Recommended composition of influenza virus vaccines for use in the 2016 southern hemisphere influenza season

September 2015

The World Health Organization (WHO) convenes technical consultations[1] in February and September each year to recommend viruses for inclusion in influenza vaccines[2] for the influenza season in northern and southern hemispheres, respectively. This recommendation relates to the influenza vaccines for the forthcoming 2016 southern hemisphere influenza season. A recommendation will be made in February 2016 relating to vaccines that will be used for the 2016-2017 northern hemisphere influenza season. For countries in equatorial regions, epidemiological considerations influence which recommendation (February or September) individual national and regional authorities consider appropriate.

Seasonal influenza activity, February 2015 – September 2015

Between February 2015 and September 2015, influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. Activity varied from sporadic to widespread and was associated with the circulation of influenza A(H1N1)pdm09, A(H3N2) and B viruses.

In the northern hemisphere, influenza activity was high from February to April and started to decline from April onwards with the exception of several countries. In the southern hemisphere, activity remained low from February until May when moderate to high activity was reported from a number of countries.

Influenza A(H1N1)pdm09 activity was variable in Africa, the Americas, Asia, Europe and Oceania. Regional and widespread outbreaks occurred in Asia, Europe and North Africa between February and April. Widespread outbreaks occurred in the Indian subcontinent between February and July. Sporadic activity was reported in North America. Activity decreased from May until September in the northern hemisphere. In Central and South America, activity was low in general with the exception of Cuba which reported regional outbreaks in August. In Africa, widespread A(H1N1)pdm09 activity occurred in South Africa from May to July. Sporadic A(H1N1)pdm09 activity was reported in Australia and New Zealand.

Influenza A(H3N2) activity was generally moderate to high in the Americas, Asia, Europe and Oceania. In the Americas, widespread outbreaks were reported by the United States of America in February while widespread and regional outbreaks occurred in some central and South American countries such as Brazil, Ecuador, El Salvador and Paraguay from May or June onwards.

In Asia, regional and widespread outbreaks were reported in February and March by Japan, and in March by Israel. Regional outbreaks were reported in June by China Hong Kong Special Administrative Region, June and July by Cambodia, and July and August by China. In the European region, many countries reported regional or widespread outbreaks of A(H3N2) in February and March with co-circulation of A(H1N1)pdm09 and influenza B. Activity was low in Africa with the exception of Madagascar which reported regional outbreaks in February and March. Activity was high in Australia and moderate in New Zealand.

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

Influenza B activity was generally variable in Africa, the Americas, Asia, Europe and Oceania. Moderate to high activity was reported by many European countries between February and April. In Asia, widespread outbreaks occurred in Kazakhstan in February and in Georgia in February and March. Regional outbreaks occurred in China in February and March and in Japan from February to April.

In Africa, the Democratic Republic of the Congo and Madagascar reported regional outbreaks in February to April, and February and March, respectively. Activity was low in the rest of Africa. Regional and widespread outbreaks were reported by the United States of America from February to March. In South America, regional influenza B outbreaks were reported in Paraguay in August but in general activity was low in other countries. In Oceania, regional and widespread outbreaks occurred in Australia from June onwards, and in New Zealand from July to September.

A summary of the extent and type of seasonal influenza activity worldwide is available on the WHO website:
http://www.who.int/influenza/vaccines/virus/recommendations/201509_influenzaactivitytable.pdf

Zoonotic influenza infections caused by A(H5), A(H7N9), A(H9N2), A(H1N1)v and A(H3N2)v viruses

From 24 February 2015 to 21 September 2015, one human infection with an A(H5N6) virus was reported by China and 69 confirmed human cases of A(H5N1) were reported by China (3), Egypt (64) and Indonesia (2). Highly pathogenic avian influenza A(H5) is present in poultry in these countries. Since December 2003, a total of 844 cases with 449 deaths have been confirmed in 16 countries. To date there has been no evidence of sustained human-to-human transmission.

During this period 105 additional human cases of avian influenza A(H7N9) virus infection have been reported in China. Since February 2013, a total of 667 cases with 275 deaths have been reported.

