# Recommended composition of influenza virus vaccines for use in the 2015-2016 northern hemisphere influenza season

## February 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 influenza season in the northern hemisphere (2015-2016). A recommendation will be made in September 2015 relating to vaccines that will be used for the influenza season in the southern hemisphere (2016). For countries in equatorial regions, epidemiological considerations influence which recommendation (February or September) individual national and regional authorities consider appropriate.

## Seasonal influenza activity, September 2014 – January 2015

Between September 2014 and January 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.

Globally, influenza activity remained low until late November/early December when activity began to increase in some countries. In the northern hemisphere, influenza activity was sporadic to regional in November except in the United States of America (USA) where widespread activity was reported. Activity increased in December and January. In the southern hemisphere, activity remained low from September to January except in Australia where widespread influenza activity was reported in September and regional activity in early October.

**Influenza A(H1N1)pdm09** activity was generally sporadic in Asia, Africa, the Americas and Europe, and was variable in Oceania. In Africa, widespread activity was reported in the Democratic Republic of the Congo from September to November and regional activity was reported in Tunisia from December to January. In the Americas, regional activity was reported in El Salvador in October, and in Paraguay in September and November. Local to regional activity was reported in Bahrain, Cambodia, China, and the Islamic Republic of Iran between September and January. Widespread outbreaks occurred in Croatia, Italy, the Netherlands, Portugal and Slovenia in January. Local to widespread outbreaks occurred in Australia, France - New Caledonia and New Zealand in September and October.

**Influenza A(H3N2) activity** was generally sporadic in Africa and Oceania, but was regional to widespread in the Americas, Asia and Europe. In Africa, widespread activity in Egypt was reported during December and January, and regional to widespread activity in Madagascar between September and January, and by Senegal in September. In Asia, there was local to regional activity in Bahrain, Cambodia, China, China Hong Kong Special Administrative Region, the Islamic Republic of Iran, Israel, Republic of Korea, Singapore and Thailand from November to January. Widespread activity occurred in Japan in December and January. In the Americas, local to widespread activity was reported across Central and North America from October to January. In North America widespread activity was reported by the USA from November to January, and by Canada during December. Regional to widespread activity was reported across Europe in January. Widespread outbreaks occurred in Belgium, Croatia, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Latvia,

[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

the Netherlands, Portugal, Spain, Sweden, Switzerland and the United Kingdom of Great Britain and Northern Ireland.

**Influenza B** activity was generally sporadic in Africa, the Americas, Europe and Oceania, and variable in Asia. In Africa, local to regional activity was reported in Algeria from November to January, in Egypt from September to January, and in Morocco from November to January. Widespread outbreaks occurred in Madagascar in December. In Central and South America, regional activity was reported by Brazil and Nicaragua during September and October, and Paraguay from September to December. In Asia, local activity was reported from September to January in Bahrain, Cambodia, Georgia, the Islamic Republic of Iran, Nepal, and Viet Nam. In Europe regional to widespread activity occurred in France and Portugal during January. Local activity was reported in Australia during November, and in New Zealand during 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/201502_influenzaactivitytable.pdf

## Zoonotic influenza infections caused by A(H5N1), A(H5N6), A(H7N9), A(H9N2), A(H1N1)v and A(H3N2)v viruses

From 24 September 2014 to 23 February 2015, two human infections with A(H5N6) viruses were reported by China and 110 confirmed human cases of A(H5N1) were reported by China (1) and Egypt (109). Highly pathogenic avian influenza A(H5) is present in poultry in both of these countries. Since December 2003, a total of 777 cases with 428 deaths have been confirmed in 16 countries. To date there has been no evidence of sustained human-to-human transmission.

During this period 148 additional human cases of avian influenza A(H7N9) virus infection have been reported. All cases were in China with the exception of two cases detected in Canada in individuals recently returning from China. Since February 2013, a total of 602 cases with 227 deaths have been reported[3].

Three A(H9N2) human cases were reported in this period, two in China and one 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 Egypt belonging to the A/quail/Hong Kong/G1/97 genetic lineage. One case each of A(H1N1)v and 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 September 2014 to January 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.

### Influenza A(H3N2) viruses

A(H3N2) viruses collected from September 2014 to January 2015 fell into the phylogenetic clades 3C.2 and 3C.3. Viruses in sub-clade 3C.2a became predominant in many regions of the world, except

[3] Communication from WHO Collaborating Center, Beijing.

China, other parts of Asia, and parts of Eastern Europe and Africa where sub-clade 3C.3a viruses predominated. In addition, 3C.3 and sub-clade 3C.3b viruses were still in circulation.

Antigenic characteristics of A(H3N2) viruses were assessed with panels of post-infection ferret antisera in HI and virus neutralization assays. However, because of their changing properties, antigenic characterization of A(H3N2) viruses, particularly 3C.2a viruses, has become technically difficult and required extensive investigations in multiple laboratories. Thus modified HI and virus neutralization assays were needed to analyse the viruses, in particular many 3C.2a viruses that had low or undetectable haemagglutination activity. The majority of recent A(H3N2) viruses were poorly inhibited by ferret antisera raised against egg- and cell-propagated reference A/Texas/50/2012 (clade 3C.1) viruses. Most viruses were well inhibited by ferret antisera raised against cell-propagated A/Switzerland/9715293/2013 (3C.3a) virus and representative 3C.2a viruses, indicating that 3C.2a and 3C.3a viruses were antigenically related.

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 A/Switzerland/9715293/2013 (the recommended vaccine virus for the southern hemisphere 2015 season) reacted well with most recently circulating viruses. Initial data obtained with antisera raised against two egg-propagated 3C.2a viruses showed variable reactivity with circulating viruses.

