**H1, **H3, *B	*B	
Mongolia		*H1		*B	*B
Nepal	*H1, *B				
Philippines	**H1, *H3, *B	**H1, *H3	*H1, *B	*H1, *B	
Qatar			*H1	*H1	
Republic of Korea		*H1, *B	*H1, *H3, *B	**H1, *H3, *B	
Singapore	*B	*H3, *B	*H3, *B		
Sri Lanka	*A, *B	*A, *B	*A	*B	
Thailand	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, **B	
Viet Nam	*H3, *B	*H3, *B	*H3, *B	*H3, *B	*H3, *B
Europe					
Austria				*H1, *A,*B	***H1, *A, *B
Belarus			*A, *B	*A,*B	***H1, *B
Belgium	*H3		*H1, *B	*H1, *H3, *B	****H1, *A, *B
Bulgaria		*H3			*H1
Croatia				*H1	***H1, *B
Czech Republic			*H1	**H1, *A	***H1, *A, *B
Denmark			*B	*H1, *B	**H1, *B
Finland				*H1, *B	***H1, *H3, *B
France	*H1	*H1, *B	*H1, *H3, *B	*H1, *H3, *B	***H1, *H3, *B

Country, area or territory	2007				2008
	September	October	November	December	January
Germany		*B	*H1, *B	*H1, *B	**H1, *H3, *B
Greece				*H1	**H1, *A, *B
Hungary				*H1, *B	***H1, ***B
Iceland					*H1, *A, *B
Israel				*B	**H1 , **B, **A
Italy			*H1	*H1, *B	**H1, *A, *B
Latvia			*H1	*H1, *B	**H1, *A, *B
Luxembourg				*H1, *B	****H1, *B
Montenegro					****H1
Netherlands		*H1			
Norway		*B	*H1, *A, *B	*H1, *A, *B	**H1, *A, *B
Poland			*A, *B		*A, *B
Portugal			*H1	*H1, *B	***H1, *B
Romania					***H1
Russian Federation		*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	**H1, *H3, *B
Serbia				*H1	*H1
Slovakia		*H1	*H1	*H1	
Slovenia			*H1, *A	*H1, *A	****H1, *A, *B
Spain		*H1, *H3, *B	*H1, *H3, *B	***H1, *H3, *B	***H1, *H3, **B
Sweden	*B	*H1, *A, *B	*H1, *A, *B	*H1, *A, *B	*H1, *H3, *B
Switzerland			*H1, *H3, *B	*H1, *A, *B	****H1, *H3, *B
Turkey			*B	*H1, *B	**H1, *B
United Kingdom of Great Britain and Northern Ireland	*H1	*H1, *B	*H1, *B	*H1, *H3, *B	***H1, *H3, *B
Ukraine					*H3
Oceania					
Australia	*H1, **H3, *B				
New Zealand	H1, *H3, **B				
United States of America, Guam		*H1			
Antarctica			*B		

Data in table 1 were provided by the Global Influenza Surveillance Network

*** = Sporadic activity**	**A = Influenza A (not subtyped)**
**** = Local activity**	**B = Influenza B**
***** = Regional outbreaks**	**H1 = Influenza A(H1N1)**
******= Widespread outbreaks**	**H3 = Influenza A(H3N2)**

Influenza A(H5N1)

Between September 2007 and 13 February 2008, 33 human cases of influenza A(H5N1) were confirmed in China, Egypt, Indonesia, Myanmar, Pakistan and Viet Nam. Many of these cases were associated with outbreaks of highly pathogenic avian influenza A(H5N1) in poultry. Since December 2003, a total of 360

human cases have been confirmed from 14 countries[2]. The WHO influenza pandemic preparedness level remains unchanged at Phase 3[3]. So far, there has been no evidence of sustained human-to-human transmission.

Antigenic characteristics of recent isolates

Influenza A(H1N1) viruses

In haemagglutination-inhibition (HI) tests with postinfection ferret sera, the majority of influenza A(H1N1) viruses was closely related to the vaccine strain A/Solomon Islands/3/2006. However, an increasing proportion of viruses was antigenically distinguishable from the vaccine strain and more closely related to A/Brisbane/59/2007 (Table 2).