Four A(H9N2) human cases were reported in this period, one in China, one in Bangladesh and two in Egypt. The associated disease in all cases was mild with the viruses from China belonging to the A/chicken/Hong Kong/Y280/97 genetic lineage and the virus from Bangladesh belonging to the A/quail/Hong Kong/G1/97 genetic lineage. Sequence data from one Egyptian case indicated the virus was genetically similar to previous G1-lineage A(H9N2) poultry viruses detected in Egypt.

Two cases of A(H1N1)v, one being fatal, and two cases of A(H3N2)v were reported in the United States of America.

Antigenic and genetic characteristics of recent seasonal influenza viruses

Influenza A(H1N1)pdm09 viruses

Antigenic characteristics of A(H1N1)pdm09 viruses collected from February 2015 to August 2015 were assessed with panels of post-infection ferret antisera in haemagglutination inhibition (HI) tests. HI tests indicated that the A(H1N1)pdm09 viruses were antigenically homogeneous and closely related to the vaccine virus A/California/7/2009. Sequence analysis of the haemagglutinin (HA) genes of A(H1N1)pdm09 viruses indicated that most of the recently circulating viruses belonged to genetic clade 6B, which continues to diversify.

Influenza A(H3N2) viruses

A(H3N2) viruses collected from February 2015 to August 2015 fell into the phylogenetic clades 3C.2 and 3C.3. Viruses in sub-clade 3C.2a are now predominant in all regions of the world. Sub-clade

3C.3a and 3C.3b viruses continued to circulate but represented the minority of viruses in this reporting period.

Antigenic characteristics of A(H3N2) viruses were assessed with panels of post-infection ferret antisera in HI and virus neutralization assays. Antigenic characterization of 3C.2a viruses remained technically challenging because many viruses had low or undetectable haemagglutination activity and required the use of modified HI and virus neutralization assays for analysis. Most recent A(H3N2) 3C.2a viruses were well inhibited by ferret antisera raised against cell-propagated reference A/Switzerland/9715293/2013 (3C.3a) virus, indicating that 3C.2a and 3C.3a viruses remain antigenically related. Ferret antisera raised against reference cell-propagated 3C.2a viruses also well inhibited a majority of viruses tested, although inhibition was somewhat reduced against 3C.3a viruses, indicating that some 3C.2a and 3C.3a viruses were antigenically distinguishable.

Egg propagation is known to introduce additional changes that may affect antigenicity. Such changes have been particularly problematic for recent A(H3N2) viruses. Ferret antisera raised against egg-propagated 3C.2a viruses, including A/Hong Kong/4801/2014, generally inhibited recently circulating viruses better than antisera raised to egg-propagated A/Switzerland/9715293/2013 virus (Table 1).

Influenza B viruses

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated with viruses of the B/Yamagata/16/88 lineage predominating in many countries. In Australia and New Zealand a rapid increase in the proportion of B/Victoria/2/87-lineage viruses was observed from June and they became the predominant lineage by August 2015.

The HA gene sequences of the B/Yamagata/16/88 lineage viruses fell into genetic clades 2 and 3, with the vast majority in clade 3. In HI assays, recently circulating B/Yamagata/16/88-lineage viruses were inhibited by post-infection ferret antisera raised against the egg or cell-propagated virus B/Phuket/3073/2013 (clade 3), the virus recommended for use in vaccine for the 2015 southern and 2015-2016 northern hemisphere influenza seasons.

All of the HA gene sequences of B/Victoria/2/87 lineage viruses fell into genetic clade 1A. In HI assays recent viruses were well inhibited by post-infection ferret antisera raised against either B/Brisbane/60/2008 or B/Texas/2/2013 viruses; these vaccine viruses were recommended for use in the 2015-2016 quadrivalent influenza vaccine.

Resistance to influenza antiviral drugs

Neuraminidase inhibitors

All but three influenza A(H1N1)pdm09 viruses tested were sensitive to the neuraminidase inhibitors. Two viruses showed reduced inhibition by oseltamivir and peramivir, due to a H275Y substitution in the neuraminidase. Both of these viruses remained sensitive to zanamivir and laninamivir. One A(H1N1)pdm09 virus had moderately reduced inhibition to oseltamivir, but contained no unique neuraminidase amino acid substitutions.

