Recommended composition of influenza virus vaccines for use in the 2017-2018 northern hemisphere influenza season

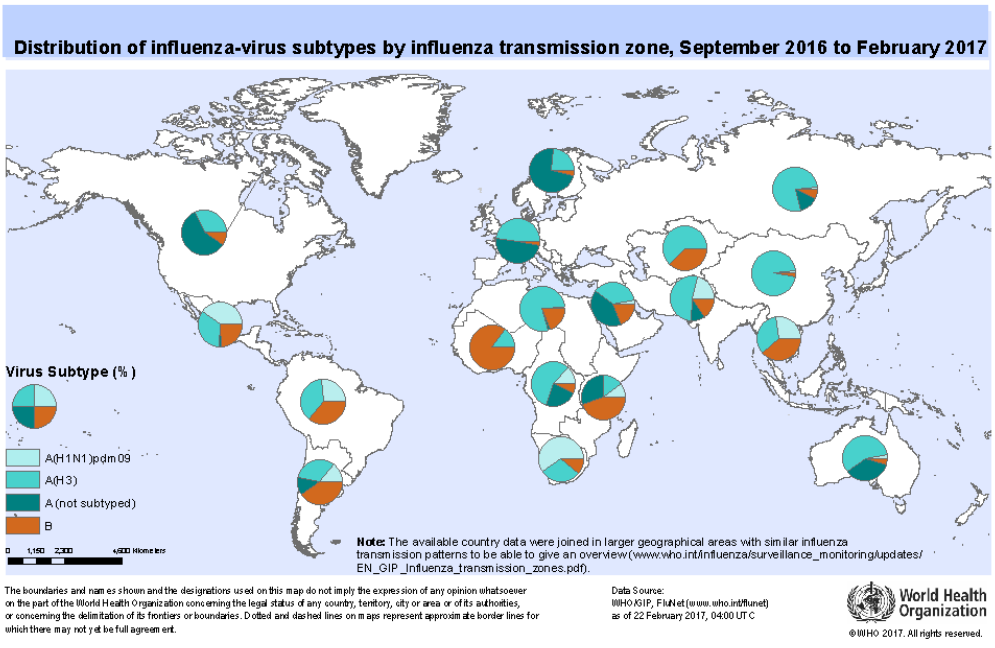
March 2017

The World Health Organization (WHO) convenes technical consultations[1] in February/March and September each year to recommend viruses for inclusion in influenza vaccines[2] for the northern and southern hemisphere influenza seasons, respectively. This recommendation relates to the influenza vaccines for use in the forthcoming northern hemisphere 2017-2018 influenza season. A recommendation will be made in September 2017 relating to vaccines that will be used for the southern hemisphere 2018 influenza season. For countries in tropical and subtropical regions, epidemiological considerations influence which recommendation (northern hemisphere or southern hemisphere) individual national and regional authorities consider appropriate.

Seasonal influenza activity, September 2016 – February 2017

Between September 2016 and February 2017 influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. In general, activity was higher compared with the same period last year. In the southern hemisphere, influenza activity was low in most countries, however, regional outbreaks continued in South Africa during September and in Australia during September and October. In the northern hemisphere, influenza activity began in Asia and Europe in October-November and had increased in most countries by December. In many countries with tropical and subtropical climates, influenza circulated during the entire reporting period.

Influenza A(H1N1)pdm09 viruses circulated at very low levels with a few exceptions. Influenza A(H3N2) viruses were dominant in most countries and regional and widespread outbreaks were reported in Asia, Europe, and North America. Influenza B viruses circulated at low levels in most countries throughout the period while regional outbreaks were reported in Asia, western Africa and the United States of America.



[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

Detailed information by country of the extent and type of seasonal influenza activity worldwide is available on the WHO website:
http://www.who.int/entity/influenza/vaccines/virus/recommendations/201703_influenzaactivitytable.pdf

Zoonotic influenza infections caused by A(H5), A(H7N9), A(H7N2), A(H9N2), A(H1)v and A(H3N2)v viruses

From 27 September 2016 to 27 February 2017, two human cases of A(H5N6) infection were reported by China and two human cases of A(H5N1) infection were reported by Egypt. Highly pathogenic avian influenza A(H5) is present in poultry in both countries. Since December 2003, a total of 874 human cases of A(H5) infection with 458 deaths have been confirmed in 16 countries. To date there has been no evidence of sustained human-to-human transmission.

During this period 460 additional human cases of avian influenza A(H7N9) virus infection have been reported to WHO by China. Since February 2013, a total of 1258 cases with 328 deaths have been reported.

One human case of A(H7N2) infection was reported by the United States of America.

Three A(H9N2) human cases were reported by China during this period. The virus from one of these cases was recovered and it belonged to the A/chicken/Hong Kong/Y280/97 genetic lineage.

