World Health Organization

Recommended composition of influenza virus vaccines for use in the 2018 southern hemisphere influenza season

September 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 southern hemisphere 2018 influenza season. A recommendation will be made in February 2018 relating to vaccines that will be used for the northern hemisphere 2018-19 influenza season. For countries in tropical and subtropical regions, WHO recommendations on influenza vaccine composition (northern hemisphere or southern hemisphere) are available on the WHO Global Influenza Programme website[3].

Seasonal influenza activity, February – September 2017

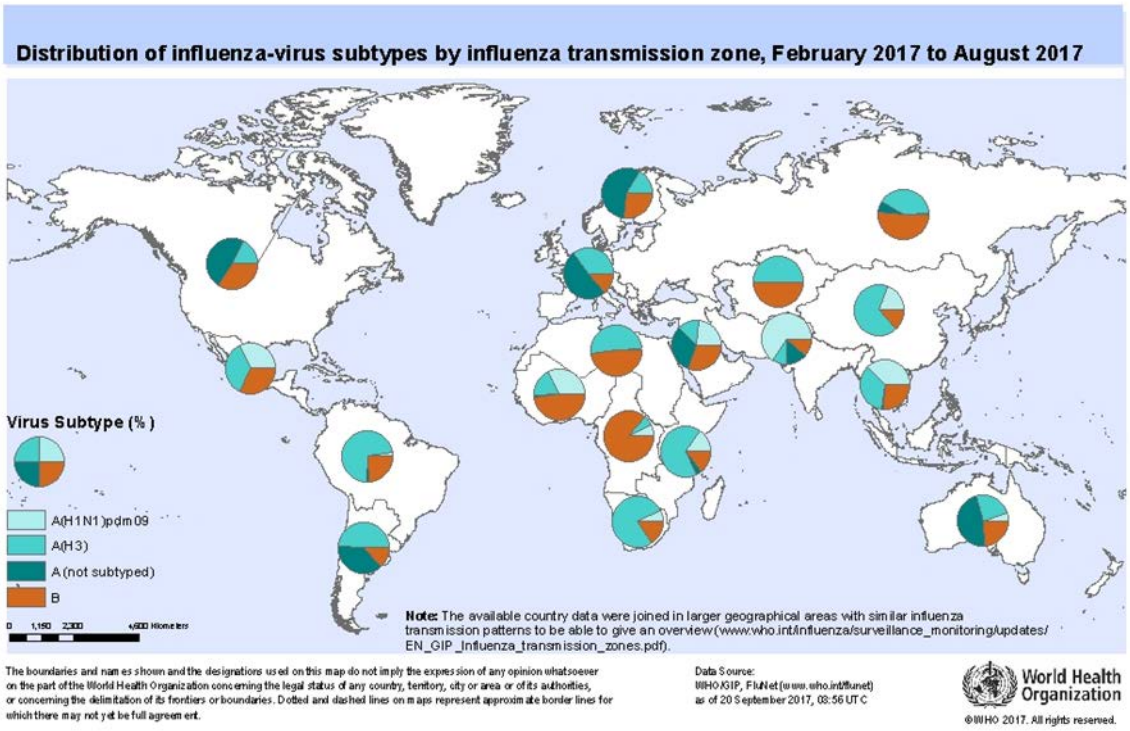
Between February and September 2017, influenza activity was reported in all regions, with a predominance of influenza A(H3N2) and influenza B viruses.

In the northern hemisphere, influenza activity was high from February to March and declined thereafter with the exception of a few countries in the Americas and Asia. Influenza A(H3N2) and B viruses co-circulated in most temperate countries of Africa, the Americas, Asia and Europe. Mexico was the only country that reported an influenza season dominated by influenza A(H1N1)pdm09 viruses.

In the southern hemisphere, activity remained low until May when regional to widespread activity was reported from a number of countries with detections of mainly influenza A(H3N2) and B viruses. Regional and widespread activity was reported from June to August in South Africa, with influenza A(H3N2) co-circulating with influenza B viruses. High levels of activity associated with influenza A(H3N2) and to a lesser extent B viruses were reported in most countries in the southern cone of the Americas from April onwards. In Oceania, high levels of influenza A(H3N2) activity followed by B viruses in the later part of the season (July – September) was reported.

In the tropical and subtropical regions of Africa, activity was generally low with regional outbreaks reported from Uganda and widespread influenza A(H1N1)pdm09 and B virus activity reported from Mauritius. In the tropical Americas influenza activity was variable with a few countries reporting regional to widespread activity of A(H3N2) virus from February to June. In tropical and subtropical Asia high influenza A(H1N1)pdm09 virus activity was reported from several countries (Bangladesh, Cambodia, India, Maldives, Myanmar, Nepal, Philippines, Sri Lanka), while A(H3N2) viruses predominated in China Hong Kong Special Administrative Region (SAR). In Singapore and Thailand, influenza A(H1N1)pdm09, A(H3N2) and B viruses co-circulated.