The great majority of influenza A(H3N2) viruses tested were sensitive to the neuraminidase inhibitors. However, seven viruses showed reduced inhibition to one or more of the neuraminidase inhibitors. Of these, one virus showed reduced inhibition to oseltamivir, peramivir and zanamivir and carried an R292K neuraminidase substitution and another virus showed reduced inhibition to zanamivir associated with a D151A neuraminidase substitution. Five viruses showed reduced inhibition to only oseltamivir, of which four carried an S331R neuraminidase substitution and one an E119V neuraminidase substitution. Two additional viruses showed reduced inhibition to zanamivir,

Table 1. Antigenic analysis of influenza A(H3N2) viruses - Plaque Reduction Neutralisation (MDCK-SIAT)

Viruses	Genetic group	Collection Date	Passage History	Neutralisation titre				
				Post-infection ferret antisera				
				A/HK 7295/14 3C.2a	A/HK 4801/14 3C.2a	A/Switz 9715923/13 3C.3a	A/Switz 9715923/13 3C.3a	A/Neth 525/14 3C.3b
				Cell	Egg	Cell	Egg	Cell
REFERENCE VIRUSES								
A/Hong Kong/7295/2014	3C.2a	2014-08-07	MDCK3	320	80	80	80	40
A/Hong Kong/4801/2014	3C.2a	2014-02-26	E6	640	320	40	40	80
A/Switzerland/ 9715293/2013	3C.3a	2013-12-06	SIAT1/SIAT2	20	20	160	20	20
A/Switzerland/ 9715293/2013	3C.3a	2013-12-06	E4/E2	80	40	40	320	40
A/Netherlands/525/2014	3C.3b	2014-12-17	SIAT2/SIAT1	80	40	80	80	1280
TEST VIRUSES								
A/Moldova/111.07/2015	3C.2a	2015-02-10	MDCK2/SIAT1	320	80	40	40	40
A/South Africa/R3777/2015	3C.2a	2015-06-26	MDCK2/SIAT1	320	80	80	80	80
A/South Africa/R3803/2015	3C.2a	2015-06-29	MDCK2/SIAT1	160	80	40	80	40
A/South Africa/R3778/2015	3C.2a	2015-06-29	MDCK2/SIAT1	160	40	20	20	10
A/Iasi/177050/2015	3C.3a	2015-02-04	MDCK1/SIAT1	80	40	80	80	40
A/Behoririka/355/2015	3C.3a	2015-02-04	MDCK1/SIAT1	80	40	80	40	80
A/Manjakaray/612/2015	3C.3a	2015-02-23	MDCK1/SIAT1	160	80	80	80	80
A/Stockholm/19/2015	3C.3b	2015-02-25	MDCK0/SIAT1	320	80	80	80	1280
A/Sweden/16/2015	3C.3b	2015-03-05	MDCK1/SIAT1	320	160	80	80	640

but remained sensitive to oseltamivir, peramivir and laninamivir, with both carrying a Q136K substitution in the neuraminidase.

The majority of influenza B/Yamagata-like viruses were sensitive to neuraminidase inhibitors, but twelve viruses carried a D197N substitution in the neuraminidase that resulted in reduced oseltamivir and peramivir inhibition. Two viruses also showed reduced oseltamivir and peramivir inhibition due to an I221T neuraminidase substitution. Two further B/Yamagata viruses showed reduced inhibition to at least one of the neuraminidase inhibitors. One had reduced oseltamivir and peramivir inhibition and contained an H273Y neuraminidase substitution and the other virus had reduced peramivir inhibition and carried a T146I neuraminidase substitution.

All B/Victoria-like viruses tested were sensitive to the neuraminidase inhibitors apart from three viruses which showed reduced inhibition to peramivir. One virus contained no unique neuraminidase amino acid substitutions while two other viruses had neuraminidase amino acid substitutions D432G or N151T.