During this period, four cases of A(H1)v were reported: one A(H1N2)v by the United States of America and three A(H1N1)v in Europe. One case of A(H3N2)v was reported by the United States of America.

Antigenic and genetic characteristics of recent seasonal influenza viruses

Influenza A(H1N1)pdm09 viruses

The vast majority of A(H1N1)pdm09 viruses collected from September 2016 to February 2017 belonged to phylogenetic clade 6B. Most recently circulating viruses belonged to genetic subclade 6B.1. A small proportion of viruses circulating in Asia and Oceania belonged to subclade 6B.2. Antigenic characteristics of A(H1N1)pdm09 viruses were assessed with post-infection ferret antisera in haemagglutination inhibition (HI) assays, which indicated that almost all recent A(H1N1)pdm09 viruses were antigenically indistinguishable from the vaccine viruses A/California/7/2009 and A/Michigan/45/2015 (viruses used in the 2016-2017 northern hemisphere and 2017 southern hemisphere vaccines, respectively). However, circulating viruses were poorly inhibited by some post-vaccination (A/California/7/2009) adult human serum pools.

HI assays were used to measure the presence of antibodies to recent A(H1N1)pdm09 viruses 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 southern hemisphere 2016 and the northern hemisphere 2016-2017 seasons (A/California/7/2009 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like and B/Brisbane/60/2008-like viruses, with the addition of B/Phuket/3073/2013-like antigens for quadrivalent vaccines). Geometric mean HI titres of antibodies against some representative recent A(H1N1)pdm09 viruses were reduced significantly as compared to HI titres to the vaccine virus; however, reductions were less pronounced for the majority of recent viruses.

Influenza A(H3N2) viruses

The large majority of A(H3N2) viruses collected from September 2016 to February 2017 belonged to the phylogenetic clade 3C.2a and subclade 3C.2a1. There has been considerable genetic

diversification of the HA gene within this clade and subclade. A small number of clade 3C.3a viruses were also detected.

Antigenic characterisation of 3C.2a viruses continued to be technically difficult because many viruses did not agglutinate red blood cells in the absence or presence of oseltamivir carboxylate, added to circumvent agglutination by the virus neuraminidase. Virus neutralisation assays supplemented HI assays for the antigenic characterisation of viruses. Most recent A(H3N2) 3C.2a viruses were well inhibited by ferret antisera raised against cell culture-propagated reference viruses in clade 3C.2a, including A/Hong Kong/4801/2014 or A/Michigan/15/2014 viruses. These antisera also well inhibited the majority of viruses in subclade 3C.2a1.

In human serology studies, using the serum panels described above, geometric mean HI titres of antibodies against many representative recent cell culture-propagated A(H3N2) viruses were reduced significantly compared to HI titres to the egg-propagated vaccine virus. However, no significant reductions in geometric mean titres were observed when compared to cell culture-propagated vaccine or reference viruses. Results were similar in microneutralisation tests using subsets of serum panels and viruses.

Influenza B viruses

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated in many countries with variable proportions in different regions.

All of the HA gene sequences of B/Victoria/2/87 lineage viruses belonged to 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 cell culture-propagated viruses.

Almost all of the HA gene sequences of B/Yamagata/16/88 lineage viruses belonged to genetic clade 3. In HI assays, recently circulating B/Yamagata/16/88 lineage viruses were well inhibited by post-infection ferret antisera raised against cell culture- and egg-propagated B/Phuket/3073/2013 viruses (clade 3).

In human serology studies, using the serum panels described above, geometric mean HI titres of antibodies against some representative recent B/Victoria/2/87 lineage viruses were reduced compared to HI titres to the egg-propagated vaccine virus B/Brisbane/60/2008; reductions were less pronounced when compared to cell culture-propagated B/Brisbane/60/2008. In studies using serum panels from subjects who had received quadrivalent vaccine, geometric mean titres against representative recent B/Yamagata/16/88 lineage viruses were similar to those against cell culture-propagated vaccine virus B/Phuket/3073/2013; somewhat greater reductions were observed when compared to HI titres to the egg-propagated vaccine virus B/Phuket/3073/2013.

Resistance to influenza antiviral drugs

Neuraminidase inhibitors

The detection of viruses with reduced susceptibility to the neuraminidase inhibitors was very rare among the 4832 viruses tested by the WHO CCs during this reporting period.

Of 693 influenza A(H1N1)pdm09 viruses tested, two viruses showed reduced susceptibility. One virus, detected in Australia from a patient treated with oseltamivir, carried an H275Y amino acid substitution in the neuraminidase which conferred highly reduced inhibition by oseltamivir and peramivir. The other virus, detected in the United States of America, carried a D199G amino acid substitution in the neuraminidase which conferred reduced inhibition by oseltamivir. The neuraminidase inhibitor treatment history of this patient is not known.