Table 2 Results of haemagglutination-inhibition tests of influenza A(H1N1) viruses with postinfection ferret sera

Antigens –	A/Solomon Islands/3/2006	A/Brisbane/59/2007	A/South Dakota/6/2007
A/Solomon Islands/3/2006	**640**	320	160
A/Brisbane/59/2007	320	**640**	640
A/South Dakota/6/2007	320	640	**640**
Recent isolates –			
A/Florida/10/2007	640	160	320
A/Paris/658/2007	640	320	ND
A/Cambodia/371/2007	640	160	ND
A/Hiroshima/96/2007	320	160	ND
A/New Jersey/22/2007	160	640	320
A/Thailand/711/2007	80	320	320
A/Lyon/1362/2007	80	320	320
A/Colorado/35/2007	80	320	320
A/Hiroshima/102/2007	80	320	ND
A/Paris/577/2007*	80	320	ND
A/Norway/1735/2007*	80	640	ND
A/Madagascar/2293/2007	40	640	ND

ND, not determined
* Oseltamivir resistant

Influenza A(H3N2) viruses

In HI tests with postinfection ferret sera, some influenza A(H3N2) viruses were antigenically similar to the northern hemisphere vaccine viruses A/Wisconsin/67/2005 and A/Hiroshima/52/2005. However, the majority was closely related to the more recently recommended vaccine virus, A/Brisbane/10/2007[4].

[2] http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_02_12/en/index.html
[3] http://www.who.int/csr/disease/avian_influenza/phase/en/index.html
[4] http://www.who.int/wer/2007/wer8240/en/index.html

Influenza B viruses

Influenza B viruses of both the B/Victoria/2/87 and the B/Yamagata/16/88 lineages continued to circulate. The B/Yamagata/16/88 lineage viruses predominated among recent isolates although the proportion of B/Victoria/2/87 viruses has recently increased in China Hong Kong Special Administrative Region.

In HI tests with postinfection ferret sera, many viruses of the B/Victoria/2/87 lineage were closely related to the northern hemisphere vaccine virus B/Malaysia/2506/2004 but an increase in antigenic heterogeneity was observed. The majority of the B/Yamagata/16/88 lineage viruses were closely related to B/Florida/4/2006, B/Brisbane/3/2007 and B/Sendai/114/2007 viruses.

Resistance to influenza antiviral drugs

M2 inhibitors

Resistance to amantadine and rimantadine remained high among influenza A(H3N2) viruses globally, notably among viruses genetically closely related to A/Brisbane/10/2007. The proportion of resistant influenza A(H1N1) viruses was variable from country to country. Resistance in both subtypes was still predominantly associated with a serine to asparagine change in residue 31 of the M2 ion channel protein.

Neuraminidase inhibitors

Resistance to the neuraminidase inhibitor oseltamivir was detected in A(H1N1) viruses in several countries in different regions of the world. The proportion of oseltamivir resistant viruses varied from 0% to 64% in individual countries. These resistant A(H1N1) viruses retained sensitivity to zanamivir, amantadine and rimantadine. Updates are available at http://www.who.int/csr/disease/influenza/h1n1_table/en/index.html. Oseltamivir resistance was rarely detected among A(H3N2) and B viruses.

Studies with inactivated influenza virus vaccines

Antibodies to haemagglutinin (HA) were measured by HI tests in panels of sera from adults who had received trivalent inactivated vaccines containing the antigens of A/Solomon Islands/3/2006 (H1N1), B/Malaysia/2506/2004 and either A/Hiroshima/52/2005 or A/Wisconsin/67/2005 (H3N2), administered in doses of 15 μg of each HA. Cross-reactions of postimmunization antibody to recent isolates were examined in 4 panels of sera, 3 of which were selected for the presence of postimmunization antibody to the vaccine viruses. In addition, a fifth panel of sera from vaccinated paediatric subjects was tested.

Vaccines containing influenza A/Solomon Islands/3/2006 (H1N1) antigen stimulated HA antibodies at titres ≥40 to the vaccine virus in the sera of 98% of children, 93% of adults and 84% of elderly people. When the sera were tested against recent isolates, the corresponding proportions were lower: 49% of children, 59% of adults and 51% of elderly people. Furthermore, the average postimmunization geometric mean HI titres were lower to recent isolates than to the vaccine virus (reductions: children 73%; adults 80%; the elderly 67%).

Vaccines containing influenza A/Wisconsin/67/2005 (H3N2)-like antigens stimulated HA antibodies at titres ≥40 to the vaccine virus in the sera of 92% of children, 91% of adults and 88% of elderly people. When the sera were tested against recent isolates, the corresponding proportions were lower: 23% of children, 41% of adults and 41% of elderly people. Furthermore, the average postimmunization geometric mean HI titres were lower to recent isolates than to the vaccine virus (reductions: children 80%; adults 75%; the elderly 71%).