[1] WHO website on influenza vaccine viruses and reagents: 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
[3] Influenza in the tropics and sub-tropics: http://www.who.int/influenza/vaccines/tropics/en/



Detailed information by country and fortnightly updates of seasonal influenza activity worldwide are available on the WHO website.[4]

Zoonotic influenza infections caused by A(H5), A(H7N9), A(H9N2), A(H1N2)v and A(H3N2)v viruses

From 28 February to 25 September 2017, two human cases of A(H5N1) infection were reported by Egypt and Indonesia. Highly pathogenic avian influenza A(H5N1) is present in poultry in both countries. Since December 2003, a total of 876 human cases of A(H5) infection with 459 deaths have been confirmed in 16 countries. To date there has been no evidence of sustained human-to-human transmission.

During the same period, 306 additional human cases of avian influenza A(H7N9) virus infection have been reported to WHO by China. Since February 2013, a total of 1564 cases with 610 deaths have been reported.

Four A(H9N2) human cases were reported by China during this period. No antigenic or genetic information has been generated from these human case samples.

During this period, two cases of A(H1N2)v and 31 cases of A(H3N2)v virus infection were reported by the United States of America.

Antigenic and genetic characteristics of recent seasonal influenza viruses

Influenza A(H1N1)pdm09 viruses

Influenza A(H1N1)pdm09 viruses circulated in most regions at low levels from February to September 2017. The vast majority belonged to phylogenetic subclade 6B.1. The 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

[4] FluNet and FluID influenza surveillance data and outputs: http://www.who.int/influenza/resources/charts/en/

viruses were antigenically indistinguishable from the vaccine virus, egg-propagated A/Michigan/45/2015.

Human serology studies used serum panels from adults and older adults who had received either trivalent or quadrivalent inactivated vaccines of the composition recommended for the southern hemisphere 2017 season (A/Michigan/45/2015 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like, B/Brisbane/60/2008-like viruses, and B/Phuket/3073/2013-like viruses in the quadrivalent vaccines). Geometric mean HI titres of antibodies against representative A(H1N1)pdm09 viruses were somewhat reduced when compared to HI titres with the vaccine virus.

Influenza A(H3N2) viruses

The majority of A(H3N2) viruses collected from February to September 2017 belonged to the phylogenetic clade 3C.2a and subclade 3C.2a1. There has continued to be considerable genetic diversification of the HA and NA genes within this clade and subclade. Only a small number of clade 3C.3a viruses were 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) 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. In contrast, the proportion of A(H3N2) viruses that were well inhibited by ferret antisera raised against egg-propagated 3C.2a reference virus A/Hong Kong/4801/2014 was significantly lower. Recent A(H3N2) viruses were better inhibited by a ferret antiserum raised against the egg-propagated reference virus, A/Singapore/INFIMH-16-0019/2016, compared to ferret antisera raised against other egg-propagated A(H3N2) viruses. The A/Singapore/INFIMH-16-0019/2016 virus, from subclade 3C.2a1, also contains the amino acid substitution N121K in the HA which is found in the majority of recent A(H3N2) viruses. Neuraminidase inhibition assays also show that the NAs of recent A(H3N2) viruses were antigenically distinct from the NA of A/Hong Kong/4801/2014.

Human serology studies used serum panels from adults and older adults who had received either trivalent or quadrivalent inactivated vaccines of the composition recommended for the southern hemisphere 2017 season (A/Michigan/45/2015 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like, B/Brisbane/60/2008-like viruses, and B/Phuket/3073/2013-like virus in the quadrivalent vaccines). In addition, panels from adults, older adults and children who received either trivalent or quadrivalent inactivated vaccines of the composition recommended for the northern hemisphere 2016-17 season (A/California/7/2009 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like, B/Brisbane/60/2008-like viruses, and B/Phuket/3073/2013-like virus in the quadrivalent vaccines) were tested. Geometric mean HI titres of antibodies against all tested cell culture-propagated A(H3N2) viruses were reduced significantly compared to HI titres against the egg-propagated vaccine virus. Significant reductions in geometric mean titres against some representative cell culture-propagated A(H3N2) viruses were observed when compared to cell culture-propagated A/Hong Kong/4801/2014 (H3N2)-like viruses. Microneutralisation tests using the same serum panels and subsets of viruses showed similar results.

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.

The HA gene sequences of all characterised B/Victoria/2/87 lineage viruses belonged to genetic clade 1A. In HI assays most 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. A small proportion of viruses were poorly inhibited by post-infection ferret antisera raised against

B/Brisbane/60/2008 cell culture-propagated virus or equivalents. The majority of these viruses had a two amino acid deletion (amino acids 162 and 163) in the HA protein and three viruses, detected in China Hong Kong SAR, had a three amino acid deletion (amino acids 162-164) in the HA protein. The global circulation of the two amino acid deletion viruses was limited, with the majority detected in the United States of America.

All of the available 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.

In human serology studies using the same serum panels as described for the A(H3N2) virus analysis, geometric mean HI titres of antibodies against most representative recent B/Victoria/2/87 lineage viruses tested were similar to HI titres against cell culture-propagated B/Brisbane/60/2008-like viruses. In studies using serum panels from subjects who had received quadrivalent vaccines geometric mean titres against most representative recent B/Yamagata/16/88 lineage viruses tested were similar to those against cell culture-propagated B/Phuket/3073/2013 virus.