All of the 3032 A(H3N2) viruses tested were sensitive to neuraminidase inhibitors.

Of the 1107 influenza B viruses tested, only two viruses of the B/Victoria/2/87 lineage demonstrated reduced sensitivity to the neuraminidase inhibitors. One virus from the United States of America carried an A200T amino acid substitution in the neuraminidase and the other virus from Malaysia contained an H431Y amino acid substitution in the neuraminidase; these substitutions were associated with reduced inhibition and highly reduced inhibition, respectively, by all four neuraminidase inhibitors – oseltamivir, zanamivir, peramivir and laninamivir. The neuraminidase inhibitor treatment history of these patients is not known.

M2 inhibitors

M gene sequencing revealed that all A(H1N1)pdm09 viruses and all but one A(H3N2) virus had the S31N amino acid substitution in their M2 proteins which is known to confer resistance to the M2 inhibitors, amantadine and rimantadine.

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Influenza A(H3N2) viruses predominated in most countries, with low levels of A(H1N1)pdm09 and influenza B viruses also circulating during the period September 2016 – February 2017.

Influenza A(H1N1)pdm09 viruses were antigenically indistinguishable by post-infection ferret antisera raised against current vaccine viruses A/California/7/2009 and A/Michigan/45/2015. However, representative circulating viruses were poorly inhibited by some post-vaccination adult human serum pools.

Influenza A(H3N2) viruses were associated with outbreaks in many countries. The majority of recent viruses were antigenically related to cell culture-propagated 3C.2a A/Hong Kong/4801/2014-like viruses. A(H3N2) viruses within the 3C.2a clade have become genetically diverse, although they remain antigenically similar. The majority of recently circulating A(H3N2) viruses belong to subclade 3C.2a1.

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated at similar levels in some regions, but in many countries in South America, Asia and Eastern Europe, B/Victoria/2/87 lineage viruses were predominant. 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 2017-2018 northern hemisphere influenza season contain the following:

– an A/Michigan/45/2015 (H1N1)pdm09-like virus;
– an A/Hong Kong/4801/2014 (H3N2)-like virus; and
– 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 egg- or cell culture-propagated candidate vaccine viruses (CVVs) suitable for use in human vaccine production are available on the WHO website[3]. A list of reagents for vaccine standardisation, including those for this recommendation, can also be found on the WHO website. CVVs for zoonotic influenza viruses are listed on the same website.

[3] http://www.who.int/influenza/vaccines/virus/candidates_reagents/home

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 standardisation of inactivated vaccines 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, 4-7-1 Gakuen, 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, 4-7-1 Gakuen, 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, 1 Midland Road, London NW1 1AT, UK (Tel: +44 203 796 1520 or +44 203 796 2444) (website: 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/).

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

[4] http://www.who.int/wer/2012/wer8747.pdf
[5] http://www.who.int/influenza/surveillance_monitoring/updates/en/
[6] http://www.who.int/influenza

Acknowledgements

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Annex. Declarations of interest

The WHO recommendation on the composition of influenza virus vaccines for the northern hemisphere 2017-2018 was made through a technical consultation with relevant WHO Collaborating Centres on Influenza (CCs) and WHO Essential Regulatory Laboratories (ERLs) of the Global Influenza Surveillance and Response System (GISRS).

In accordance with the WHO policy, all Directors of the WHO CCs and ERLs, in their capacity as representatives of their respective institutions ("Advisers") completed the WHO form for 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 (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 Kanta Subbarao	• Being co-owner with NIH of a patent: Influenza Hemagglutinin and Neuraminidase Variants, USD 7,504,109 B2, 17 March 2009. The patent is current, but being abandoned as agreed by all owners. No benefit generated or expected from it. • For about 10 years until November 2016, being Principle Investigator of a CRADA with MedImmune, with no funding received, on the development of live attenuated vaccines against pandemic influenza. • Being on Scientific Advisory Board for BMGF grant to Mount Sinai School of Medicine in New York on a project on universal influenza vaccine development. • Being on Scientific Advisory Board for FLUCOP, a European Consortium for development of assays for influenza vaccine correlates of protection.
WHO CC Memphis	Dr Richard Webby	US$500/year from HHS/BARDA US for participating its annual retreat on program review.
WHO CC and ERL Tokyo	Dr Takato Odagiri	None
WHO ERL Canberra	Dr Mandvi Bharadwaj	None
WHO ERL Potters Bar	Dr Othmar Engelhardt	None
WHO ERL Washington	Dr Zhiping Ye	None

Based on the WHO assessment of the interest declared by Dr Subbarao, it was concluded that with disclosure at the beginning of the consultation to all participants, Dr Subbarao should continue to serve as an Adviser.

The interest declared by Dr Webby was reviewed by WHO and determined not to present a conflict of interest with the objectives of the WHO consultation. Therefore Dr Webby participated in the consultation as Adviser.