Recommended composition of influenza virus vaccines for use in the 2009 southern hemisphere influenza season

The World Health Organization (WHO) convenes technical meetings[1] in February and September each year to recommend the composition of seasonal influenza vaccines[2] for the northern and southern hemispheres, respectively. This recommendation relates to the composition of vaccines for the forthcoming influenza season in the southern hemisphere (May to October 2009). A recommendation will be made in February 2009 relating to vaccines that will be used for the influenza season in the northern hemisphere (November 2009 to April 2010). For countries in equatorial regions epidemiological considerations will influence which recommendation (February or September) individual National Authorities consider more appropriate.

Influenza activity, February – September 2008

From February to September 2008, influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. In general, activity was mild.

In the northern hemisphere, influenza viruses continued to circulate and caused outbreaks in Asia, Europe and North America. Activity in general declined in March in Europe and in April in Asia and North America. A(H1N1) viruses circulated extensively and predominated in many countries. A(H3N2) viruses predominated in the United States of America and circulated less extensively in Asia and Eastern Europe. B viruses co-circulated and outbreaks were reported in some countries.

In the southern hemisphere, influenza activity began in March and increased in April in South America, while in Africa and Oceania, activity started in May and increased in July. Overall, activity declined in August except for Australia, Brazil and New Zealand. In Africa A(H1N1) viruses predominated and caused outbreaks. In South America, A(H1N1) and B viruses co-circulated and were associated with outbreaks. In Oceania, A(H3N2) and B viruses co-circulated with outbreaks being reported.

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

Table 1: Extent and type of seasonal influenza activity worldwide, February - September 2008

Country, area or territory	February	March	April	May	June	July	August	September
Africa								
Cameroon	*H1	*H1	*H1	*H1		*B		*H1
Côte d'Ivoire	*H1		*B, *H1	B, *H1				
Egypt	*A, ***B	*A	*A					
Ghana				*H1	*H1	*H1, *H3		
Kenya	*A, *B, *H3	*A, *B, *H1	*B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	
Madagascar	*H1, *B	*H1	*H1	*H1, *B	*H1	*H1, *B	*H1	
Mauritius					*B	*H1, *B, *H3		
Morocco	*H1, *B	*B	*B					
Senegal			*B	*B	*H1, *H3, *B	*H1, *H3, *B	**H1, *B	

[1] http://www.who.int/csr/disease/influenza/vaccinerecommendations/en/index.html
[2] Description of the process of influenza vaccine virus selection and development available at: http://www.who.int/gb/pip/pdf_files/Fluvaccvirusselection.pdf

