Recommended composition of influenza virus vaccines for use in the 2016-2017 northern hemisphere influenza season

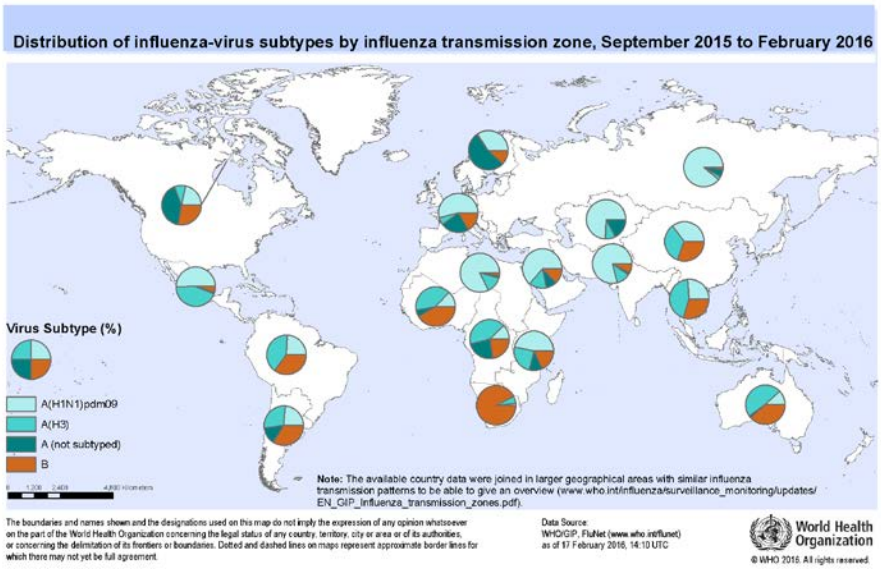
February 2016

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 northern and southern hemisphere influenza season, respectively. This recommendation relates to the influenza vaccines for use in the forthcoming northern hemisphere 2016-2017 influenza season. A recommendation will be made in September 2016 relating to vaccines that will be used for the southern hemisphere 2017 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, 6 September 2015 – 6 February 2016

Between 6 September 2015 and 6 February 2016, influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. Activity varied from low to high and was associated with the co-circulation of influenza A(H1N1)pdm09, A(H3N2) and B viruses. Influenza A(H1N1)pdm09 was the most frequently detected virus.

Globally, with exception of the tropical/subtropical areas, influenza activity remained low until late November/early December when activity began to increase. In the northern hemisphere, influenza activity was low to moderate in November, with the exception of a few countries where high activity was reported, and started to increase from December. In the southern hemisphere, activity was low from October.



Detailed information by country of the extent and type of seasonal influenza activity worldwide is available on the WHO website:
http://www.who.int/influenza/vaccines/virus/recommendations/201602_influenzaactivitytable.pdf

[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

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

From 22 September 2015 to 22 February 2016, five human cases with A(H5N6) viruses were reported by China and two human cases of A(H5N1) were reported, one by Bangladesh and the other by China. Highly pathogenic avian influenza A(H5) is present in poultry in both countries. Since December 2003, a total of 846 human cases of A(H5N1) infection 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 44 additional human cases of avian influenza A(H7N9) virus infection have been reported in China. Since February 2013, a total of 721 cases with 286 deaths have been reported.

Six A(H9N2) human cases were reported during this period, one in Bangladesh and five in China. The associated disease in all these cases but one was mild. The viruses from cases in China belonging to the A/chicken/Hong Kong/Y280/97 genetic lineage and the virus from the case in Bangladesh belonging to the A/quail/Hong Kong/G1/97 genetic lineage.

During this period, three cases of A(H1N1)v, two in China and one in the United States of America, and one case of A(H3N2)v in the United States of America were reported.

Antigenic and genetic characteristics of recent seasonal influenza viruses

Influenza A(H1N1)pdm09 viruses

Antigenic characteristics of A(H1N1)pdm09 viruses collected from September 2015 to January 2016, including viruses from severe cases and fatal cases, were assessed with panels of post-infection ferret antisera in haemagglutination inhibition (HI) tests and a subset of viruses were also tested by virus neutralisation. HI and virus neutralisation assays indicated that almost all the A(H1N1)pdm09 viruses were antigenically similar 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 there were two newly emerging sub-clades within the 6B clade (6B.1 and 6B.2). In most countries the proportion of 6B.1 viruses expanded very rapidly from October 2015 to become predominant; however, in China the 6B.2 sub-clade viruses predominated. Viruses within sub-clades 6B.1 and 6B.2 are currently not antigenically distinguishable from A/California/7/2009-like viruses. Both clades are continuing to evolve.