Immunization with vaccines containing influenza B/Malaysia/2506/2004 antigen stimulated HA antibodies at titres ≥40 to the vaccine virus in the sera of 75% of children, 80% of adults and 63% of elderly people. When the sera were tested against recent B/Malaysia/2506/2004-like isolates (B/Victoria/2/87 lineage), the corresponding proportions were similar: 73% of children; 74% of adults; 62% of elderly people. When sera were tested against recent B/Florida/4/2006-like isolates (B/Yamagata/16/88 lineage), the corresponding proportions were lower: 10% of children; 61% of adults; 43% of elderly people. The average postimmunization geometric mean HI titres to recent B/Malaysia/2506/2004-like isolates were similar to those of the vaccine virus, but the average postimmunization geometric mean HI titres were lower to recent B/Florida/4/2006-like isolates than to the vaccines virus (reductions: children 84%; adults 48%; elderly 53%).

Recommended composition of influenza virus vaccines for use in the 2008–2009 influenza season

During the period October 2007 to January 2008, influenza A(H1N1), A(H3N2) and B viruses circulated in many parts of the world.

Outbreaks caused by influenza A(H1N1) viruses were reported in many countries. While some isolates were antigenically similar to the vaccine virus, A/Solomon Islands/3/2006, the majority of recent isolates were distinguishable from the vaccine virus and antigenically similar to A/Brisbane/59/2007. Current vaccines containing A/Solomon Islands/3/2006 antigens stimulated HA antibodies that were lower in titre and frequency to recent isolates than to the vaccine virus.

Influenza A(H3N2) viruses were associated with outbreaks in the United States of America. While some isolates were antigenically similar to the northern hemisphere vaccine virus, A/Wisconsin/67/2005, the majority of recent isolates were antigenically similar to A/Brisbane/10/2007. Vaccines containing A/Wisconsin/67/2005 or A/Hiroshima/52/2005 antigens stimulated HA antibodies that were lower in titre and frequency to recent isolates than to the vaccine virus.

Influenza B outbreaks were reported in several countries. Viruses of both B/Victoria/2/87 and B/Yamagata/16/88 lineages were reported in many countries but B/Yamagata/16/88 lineage viruses predominated. For the B/Victoria/2/87 lineage viruses, the majority of recent isolates were antigenically similar to B/Malaysia/2506/2004. Most of the recent B/Yamagata/16/88 lineage viruses were antigenically similar to B/Florida/4/2006. Northern hemisphere vaccines containing B/Malaysia/2506/2004 antigen stimulated HA antibodies that were similar in titre to recently isolated B/Malaysia/2506/2004-like viruses, but were lower in titre to recently isolated B/Yamagata/16/88 lineage viruses.

It is recommended that vaccines for use in the 2008-2009 influenza season (northern hemisphere winter) contain the following:

— an A/Brisbane/59/2007 (H1N1)-like virus;
— an A/Brisbane/10/2007 (H3N2)-like virus;*
— a B/Florida/4/2006-like virus.#

*** A/Brisbane/10/2007 is a current southern hemisphere vaccine virus**
 # B/Florida/4/2006 and B/Brisbane/3/2007 (a B/Florida/4/2006-like virus) are current southern hemisphere vaccine viruses

As in previous years, national control authorities should approve the specific vaccine viruses used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine. WHO has published recommendations on the prevention of influenza[5]. Most of the population is

[5] http://www.who.int/docstore/wer/pdf/2002/wer7728.pdf

likely to have been infected with influenza A(H1N1), influenza A(H3N2) and influenza B viruses. As a consequence, 1 dose of inactivated influenza vaccine should be immunogenic for individuals of all ages except young children. Previously unimmunized children should receive 2 doses of inactivated vaccine, with an interval of at least 4 weeks between doses.

Vaccine viruses (including reassortants) and reagents for use in the laboratory standardization of inactivated vaccine may be obtained from: Immunobiology Section, Therapeutic Goods Administration Laboratories, P.O. Box 100, Woden ACT, 2606 Australia (fax: +61 2 6232 8564, web site: http://www.tga.gov.au); Division of Virology, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QG England (fax: +44 1707 641050, e-mail: enquiries@nibsc.ac.uk, web site: http://www.nibsc.ac.uk/flu_site/index.html); or Division of Product Quality, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20892, United States (fax: +1 301 480 9748).

Requests for reference strains for antigenic analysis should be addressed to the WHO Collaborating Centre for Reference and Research on Influenza, 45 Poplar Road, Parkville, Victoria 3052, Australia (fax: +61 3 9389 1881, web site: http://www.influenzacentre.org); the WHO Collaborating Centre for Reference and Research on Influenza, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashi-Murayama, Tokyo 208-0011, Japan (fax: +81 42 561 0812 or +81 42 565 2498, web site: http://www.nih.go.jp/niid/index.html); the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop G16, Atlanta, GA 30333, United States (fax: +1 404 639 0080, web site: http://www.cdc.gov/flu/); or the WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, England (fax: +44 208 906 4477), web site: http://www.nimr.mrc.ac.uk/wic/ .

Updated epidemiological information is available on WHO's web site at http://www.who.int/influenza .