Country, area or territory	February	March	April	May	June	July	August	September
Seychelles			*H1		*H1			
South Africa			*H3, *B	*H1, *B	***H1, *H3, *B	***H1, *H3, *B	*H1, *B	
Tunisia	***H1, **H3, ***B	***H1, ***B						
Uganda		*B	*B	*B	*H3	**B, *H1, *H3	*B, *H1	
America								
Argentina			*H1, *B	*H1, **B	**A, *H1, ***B	****A, ***H1, ****B	*H1, *B	*A, *B
Brazil	*H1, *A, *B	*H1, *A, ****B	**H1, **A, ** B	****H1, **A, **B	***H1, ***B	***H1, *A, ****B	****A, ****B	*A
Canada	****H1, *H3, *B	****H1, *H3, *B	***H1, *H3, **B	*H1, *H3, **B	*H1, *A, *B	*H1, *A, *B	*H1, *A, *B	*B
Chile	*H1	*H1, *A, *B	***H1, *B	***H1, **A	**H1, **A, *B	**A, *H1, *B	*H1, *B	*B
Colombia	*H1, *H3, B	*B	*H1					
Costa Rica	*A	*B	*A	*A	**A	*A, *B	*B	
Ecuador	***H1	*H1, *H3		*B				
El Salvador					*H1, *A, *B	*H1, *A, *B		
France, French Guiana	*H1, *B	*H1, *B	*A, H1	*H1, *B	*A			
France, Guadeloupe	**H1			*H1				
France, Martinique		*B						
Guatemala	*H1	*H3	*H3	*H1, *H3	*B, *H3, *H1	*B, *H3, *H1		
Honduras			*H1	*H1	*H1	*H1		
Mexico	*H1, **H3, *B	*H1, *H3, *B	*H3, *B	*A				
Panama	*A		*H1, *B	*H1, *A, *B	****A, ****B	**A, **B		
Paraguay				*H1				
Peru	*A, *B, *H3	*B, *H1, *H3	*H1, *B, *H3	*B, *H1, *H3	*A, *B, *H1	*A, *B, *H1		
Suriname	*H1							
Trinidad and Tobago			*H3					
United Kingdom, Montserrat	*H1							
United States	***H1, ****H3, ***B	***H1, ****H3, ***B	**H1, **H3, **B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	*A, *B	
Uruguay			*H1	*H1, *B	****H1, ****B	*H1, *B	*A, *B	
Venezuela	*B							
Asia								
Bangladesh				*B, *H1	*B, *H1, *H3			
China	*H1, **H3	*H1, **H3, *B	*H1, **H3, *B	**H1, *H3, *B	**H1, *H3, *B	**H1, *H3, *B	**H1, *H3, *B	
China (Province of Taiwan)		*B, *H1	*B, *H1, *H3	*B,* H1	*B, *H3			
China, Hong Kong SAR	**H1, *H3, **B	***H1, *H3, ***B	**H1, *H3, **B	*H1, *H3, *B	**H1, **H3, **B	**H1, **H3, **B	**H1, **H3, **B	**H1, **H3, *B
India	*H1, *H3, *B	*H3, *B	*H1, *H3, *B	*H1, *H3, *B	*B			
Iran (Islamic Republic of)	*H1		*H3		*B	*H3, *B		
Japan	****H1, **H3, **B	***H1, **H3, ***B	*H1, **H3, **B	**H3, *B	*H3, *B	*H1, *H3, *B	*H1, *H3	

Country, area or territory	February	March	April	May	June	July	August	September
Jordan		***B	***B	***H1				
Kuwait	*B, *H3	*H3						
Mongolia	***H3, ***B	*H3, *B						
Oman		*B	*B	*B	*B	*B	*B	
Philippines			*H3, *B	*B	*H3, **B	*H3, **B		
Republic of Korea	**H1, **H3, ****B	*H1, ***H3, ***B	*H1, ***H3, **B	*H3, *B				
Qatar	*B	*H3						
Singapore	*H1, **H3, **B	*H1, **H3, *B	*H1, **H3, **B	*H1, **H3, **B	*H1, *H3, **B	*H3, *B		
Sri Lanka		*A	*A, *B	*A	*A			
Thailand	*H1, **H3, *B	*H1, **H3, *B	*H1, **H3, *B	*H1, **H3, *B	*H1, **H3, *B	*H1, **H3, *B		
Europe								
Austria	****H1, ***B	**H1,**B						
Belarus	****H1, ****H3, ***B	*H1						
Belgium	****H1	***H1, *H3, **B	*H1, *H3, *B					
Bulgaria		*H1						
Croatia	****H1, *B	****H1, **B	*B					
Czech Republic	**H1, *B	*H1, *B						
Denmark	*H1, *H3	*H1, *B	*H3, *B	*B	*B			
Estonia	****H1, **B	*H1,*B	*A, *B					
Finland	***H1, *H3, *B	**H1, *A	*B	*B				
France	**H1, *H3, **B	*H1,*H3, *B	*H1,*B	*B	*H1, *H3, *B			
Georgia	*H1	*H1						
Germany	***H1, *H3, **B	***H1, *H3, **B	*H1, *H3, *B	*H1, *H3, *B	*B			
Greece	**H1, *B	*B	*B	*B	*H3			
Hungary	***H1, **B	*B	*A					
Iceland	*H1, *B	*H1, *H3, *B	**H3, *B	*H3, *B				
Ireland	****H1, A	*H1, *B, A	*B					
Israel	***H1, *H3, ***B	**A						
Italy	*H1, *H3, *B	*H3, *B	*H3, *B					
Kazakhstan	*B	***B, ***H1	*B, *H1					
Kyrgyzstan	*H3							
Latvia	***H1, *A, *B	*H1, *H3, *B	*H1,*B	*B				
Lithuania	**A	*A						
Luxembourg	****H1, *B	****B, **H1	*B					
Netherlands	****H1, **B, A	**H1, ****B, A	**H1, ****B, A					
Norway	****H1, *H3, ***B	***H1, *H3, ***B	*H1, *H3, ***B	*H1, *H3, *B	*B	*B		
Poland	*H1, *B	*H1, *B	*H1, *B	*H1, *B		*A, *B	*A	
Portugal	***H1,*B	*H1, *B	*B	*B				
Romania	**H1, **B	*H1, *B	*B					

