

Recommended composition of influenza virus vaccines for use in the 2009–2010 influenza season

February 2009

This recommendation relates to the composition of vaccines for the forthcoming influenza season in the northern hemisphere (November 2009 to April 2010). A recommendation will be made in September 2009 relating to vaccines that will be used for the influenza season in the southern hemisphere (May to October 2010). For countries in equatorial regions epidemiological considerations will influence which recommendation (February or September) individual National Authorities consider more appropriate.

Influenza activity, September 2008–January 2009

Between September 2008 and January 2009, influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. In general, activity was lower compared with the same period the previous year¹ but in some European countries activity was higher.

In the southern hemisphere, influenza activity continued in many countries in September - November and in particular peaked in Australia during September. Influenza B viruses predominated in Australia and New Zealand while A(H1N1), A(H3N2) and B viruses circulated in other countries to varying extents.

In most parts of the northern hemisphere, influenza activity was mild. Regional outbreaks, particularly in Japan, Tunisia and many European countries, due to A(H3N2) were reported in December and January. In North America, while A(H1N1), A(H3N2) and B viruses co-circulated, A(H1N1) viruses predominated in the USA and B viruses predominated in Canada.

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

Table 1 Extent and type of seasonal influenza activity worldwide, September 2008 - January 2009

Country, area or territory	2008				2009
	September	October	November	December	January
Africa					
Cameroon	*H1, *B	*H1, *B	*H1, *B	*H1, *B	*H1, *H3, *B
Egypt	**A, **B	*H3	*H3	*H3	*B
France, Réunion		*A			
Ghana	*B	*H1, *B	*H1, *H3, *B	*B	
Kenya	*H1, *H3, *B	*H3, *B	*A, *B	*A, *B	
Madagascar	*H1, *H3	*H1, *H3	*H1, *H3	*H1	
Mauritius	*H1, *H3, *B		*H3		
Morocco				*H1, *B	*H1, *H3, *B
Senegal	*H1, *B	*B			
South Africa	*B	*H1	*H3		
Tunisia			*H1	*H1, *B	*H1, ***H3, *B
Uganda		A	A	A	
America					
Argentina	*H1, *B	*H1, *H3, *B	*H1		
Bolivia		B	B		
Brazil	*H1, *B		*A	*A	*A
Canada	*B, *H1	*A, *B, *H3	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, **B
Chile	*A, *B	*H1, *B	*A, *B		

¹ <http://www.who.int/wer/2008/wer8309/en/index.html>

Country, area or territory	2008				2009
	September	October	November	December	January
Costa Rica		*B	*H1	*H1	
Ecuador	**H3, *B	**B			
France, French Guiana					*H3
France, Martinique			*H3, *B		
Honduras		*B	*B		
Mexico	*H1, *B	*H1, *B	*H1		
Peru	*B				
United States of America	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	**H1, *H3, *B	**H1, *H3, **B
Asia					
Bangladesh	*H1, *H3, *B	*H3			
China		*H1	*H1, *B	*H1, *H3, *B	*H1, *H3, *B
China (Province of Taiwan)	*H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, **H3, *B
China, Hong Kong SAR	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	**H1, *H3, *B
India	*H3, *B	*H3, *B	*H1, *H3, *B	*H1, *B	
Iran (Islamic Republic of)			*H1, *H3	*H3	*H1, *H3
Japan	*H3, *B	*H1, *H3, *B	**H1, ** H3, *B	***H1, ***H3, *B	****H1, ****H3, *B
Malaysia	*B				
Mongolia				*H1	*H1
Philippines	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B		
Republic of Korea	*H3	*H3	*H1, *H3	**H1, *H3	**H1, *H3
Singapore	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B
Thailand	*H1, *H3, *B	*H1, *H3, *B	*H1, *B	*H1, *B	
Europe					
Austria				*H3	***A
Belarus		*A	*A, *B	*A, *B	
Belgium		*B	*B	*H3, *B	*H1, ****H3,
Bulgaria				*H1	
Croatia					*H1, *H3, *B
Czech Republic				*H3	***H3, *B
Denmark		*H3	*H3	*H1, ****H3	*H1, ****H3
Estonia					*H1, ****H3, *B
Finland				**H3, *B	*H3
France		*H3	*H1, *H3, *B	*H1, ***H3, *B	*H1, ****H3, *B
Germany		*H3, *B	*H1, *H3, *B	*H1, *H3, *B	*H1, ****H3, *B
Greece				*H1	*H1, **H3, *B
Hungary					***H3
Israel	*H1, *B	*B		*H1, *H3, *B	*H1, *H3, *B
Italy			*H3, *B	**H3	*H1, ****H3, *B
Latvia				*A, *H3	*H1, ***H3, *B
Luxembourg				*H1, *H3	****H3
Netherlands	*H3, *B	*H3	**H3	*H1, ***H3	****H3, *B
Norway	*B	*H1, *H3	*H1, *H3, *B	*H1, ****H3, *B	*H1, ****H3, *B
Poland	*A	*A			**H3, *B
Portugal			*H1, *H3	*H1, ****H3, *B	*H1, ****H3, *B
Romania			*H3		*H1, **H3, *B
Russian Federation		*H1, *H3, *B	*H1, *H3, *B	*H1, *H3, *B	**H1, *H3, *B
Serbia				*B	*H1, *H3, *B
Slovakia					*H3
Slovenia				*H1, *H3	*H1, ****H3, *B
Spain		*H1,	*H1, *H3, *B	*H1, ***H3, *B	****H3, *B