**Influenza B viruses**

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated but viruses of the B/Yamagata/16/88 lineage predominated.

The HA genes of the B/Yamagata/16/88 lineage viruses fell into genetic clades 2 and 3, with the vast majority in clade 3. Recently circulating viruses were inhibited well by ferret antisera raised against the egg-propagated virus B/Phuket/3073/2013, the virus recommended for use in vaccine for the southern hemisphere 2015 influenza season.

The majority of B/Victoria/2/87 lineage viruses were well recognised by antisera raised against B/Brisbane/60/2008 and B/Texas/2/2013.

## Resistance to influenza antiviral drugs

**Neuraminidase inhibitors**

All but two influenza A(H1N1)pdm09 viruses tested were sensitive to neuraminidase inhibitors. One virus from Australia and one virus from the USA showed reduced inhibition by oseltamivir and peramivir, but remained sensitive to zanamivir and laninamivir. In both instances, reduced inhibition was due to a histidine to tyrosine substitution at amino acid 275 (H275Y) in the neuraminidase.

The great majority of influenza A(H3N2) viruses tested were sensitive to neuraminidase inhibitors. Three viruses from China showed reduced inhibition to zanamivir, but remained sensitive to oseltamivir. One virus from Australia showed reduced inhibition to zanamivir, but remained sensitive to oseltamivir, peramivir and laninamivir. These four viruses carried a Q136K substitution in the neuraminidase. One virus from the USA showed reduced inhibition by oseltamivir, zanamivir, peramivir and laninamivir. This virus carried a N142S substitution in the neuraminidase.

All but four influenza B viruses tested were sensitive to neuraminidase inhibitors. Three influenza B/Yamagata viruses from China showed reduced inhibition by oseltamivir and zanamivir, and carried a D197N substitution in the neuraminidase. One influenza B/Victoria virus from Singapore showed reduced inhibition by peramivir, but remained sensitive to oseltamivir, zanamivir, and laninamivir. This virus carried a N151T substitution in the neuraminidase.

**M2 inhibitors**

M gene sequencing of A(H1N1)pdm09 and A(H3N2) viruses revealed that all those analysed had a 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(H3N2) viruses a subset of sera were assessed by virus neutralization assays. Three panels of sera from adults and older adults, as well as one panel from children, were from trials of egg-grown trivalent 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 and B/Massachusetts/2/2012-like viruses); two panels of sera from adults and older adults, as well as one panel from children were from trials of egg-grown quadrivalent vaccine of the same composition with the addition of B/Brisbane/60/2008-like antigen.

For the majority of panels tested, post-vaccination geometric mean HI titres of antibodies against representative recent A(H1N1)pdm09 viruses were not significantly lower than HI titres to the vaccine virus.

For A(H3N2), serum panels were tested against viruses representative of circulating viruses belonging to genetic groups 3C.3a and 3C.2a. Geometric mean HI titres of antibodies against the majority of representative recent viruses were reduced significantly compared to HI titres to the vaccine virus, when measured against egg- or cell-propagated A/Texas/50/2012-like reference viruses.

Serum panels were tested against representative recent B/Yamagata/16/88 lineage viruses of genetic group 3 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 reduced significantly compared to HI titres to the vaccine virus (B/Massachusetts/2/2012). As expected, geometric mean HI titres to B/Victoria/2/87 lineage viruses were also reduced for serum panels from recipients of trivalent vaccines not containing a B/Victoria/2/87 lineage antigen.

## Recommended composition of influenza virus vaccines for use in the 2015-2016 northern hemisphere influenza season

A(H1N1)pdm09 viruses co-circulated in varying proportions with A(H3N2) and B viruses during the period September 2014 – January 2015, with outbreaks 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 A/Switzerland/9715293/2013.

Influenza B activity was reported in many countries. B/Yamagata/16/88 lineage viruses predominated over those of the B/Victoria/2/87 lineage. The majority of recent B/Victoria/2/87 lineage viruses were antigenically and genetically closely related to B/Brisbane/60/2008. Most recently isolated B/Yamagata/16/88 lineage viruses were antigenically closely related to the vaccine virus recommended for use in the 2015 southern hemisphere influenza season, B/Phuket/3073/2013.

**It is recommended that vaccines for use in the 2015-2016 influenza season (northern hemisphere winter) contain the following:**

**– an A/California/7/2009 (H1N1)pdm09-like virus;**
**– an A/Switzerland/9715293/2013 (H3N2)-like virus;**
**– a B/Phuket/3073/2013-like virus.**

**It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-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[4]. 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[5].

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); Center for Influenza Virus Research, 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: +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 WHO Collaborating Centre for Reference and Research on Influenza, MRC National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK (fax: +442089064477, web site: http://www.nimr.mrc.ac.uk/wic/, email: whocc@nimr.mrc.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[6].

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

## Annex 1

### Declarations of interest

The WHO recommendation on composition of influenza vaccines for the northern hemisphere 2015-2016 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 WHO 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 | Prof Anne Kelso | Shareholdings (significant) of the company CSL Limited |
| WHO CC Memphis | Dr Richard Webby | None |
| WHO CC and<br>WHO ERL NIID Tokyo | Dr Takato Odagiri | None |
| WHO ERL CBER Bethesda | Dr Zhiping Ye | None |
| WHO ERL NIBSC Potters Bar | Dr Othmar Engelhardt | None |
| WHO ERL TGA Canberra | Ms Tania Dalla Pozza | None |

Based on the WHO assessment of the interest declared by Professor Kelso, it was concluded that Professor Kelso 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, Prof Kelso has agreed to refrain from acquiring additional shares in companies involved in influenza vaccine manufacture.

In view of the foregoing, Professor Kelso participated in the consultation as Adviser.