Country, area or territory	February	March	April	May	June	July	August	September
Russian Federation	***H1, ***H3, **B	****H1, ****H3, ***B	***H1, ***H3, ***B	*H1, *H3, *B	*H1, *H3, *B			
Serbia	*H1, *B							
Slovakia	**H1, *A, **B	**B	**B					
Slovenia	**H1, *H3, *B							
Spain	**B	*B	*B					
Sweden	*H1, *H3, *B	*A, *B	*A, *H3, *B	*H3, *B				
Switzerland	****H1,*H3, **B	*H1, *H3, *B	*B					
Ukraine	****H1,**B	***H1, **B	*H1, *B					
United Kingdom	**H1, *H3, **B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B				
Oceania								
Australia	*H1, *H3, *B	*H1, *H3, *B	*H3, *B	*H3, *B	*H1, **H3, **B	*H1, ***H3, ***B	*H1, **H3, **B	**H3, **B
France, New Caledonia							**H1	
New Zealand				**H3, *B	****H3, ***B	****H3, ****B	*H1, ***H3, ****B	**H3, ***B

Data in Table 1 were provided by the Global Influenza Surveillance Network	
* = Sporadic activity	A= Influenza A (Not subtyped)
**= Local outbreaks	B= Influenza B
***= Regional outbreaks	H1= Influenza A(H1N1)
****=Widespread outbreaks	H3= Influenza A(H3N2)

The definition used in FluNet reporting :

No activity:	No influenza viral isolates or clinical signs of influenza activity
Sporadic activity:	Isolated cases of ILI or laboratory confirmed cases in a limited area
Local activity:	Activity of ILI above baseline values with laboratory confirmed cases in a limited area
Regional activity:	Outbreaks of ILI or laboratory confirmed influenza in one or more regions with a population comprising less than 50% of the country's total population
Widespread activity:	Outbreaks of ILI or laboratory confirmed influenza in one or more regions with a population comprising 50% or more of the country's population

Influenza A(H5N1)

From 1 February to 19 September 2008, 36 human cases of influenza A(H5N1) were confirmed in Bangladesh, China, Egypt, Indonesia 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 387 human cases have been confirmed from 15 countries[3]. So far, there has been no evidence of sustained human-to-human transmission. The WHO influenza pandemic preparedness level remains unchanged at Phase 3[4].

[3] http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_09_10/en/index.html
[4] http://www.who.int/csr/disease/avian_influenza/phase/en/

Antigenic and genetic characteristics of recent isolates

A combination of antigenic and genetic analyses is used to identify emergent antigenic variants of potential future epidemic importance and for consideration of their inclusion in vaccines. Antigenic relationships among contemporary viruses and vaccine strains are of prime importance in determining vaccine composition. These relationships are evaluated mainly in HI tests using postinfection ferret sera against egg and/or cell grown reference and vaccine viruses using red blood cells principally from turkeys but also from other species, as appropriate. Virus neutralization tests provide complementary data. Antigenic cartography is used as an additional analytical tool to visualize and integrate antigenic data. Phylogenetic analyses of haemagglutinin (HA) and neuraminidase (NA) genes help to define the genetic relatedness of antigenic variants to their predecessors and to elucidate the molecular basis for antigenic drift. The spread of antigenic variants associated with influenza outbreaks in different countries is also an important criterion for selection of epidemiologically relevant vaccine candidates.