Country, area or territory	2008				2009
	September	October	November	December	January
Sweden	*H3, *B	*H3	*H1, *H3	*H1, *H3	*H1, ***H3
Switzerland			*H3, *B	*H3, *B	****H3, *B
Turkey				*H3	*H3, *B
United Kingdom of Great Britain and Northern Ireland	*H3	*H1, *H3, *B	*H1, *H3, *B	*H1, ****H3, *B	*H1, **H3, *B
Oceania					
Australia	*H1, *H3, ***B	*H1, *H3, *B	*H1, *H3, *B		
New Zealand	*H1, *H3, ****B	*H3, *B			
United States of America, Guam		*H3, *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)		

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 haemagglutination inhibition (HI) tests using postinfection ferret sera against egg and/or cell grown reference and vaccine viruses using red blood cells principally from turkeys and guinea pigs, 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 HI tests with postinfection ferret sera, the majority of influenza A(H1N1) viruses were closely related to the 2008-2009 vaccine strain A/Brisbane/59/2007. Phylogenetically the haemagglutinins of recent viruses belonged to two distinct clades represented by A/Brisbane/59/2007 and A/Hong Kong/2652/2006. Viruses within the former clade predominated among isolates from most parts of the world while those within the A/Hong Kong/2652/2006 clade were predominant in China. The haemagglutinins of 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. Although a proportion of viruses gave reduced HI titres with ferret antisera against the vaccine viruses, neutralization tests revealed that representatives of these viruses were antigenically indistinguishable from the vaccine viruses.

Influenza B viruses

Influenza B viruses of both the B/Yamagata/16/88 and the B/Victoria/2/87 lineages continued to co-circulate. The proportion of B/Victoria/2/87 lineage viruses has continued to increase and these viruses have become predominant in many countries.

The haemagglutinins of the B/Victoria lineage viruses are in four main phylogenetic clades represented by B/Brisbane/60/2008, B/Townsville/2/2008, B/Hubei-Songzi/51/2008, and B/Bangladesh/4008/2008. Strains in all four clades were antigenically distinguishable from the previous B/Victoria lineage vaccine strain B/Malaysia/2506/2004. The B/Brisbane/60/2008 and B/Townsville/2/2008 clades formed one antigenic cluster represented by B/Brisbane/60/2008. The B/Hubei-Songzi/51/2008 and B/Bangladesh/4008/2008 clades formed another antigenic cluster represented by B/Hubei-Songzi/51/2008. Viruses in the B/Brisbane/60/2008 cluster were more antigenically distinct from the B/Malaysia/2506/2004-like strains than viruses in the B/Hubei-Songzi/51/2008 cluster. Most recent isolates from Europe, Oceania, North America and South America were in the B/Brisbane/60/2008 antigenic cluster. Currently, B/Hubei-Songzi/51/2008 clade viruses are predominant in China.

In HI tests with postinfection ferret sera the majority of viruses of the B/Yamagata/16/88 lineage were closely related to the vaccine strains B/Florida/4/2006 and B/Brisbane/3/2007. The haemagglutinins of the B/Yamagata/16/88 lineage viruses fell into three clades represented by B/Florida/4/2006, B/Brisbane/3/2007 or B/Bangladesh/3333/2007, with the B/Bangladesh/3333/2007 clade predominating. These three clades were antigenically indistinguishable.

Table 2 Results of haemagglutination inhibition tests of influenza B Victoria lineage viruses with postinfection ferret sera

	B/Malaysia/2506/2004	B/Brisbane/60/2008	B/Brisbane/33/2008
Antigens			
B/Malaysia/2506/2004	320	160	320
B/Brisbane/60/2008	160	640	1280
B/Brisbane/33/2008	160	640	1280
Recent isolates			
B/SouthAustralia/263/2008	20	320	1280
B/Sakai/14/2008	10	160	640
B/Wellington/21/2008	20	160	640
B/England/457/2008	80	320	1280
B/Berlin/42/2008	20	160	640
B/Belgium/G086/2008	40	160	640
B/Florida/31/2008	10	160	640

Influenza A(H5N1)

From September 2008 to 11 February 2009, 21 human cases of influenza A(H5N1) were confirmed in Cambodia, China, Egypt, Indonesia and Viet Nam. Many of these people had visited live bird markets or had contact with sick or dead poultry. Since December 2003, a total of 406 human cases have been confirmed from 15 countries². To date, there has been no evidence of sustained human-to-human transmission. The WHO influenza pandemic preparedness level remains unchanged at Phase 3³.