M2 inhibitors

M gene sequencing of A(H1N1)pdm09 and A(H3N2) viruses revealed that all but one of those analysed had an amino acid substitution S31N of the M2 protein which is known to confer resistance to the M2 inhibitors, amantadine and rimantadine.

Human serology studies with inactivated influenza virus vaccines

HI assays were used to measure the presence of antibodies to recent virus isolates in panels of sera from children, adults and older adults who had received seasonal trivalent or quadrivalent inactivated vaccines. For A(H1N1)pdm09 and A(H3N2) viruses, virus neutralization assays were used for a subset of sera. One panel of sera from adults and one from older adults were from trials of egg-grown trivalent vaccine of the composition recommended for the southern hemisphere 2015 season (A/California/7/2009 (H1N1)pdm09-like, A/Switzerland/9715293/2013 (H3N2)-like and B/Phuket/3073/2013-like viruses); in addition, one panel of sera from children who had received egg-grown quadrivalent vaccine of the composition recommended for the northern hemisphere 2014-2015 season (A/California/7/2009 (H1N1)pdm09-like, A/Texas/50/2012 (H3N2)-like, B/Massachusetts/02/2012-like and B/Brisbane/60/2008-like viruses) was used for analysis of A(H1N1)pdm09 and B viruses in one laboratory.

Geometric mean HI titres of antibodies against the majority of representative recent A(H1N1)pdm09 viruses were not reduced significantly as compared to HI titres to the vaccine virus.

For A(H3N2), serum panels were tested against viruses representative of circulating viruses belonging to genetic groups 3C.2a, 3C.3a and 3C.3b. Geometric mean HI titres of antibodies against the majority of cell-propagated 3C.2a viruses were reduced significantly compared to HI titres to the vaccine virus, when measured against egg-propagated A/Switzerland/9715293/2013 virus but not when compared to cell-propagated A/Switzerland/9715293/2013 virus. Geometric mean microneutralization titres of antibodies against 2 of 3 cell-propagated 3C.2a viruses tested were reduced significantly compared to microneutralization titres against cell-propagated A/Switzerland/9715293/2013 virus.

Serum panels were tested against representative recent B/Yamagata/16/88 lineage viruses as well as against a few B/Victoria/2/87 lineage viruses. Geometric mean HI titres of antibodies against most representative recent B/Yamagata/16/88 lineage viruses were not reduced significantly compared to HI titres to the vaccine virus. As expected, geometric mean HI titres to B/Victoria/2/87 lineage viruses were reduced in panels from trials of trivalent vaccines not containing a B/Victoria/2/87 lineage antigen.

Recommended composition of influenza virus vaccines for use in the 2016 southern hemisphere influenza season

Influenza A(H1N1)pdm09 viruses co-circulated in varying proportions with A(H3N2) and B viruses during the period February 2015 – September 2015, with outbreaks reported in several countries. The majority of A(H1N1)pdm09 viruses were antigenically similar to A/California/7/2009. Vaccines containing A/California/7/2009-like antigens elicited anti-HA antibodies in humans of similar titres against the vaccine virus and recent A(H1N1)pdm09 viruses.

Influenza A(H3N2) viruses were associated with outbreaks in several countries. The majority of recent viruses were antigenically related to cell-propagated 3C.2a reference viruses.

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated, with viruses of the B/Yamagata/16/88 lineage predominating in many countries. In Australia and New Zealand a rapid increase in the proportion of B/Victoria/2/87-lineage viruses was observed from June and they became the predominant lineage by August 2015.

It is recommended that trivalent vaccines for use in the 2016 southern hemisphere influenza season contain the following:

– an A/California/7/2009 (H1N1)pdm09-like virus;
– an A/Hong Kong/4801/2014 (H3N2)-like virus;
– a B/Brisbane/60/2008-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.

Lists of candidate influenza vaccine viruses that are available or under development and reagents for vaccine standardization, including those for this recommendation, can be found on the WHO website[3]. Candidate vaccine viruses for zoonotic influenza viruses are updated on the same website.

As in previous years, national or regional authorities approve the composition and formulation of vaccines 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[4].