Influenza A(H1N1) viruses

In haemagglutination-inhibition (HI) tests with postinfection ferret sera, the majority of influenza A(H1N1) viruses were closely related to the northern hemisphere 2008-2009 vaccine strain A/Brisbane/59/2007. Phylogenetically the haemagglutinins of recent viruses belonged to one of two distinct clades represented by A/Brisbane/59/2007 and A/Hong Kong/2652/2006, with most belonging to the A/Brisbane/59/2007 clade. These two clades were antigenically indistinguishable.

Influenza A(H3N2) viruses

In HI tests with postinfection ferret sera, the majority of recent influenza A(H3N2) viruses were antigenically similar to the vaccine viruses A/Brisbane/10/2007 and A/Uruguay/716/2007, and phylogenetically belonged to the A/Brisbane/10/2007 clade.

Influenza B viruses

Influenza B viruses of both the B/Yamagata/16/88 and the B/Victoria/2/87 lineages continued to circulate. The B/Yamagata/16/88 lineage has remained predominant in the world, although recently B/Victoria/2/87 lineage viruses have been increasing in some countries, areas or territories, for example in Australia, China, China Hong Kong Special Administrative Region and New Zealand.

In HI tests with post-infection ferret sera the majority of viruses of the B/Yamagata/16/88 lineage were closely related to B/Florida/4/2006 and B/Brisbane/3/2007, the vaccine strains for the northern hemisphere, 2008-2009. The haemagglutinin genes of the B/Yamagata/16/88 lineage viruses fell into three different clades (represented by B/Florida/4/2006, B/Brisbane/3/2007 and B/Bangladesh/3333/2007); these three clades were antigenically indistinguishable. The haemagglutinins of the B/Victoria/2/87 lineage viruses were genetically homogeneous except for a small clade represented by B/Sydney/12/2008. Viruses from this clade circulated in Australia and New Zealand but were antigenically indistinguishable from other B/Victoria/2/87 lineage viruses.

Resistance to influenza antiviral drugs

Neuraminidase inhibitors

Resistance of A(H1N1) viruses to the neuraminidase inhibitor oseltamivir, due to the H275Y mutation[5] (numbered according to N1 sequence), increased in many countries in different regions of the world. The proportion varied from 0% to 100% in individual countries. Phylogenetically the majority of oseltamivir resistant viruses fell into the A/Brisbane/59/2007 clade. Only a few of the A/Hong Kong/2652/2006 clade viruses were resistant to oseltamivir. Resistant viruses from both clades retained sensitivity to zanamivir.
Updates are available at http://www.who.int/csr/disease/influenza/h1n1_table/en/index.html . No oseltamivir resistant A(H3N2) or B viruses were detected.

M2 inhibitors

The proportion of influenza A(H3N2) viruses resistant to amantadine and rimantadine remained very high. The proportion of resistant influenza A(H1N1) viruses was variable from country to country; A/Brisbane/59/2007 clade viruses were sensitive whereas A/Hong Kong/2652/2006 clade viruses were resistant. Resistance in both subtypes was still predominantly associated with a serine to asparagine change in residue 31 of the M2 ion channel protein.

A few viruses (of the A/Hong Kong/2652/2006 clade) were resistant to both oseltamivir and M2 inhibitors but retained sensitivity to zanamivir.

Studies with inactivated influenza virus vaccines

The presence of antibodies to the haemagglutinin (HA) of recent virus isolates was determined by haemagglutination inhibition (HI) tests in panels of sera from adults and elderly who had received trivalent inactivated vaccines. In total, 3 panels of sera were used: one from subjects who had received vaccines containing the antigens of A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007; one from subjects who had received vaccines containing the antigens of A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Florida/4/2006; and one from subjects who had received vaccines containing the antigens of A/Solomon Islands/3/2006 (H1N1), A/Brisbane/10/2007 and B/Brisbane/3/2007. The latter panel was excluded from the analysis of antibodies against influenza A(H1N1) viruses because the corresponding vaccine strain was obsolete at the time of analysis.