² http://www.who.int/csr/disease/avian_influenza/country/cases_table_2009_02_09/en/index.html

³ http://www.who.int/csr/disease/avian_influenza/phase/en/index.html

Resistance to influenza antiviral drugs

Neuraminidase inhibitors

H1N1 viruses that were resistant to the neuraminidase inhibitor oseltamivir were predominant in most regions of the world. Resistance was associated with the H275Y mutation in the neuraminidase gene within the A/Brisbane/59/2007 clade. All recent A/Hong Kong/2652/2006 clade viruses were sensitive to oseltamivir. There were no reports of oseltamivir resistant A(H3N2) or B viruses. No zanamivir resistant viruses were reported. Updates are available at http://www.who.int/csr/disease/influenza/h1n1_table/en/index.html.

M2 inhibitors

Most influenza A(H3N2) viruses were resistant to amantadine and rimantadine. The majority of A(H1N1) viruses of the A/Hong Kong/2652/2006 clade were resistant, whereas those of the A/Brisbane/59/2007 clade were sensitive. Resistance in both subtypes was still predominantly associated with a serine to asparagine change in residue 31 of the M2 ion channel protein.

Studies with inactivated influenza virus vaccines

The presence of antibodies to the haemagglutinin (HA) of recent virus isolates was determined by HI tests in panels of sera from paediatric, adult and elderly subjects who had received trivalent inactivated vaccines. The following panels were used: three panels from adult, three from elderly and two from paediatric 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 panel each from adult and elderly subjects who had received vaccines containing the antigens of A/Solomon Islands/3/2006 (H1N1), A/Brisbane/10/2007 (H3N2) and B/Brisbane/3/2007. The last two panels were only used for the analysis of influenza A(H3N2) and B viruses because the A(H1N1) component of this vaccine was obsolete at the time of analysis. Although HI tests were somewhat variable between laboratories the following conclusions could be made.

Vaccines containing influenza A/Brisbane/59/2007 (H1N1) antigen stimulated anti HA antibodies with geometric mean HI titres that were somewhat lower to recent isolates than to the vaccine virus (average reductions: children 51 %; adults 56 %; elderly 42 %).

Vaccines containing influenza A/Brisbane/10/2007 (H3N2)-like antigens stimulated anti HA antibodies with similar geometric mean HI titres to the vaccine virus and recent isolates. On a subset of sera, these HI results were supported by results from microneutralization tests.

Vaccines containing influenza B/Florida/4/2006-like antigens stimulated anti HA antibodies with similar geometric mean HI titres to the vaccine virus and recent B/Yamagata/16/88 lineage isolates. However, geometric mean HI titres were lower to recent B/Victoria/2/87 lineage isolates than to the vaccine virus (average reductions: children 35%; adults 67 %; elderly 56 %).

Recommended composition of influenza virus vaccines for use in the 2009–2010 influenza season

During the period September 2008 to January 2009, 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 several 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 which were somewhat lower in titre to recent isolates than to the vaccine virus.

Influenza A(H3N2) viruses were associated with outbreaks in many countries. The majority of recent isolates were antigenically similar to the vaccine viruses A/Brisbane/10/2007 and A/Uruguay/716/2007. Current vaccines containing A/Brisbane/10/2007 or A/Uruguay/716/2007 antigens stimulated anti HA antibodies which were of similar titre to recent isolates than to 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 co-circulated, B/Victoria/2/87 lineage viruses predominated. The majority of recent B/Victoria/2/87 lineage isolates were antigenically closely related to B/Brisbane/60/2008. Most 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 that had similar titers against vaccine viruses and recent isolates of the B/Yamagata/16/1988-lineage; however, titers were consistently lower to recent isolates of the B/Victoria/2/1987-lineage.

It is recommended that vaccines for use in the 2009–2010 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/Brisbane/60/2008-like virus.#**

*** A/Brisbane/59/2007 is a current vaccine 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/Brisbane/33/2008 is a B/Brisbane/60/2008-like virus

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 influenza⁴. 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, 10 Wreckyn Street, North Melbourne, Victoria 3051, Australia (fax: +61 3 9342 3939, 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, email whocc@nimr.mrc.ac.uk, 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>.

⁴ <http://www.who.int/docstore/wer/pdf/2002/wer7728.pdf>