Candidate vaccine viruses (including reassortants) and reagents for use in the laboratory standardization of inactivated vaccine may be obtained from: Immunobiology, Office of Laboratories, Monitoring and Compliance Division, Therapeutic Goods Administration, P.O. Box 100, Woden, ACT, 2606, Australia (fax: +61262328564, email: influenza.reagents@tga.gov.au; web site: http://www.tga.gov.au); Division of Virology, National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QG UK (fax: +441707641050, e-mail: enquiries@nibsc.org, web site: http://www.nibsc.org/science_and_research/virology/influenza_resource_.aspx; Division of Biological Standards and Quality Control, Center for Biologics Evaluation and Research, Food and Drug Administration, 10905 New Hampshire Avenue, Silver Spring, Maryland, 20993, USA (fax: +1 301 480 9748), email: cbershippingrequests@fda.hhs.gov); Influenza Virus Research Center, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashi-Murayama, Tokyo 208-0011, Japan (fax: +81425616156, email: flu-vaccine@nih.go.jp).

Requests for reference viruses should be addressed to the WHO Collaborating Centre for Reference and Research on Influenza, VIDRL, 792 Elizabeth Street, Melbourne, Victoria 3000, Australia (fax:

[3] http://www.who.int/influenza/vaccines/virus/candidates_reagents/home
[4] http://www.who.int/wer/2012/wer8747.pdf

+61393429329, web site: http://www.influenzacentre.org, email: whoflu@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: +81425616149 or +81425652498, email: whocc-flu@nih.go.jp the WHO Collaborating Centre 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: +14046390080, web site: http://www.cdc.gov/flu/, email: influenzavirussurveillance@cdc.gov); the Worldwide Influenza Centre, The Francis Crick Institute, Mill Hill Laboratory, The Ridgeway, Mill Hill, London NW7 1AA, UK (fax: +442089064477, web site: http://www.crick.ac.uk/research/worldwide-influenza-centre email: whocc@crick.ac.uk) or the WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Viral Disease Control and Prevention, China CDC, 155 Changbai Road, Changping District, 102206, Beijing, P.R. China. (tel: +86 10 5890 0851, fax: +86 10 5890 0851, email: whocc-china@cnic.org.cn, website: http://www.cnic.org.cn/eng/).

Influenza surveillance information is updated on the WHO Global Influenza Programme web site[5].

[5] http://www.who.int/influenza

Annex 1

Declarations of interest

The WHO recommendation on the composition of influenza vaccines for the southern hemisphere 2016 was made through a technical consultation with relevant WHO Collaborating Centres on Influenza (CCs) and Essential Regulatory Laboratories (ERLs) of the WHO Global Influenza Surveillance and Response System.

In accordance with WHO policy, Directors and Experts of the relevant WHO CCs and ERLs, in their capacity as representatives of their respective institutions ("Advisers") completed the WHO form of Declaration of Interests for WHO Experts before being invited to the consultation. At the start of the consultation, the interests declared by the Advisers were disclosed to all consultation participants.

The Advisers declared the following personal current or recent (within the past 4 years) financial or other interests relevant to the subject of work:

Institution	Representative	Personal interest
WHO CC Atlanta	Dr Jacqueline Katz	None
WHO CC Beijing	Dr Yuelong Shu	None
WHO CC London	Dr John McCauley	None
WHO CC Melbourne	Dr Ian Barr	Shareholdings (significant) of the company CSL Limited
WHO CC Memphis	Dr Richard Webby	None
WHO CC and ERL NIID Tokyo	Dr Takato Odagiri	None
WHO ERL CBER Bethesda	Dr Zhiping Ye	None
WHO ERL NIBSC London	Dr Othmar Engelhardt	None
WHO ERL TGA Canberra	Dr Mandvi Bharadwaj	None

Based on the WHO assessment of the interest declared by Dr Barr, it was concluded that Dr Barr should continue to serve as an Adviser, considering that the interest was disclosed at the beginning of the consultation, and that, in accordance with the conditions required of all WHO CC Melbourne staff, Dr Barr has agreed to refrain from acquiring additional shares in companies involved in influenza vaccine manufacture.

In view of the foregoing, Dr Barr participated in the consultation as Adviser.