Resistance to influenza antiviral drugs

Neuraminidase inhibitors

The detection of viruses with reduced susceptibility to the neuraminidase inhibitors was very rare among the 7595 viruses tested by the WHO CCs during this reporting period.

Of 2128 influenza A(H1N1)pdm09 viruses tested, 17 viruses showed reduced susceptibility. Thirteen viruses from Australia, China, France, Singapore or United States of America carried an H275Y amino acid substitution in the neuraminidase which conferred highly reduced inhibition by oseltamivir and peramivir. Four A(H1N1)pdm09 viruses from China carried either S110F, D199G, I223V+S247N or I223T amino acid substitutions in the neuraminidase, which conferred reduced inhibition by either oseltamivir or zanamivir, or both.

Of 2763 influenza A(H3N2) viruses tested, 9 viruses showed reduced susceptibility. Six viruses from Austria, Belgium and Russian Federation carried a S331R amino acid substitution in the neuraminidase which conferred reduced inhibition by oseltamivir and zanamivir, and three viruses from Latvia, Germany and Poland carried a N329K amino acid substitution in the neuraminidase which conferred reduced inhibition by oseltamivir.

Of the 2704 influenza B viruses tested, 4 viruses of the B/Victoria/2/87 lineage and 4 viruses of the B/Yamagata/16/88 lineage demonstrated reduced sensitivity to the neuraminidase inhibitors. Of the B/Victoria/2/87 lineage viruses, two viruses from China carried a T43A or a P76S amino acid substitution in the neuraminidase that conferred highly reduced inhibition by zanamivir and reduced inhibition by oseltamivir and zanamivir, respectively. The other two B/Victoria/2/87 lineage viruses contained H273Y or I221T amino acid substitutions in the neuraminidase which conferred reduced inhibition by one or more of the neuraminidase inhibitors. Of the B/Yamagata/16/88 lineage viruses, two from the USA carried a D432N or a D197N amino acid substitution in the neuraminidase that conferred reduced inhibition by peramivir and reduced inhibition by oseltamivir and peramivir, respectively. Two other B/Yamagata/16/88 lineage viruses contained I115T and R150K amino acid substitutions in the neuraminidase, of which the latter conferred highly reduced inhibition by all neuraminidase inhibitors – oseltamivir, zanamivir, peramivir and laninamivir.

M2 inhibitors

M gene sequencing revealed that all A(H3N2) viruses analysed, other than nine from Australia, and all A(H1N1)pdm09 viruses analysed had the S31N amino acid substitution in their M2 proteins which is known to confer resistance to the M2 inhibitors, amantadine and rimantadine.

Recommended composition of influenza virus vaccines for use in the 2018 southern hemisphere influenza season

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

The vast majority of influenza A(H1N1)pdm09 viruses belonged to genetic subclade 6B.1 and were antigenically indistinguishable by post-infection ferret antisera raised against the vaccine virus A/Michigan/45/2015.

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 but reacted poorly with ferret antisera raised to egg-propagated A/Hong Kong/4801/2014-like viruses. A(H3N2) viruses within the 3C.2a clade and 3C.2a1 subclade have become genetically diverse.

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated in varying proportions in different regions. B/Yamagata/16/88 lineage viruses predominated in Oceania, Europe, North America and Central and South America, while B/Victoria/2/87 lineage viruses predominated in Asia and Africa. Most B/Victoria/2/87 lineage viruses were antigenically and genetically closely related to B/Brisbane/60/2008 and B/Texas/2/2013 viruses. The majority of recent B/Yamagata/16/88 lineage viruses were antigenically and genetically closely related to B/Phuket/3073/2013 virus.

It is recommended that trivalent vaccines for use in the 2018 southern hemisphere influenza season contain the following:

– an A/Michigan/45/2015 (H1N1)pdm09-like virus;
– an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; and
– 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 egg- or cell culture-propagated candidate vaccine viruses (CVVs) suitable for use in human vaccine production are available on the WHO website[5]. 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.

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[6].

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 (email: influenza.reagents@health.gov.au ; website: 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,

[5] Availability of CVVs and reagents: http://www.who.int/influenza/vaccines/virus/candidates_reagents/home
[6] Vaccines against influenza WHO position paper –November 2012 http://www.who.int/wer/2012/wer8747.pdf

Potters Bar, Hertfordshire, EN6 3QG UK (fax: +441707641050, e-mail: enquiries@nibsc.org, website: 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, website: 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, website: 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/).

More information about influenza surveillance can be found on the WHO Global Influenza Programme website[7].

Acknowledgements

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[7] Website of the WHO Global Influenza Programme: http://www.who.int/influenza

Annex Declarations of interest

The WHO recommendation on the composition of influenza virus vaccines for the southern hemisphere 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 Dayan Wang	None
WHO CC London	Dr John McCauley	None
WHO CC Melbourne	Dr Kanta Subbarao	• Being co-owner with NIH USA 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 in 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 Advisers.