Influenza A(H3N2) viruses

A(H3N2) viruses collected from September 2015 to January 2016 fell into the phylogenetic clades 3C.2 and 3C.3. Viruses in sub-clade 3C.2a predominated in all regions of the world. Sub-clade 3C.3a has continued to circulate but represented a lower proportion of viruses circulating in this reporting period. Viruses in genetic sub-clade 3C.3b were only detected sporadically.

Antigenic characteristics of A(H3N2) viruses were assessed with panels of post-infection ferret antisera in HI and virus neutralisation assays. Antigenic characterization of 3C.2a viruses was technically challenging because many viruses had low or undetectable haemagglutination activity and required the use of HI tests done in the presence of oseltamivir and virus neutralisation assays for analysis. Most recent A(H3N2) 3C.2a viruses were well inhibited by ferret antisera raised against cell culture-propagated reference viruses in sub-clade 3C.2a, for example A/Hong Kong/4801/2014 or A/Michigan/15/2014. These antisera also inhibited a majority of viruses in sub-clades 3C.3a and 3C.3b.

Egg propagation is known to introduce additional changes that can 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.

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/Victoria/2/87 lineage predominating in many countries.

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 cell culture-propagated B/Brisbane/60/2008 or B/Texas/2/2013 viruses. These viruses were recommended for use in vaccines for the 2016 southern hemisphere influenza season.

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

Resistance to influenza antiviral drugs

Neuraminidase inhibitors

During this reporting period, the detection of viruses with reduced susceptibility to the neuraminidase inhibitors was very rare among the >5000 viruses tested.

All influenza A(H1N1)pdm09 viruses tested were sensitive to the neuraminidase inhibitors, apart from five viruses which carried an H275Y amino acid substitution in the neuraminidase which conferred highly reduced inhibition by oseltamivir and peramivir. Two of the five viruses were from patients who had been treated with oseltamivir.

All influenza A(H3N2) viruses tested were sensitive to the neuraminidase inhibitors apart from one virus, which contained dual Q391K and K249E neuraminidase amino acid substitutions and showed reduced inhibition by oseltamivir, zanamivir and peramivir.

All influenza B/Yamagata/16/88 lineage viruses tested were sensitive to the neuraminidase inhibitors apart from six viruses that showed reduced inhibition by oseltamivir and peramivir. Three of these viruses carried a D197N neuraminidase amino acid substitution that resulted in reduced oseltamivir and peramivir inhibition, while the other three viruses contained an H273Y neuraminidase amino acid substitution that conferred reduced oseltamivir inhibition and highly reduced peramivir inhibition.

All of the influenza B/Victoria/2/87 lineage viruses tested were sensitive to the neuraminidase inhibitors apart from one virus which showed reduced inhibition by peramivir due to an H134Y neuraminidase amino acid substitution.

M2 inhibitors

M gene sequencing of A(H1N1)pdm09 and A(H3N2) viruses revealed that all viruses 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 of the composition recommended for the northern hemisphere 2015-16 season (A/California/7/2009 (H1N1)pdm09-like, A/Switzerland/9715293/2013 (H3N2)-like and B/Phuket/3073/2013-like viruses, with the addition of B/Brisbane/60/2008-like antigens for quadrivalent vaccines). For A(H3N2) viruses, virus neutralisation assays were used for a subset of sera. Two panels of sera from adults and older adults as well as one panel of sera from children were from trials of trivalent vaccine; three panels of sera from adults and older adults as well as one panel from children were from trials of quadrivalent vaccine.

Geometric mean HI titres of antibodies against some of the representative recent A(H1N1)pdm09 viruses were reduced significantly compared to HI titres to the vaccine virus, in particular for paediatric serum panels; however, reductions were less pronounced for other recent viruses.

For A(H3N2), geometric mean HI titres of antibodies against some representative recent viruses were reduced significantly compared to HI titres to the egg-propagated vaccine virus; when measured against cell culture-propagated A/Switzerland/9715293/2013 virus, geometric mean titres against recent viruses were relatively higher. Neutralisation tests using a subset of serum panels confirmed these findings.