Vaccines containing influenza A/Brisbane/59/2007 (H1N1) antigen stimulated anti HA antibodies at titres ≥40 to the vaccine virus in the sera of 72% of adults and 58% of elderly subjects. When the sera were tested against recent isolates, the corresponding proportions were similar. Furthermore, the average postimmunization geometric mean HI titres to the vaccine virus and recent isolates were similar.

Vaccines containing influenza A/Brisbane/10/2007 (H3N2)-like antigens stimulated anti HA antibodies at titres ≥40 to the vaccine virus in the sera of 76% of adults and 80% of elderly subjects. When the sera were tested against recent isolates, the corresponding proportions were somewhat lower: 63% of adults and 61% of elderly subjects. However, the average postimmunization geometric mean HI titres to the vaccine virus and recent isolates were similar. On a subset of the sera, these HI results were supported by results from microneutralization tests.

[5] H274Y according to N2 sequence numbering

Immunization with vaccines containing influenza B/Florida/4/2006-like antigen stimulated anti HA antibodies at titres ≥40 to the vaccine virus in the sera of 73% of adults and 58% of elderly subjects. When the sera were tested against recent B/Florida/4/2006-like isolates (B/Yamagata/16/88 lineage), the corresponding proportions were similar. When sera were tested against recent B/Malaysia/2506/2004-like isolates (B/Victoria/2/87 lineage), the corresponding proportions were lower: 49% of adults; 36% of elderly subjects. The average postimmunization geometric mean HI titres to recent B/Florida/4/2006-like isolates were similar to those against the vaccine virus, but the average postimmunization geometric mean HI titres were somewhat lower to recent B/Malaysia/2506/2004-like isolates than to the vaccine virus (reductions of 47% in adults and 49% in elderly subjects).

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

During the period February to September 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. The majority of recent isolates were antigenically similar to the vaccine virus A/Brisbane/59/2007. Current vaccines containing A/Brisbane/59/2007 antigens stimulated anti HA antibodies to recent influenza virus A(H1N1) isolates, which were of similar titer and frequency to those against the vaccine virus.

Influenza A(H3N2) viruses were associated with outbreaks in several countries. While some isolates were antigenically distinguishable from the vaccine viruses A/Brisbane/10/2007 and A/Uruguay/716/2007, the majority of recent isolates were antigenically similar to the vaccine viruses. Current vaccines containing A/Brisbane/10/2007 or A/Uruguay/716/2007 antigens stimulated anti HA antibodies to recent influenza virus A(H3N2) isolates, which were of similar titer and frequency to those against the vaccine virus.

Influenza B outbreaks were reported in several countries. While viruses of both B/Victoria/2/87 and B/Yamagata/16/88 lineages circulated, B/Yamagata/16/88 lineage viruses predominated. Most of the recent B/Yamagata/16/88 lineage viruses were antigenically similar to B/Florida/4/2006. Current vaccines containing B/Florida/4/2006 or B/Brisbane/3/2007 antigens stimulated anti HA antibodies to recent influenza virus B isolates of the B/Yamagata/16/88 lineage, which were of similar titer and frequency to those against the vaccine virus.

It is recommended that vaccines for use in the 2009 influenza season (southern 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/South Dakota/6/2007 (an A/Brisbane/59/2007-like virus) is a current vaccine virus used in live attenuated vaccines**
**** A/Brisbane/10/2007 and A/Uruguay/716/2007 (an A/Brisbane/10/2007-like virus) are current vaccine viruses**
 # B/Florida/4/2006 and B/Brisbane/3/2007 (a B/Florida/4/2006-like virus) are current 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[6]. Most of the population is 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, Office of Laboratory and Scientific Services, Therapeutic Goods Administration, 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/fl u/); 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 the WHO web site at http://www.who.int/influenza .

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