Serum panels were tested against representative recent B/Yamagata/16/88 and B/Victoria/2/87 lineage viruses. Geometric mean HI titres of antibodies against the majority of recent B/Yamagata/16/88 lineage viruses were similar 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, whereas serum panels from trials of quadrivalent vaccines showed good reactivity with recent B/Victoria/2/87 lineage viruses.

Recommended composition of influenza virus vaccines for use in the 2016-2017 northern hemisphere influenza season

Influenza A(H1N1)pdm09 viruses, which predominated in many countries, co-circulated with A(H3N2) and influenza B viruses during the period September 2015 – January 2016. The majority of A(H1N1)pdm09 viruses were antigenically similar to A/California/7/2009, although there was a notable emergence of two new genetically distinguishable subclades (6B.1 and 6B.2) within the 6B clade. Some recent A(H1N1)pdm09 viruses within the 6B.1 and 6B.2 subclades reacted poorly with human sera collected from individuals who received vaccines containing A/California/7/2009-like viruses.

Influenza A(H3N2) viruses were associated with outbreaks in some countries. The majority of recent viruses were antigenically related to cell culture-propagated 3C.2a A/Hong Kong/4801/2014-like viruses.

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated, with viruses of the B/Victoria/2/87 lineage predominating in many countries. Most B/Victoria/2/87 lineage viruses were antigenically and genetically closely related to B/Brisbane/60/2008 and B/Texas/2/2013. The majority of recent B/Yamagata/16/88 lineage viruses were antigenically and genetically closely related to B/Phuket/3073/2013.

It is recommended that trivalent vaccines for use in the 2016-2017 northern 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 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, Laboratories Branch, Medical Devices and Product Quality 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, 10903 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:

- WHO Collaborating Centre for Reference and Research on Influenza, VIDRL, Peter Doherty Institute, 792 Elizabeth Street, Melbourne, Victoria 3000, Australia (fax: +61393429329, web site: http://www.influenzacentre.org, email: whoflu@influenzacentre.org)
- 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
- WHO Collaborating Centre for Surveillance, Epidemiology and Control of Influenza, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop G16, Atlanta, GA 30329, United States (fax: +14046390080, web site: http://www.cdc.gov/flu/, email: influenzavirussurveillance@cdc.gov)
- WHO Collaborating Centre for Reference and Research on Influenza, 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)
- 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/).

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

WHO provides fortnightly updates[5] of the global influenza activity. Other information of influenza surveillance can be found on the WHO Global Influenza Programme website[6].

Acknowledgements

The WHO recommendation on vaccine composition is based on the year-round work of the WHO Global Influenza Surveillance and Response System (GISRS). We thank the National Influenza Centres of GISRS, and non-GISRS laboratories, who contributed information, clinical specimens and viruses, and associated data; WHO Collaborating Centres of GISRS for their in-depth characterization and comprehensive analysis of viruses; University of Cambridge for performing antigenic cartography and phylogenetic analysis; WHO Essential Regulatory Laboratories of GISRS for their complementary virus analyses and contributions from a regulatory perspective; and laboratories involved in the production of high growth/yield reassortants as candidate vaccine viruses. We also acknowledge GISAID for the EpiFlu database which was used to share gene sequences and associated information, modelling groups and the Global Influenza Vaccine Effectiveness (GIVE) Collaboration for sharing estimates of influenza vaccine effectiveness on a confidential basis.

[5] http://www.who.int/influenza/surveillance_monitoring/updates/en/
[6] http://www.who.int/influenza

Annex 1

Declarations of interest

The WHO recommendation on composition of influenza vaccines for the northern hemisphere 2016-2017 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, CDC, Atlanta	Dr Jacqueline Katz	None
WHO CC, CNIC, Beijing	Dr Yuelong Shu	None
WHO CC, The Francis Crick Institute, London	Dr John McCauley	None
WHO CC, VIDRL, Melbourne	Dr Ian Barr	Shareholdings in significant amount of the company CSL Limited.
WHO CC, St Jude Children's Hospital, Memphis	Dr Richard Webby	None
WHO CC and ERL, NIID, Tokyo	Dr Takato Odagiri	None
WHO ERL, CBER, Silver Spring	Dr Zhiping Ye	None
WHO ERL, TGA, Canberra	Dr Mandvi Bharadwaj	None
WHO ERL, NIBSC, Potters Bar	Dr Othmar Engelhardt	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 Advisers.