Recommended composition of influenza virus vaccines for use in the 2018-2019 northern hemisphere influenza season

February 2018

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 seasons, respectively. This recommendation relates to the influenza vaccines for use in the forthcoming northern hemisphere 2018-2019 influenza season. A recommendation will be made in September 2018 relating to vaccines that will be used for the southern hemisphere 2019 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, September 2017 – January 2018

Between September 2017 and January 2018, influenza activity was reported in all regions, with influenza A(H1N1), A(H3N2) and influenza B viruses co-circulating.

In the temperate countries of the southern hemisphere, influenza activity remained high until October. In temperate South America, activity remained above seasonal threshold until October with influenza B viruses predominating. In Oceania, seasonal activity continued until late October with co-circulation of influenza A(H3N2) and B viruses. In southern Africa there was regional activity with predominantly influenza B viruses until October.

In the temperate countries of the northern hemisphere, influenza activity started early in North America from November with predominantly influenza A(H3N2) viruses. There were very high levels of influenza-like illness (ILI), hospitalizations and mortality due to influenza in the United States of America compared to recent seasons.

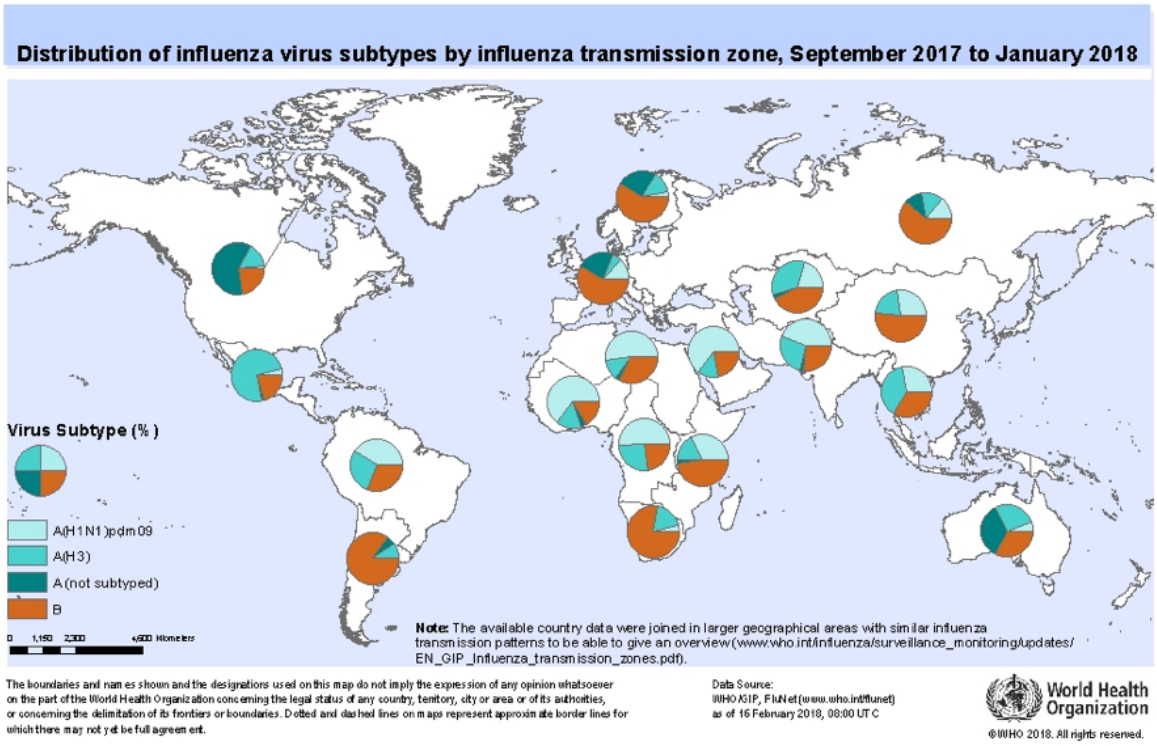
Influenza activity in Europe started in December in the south and west followed by the north and east. Influenza B viruses (Yamagata lineage) predominated followed by influenza A viruses. The dominant subtype of influenza A viruses varied depending on the country. The majority of countries reported ILI reaching moderate levels in comparison with recent years, with few countries reaching levels exceeding those of recent years. Some countries reported levels of hospitalization and intensive care unit admissions reaching or exceeding peak levels of recent influenza seasons.

In East Asia[4], influenza activity started to increase from December with influenza A(H1N1)pdm09 and B (Yamagata lineage) viruses with the exception of the Republic of Korea which had predominantly influenza A(H3N2) and B viruses. ILI activity in China (northern and southern) and Japan reached levels higher than recent influenza seasons. In western Asia, influenza activity started to increase from October with predominantly influenza A(H1N1)pdm09 viruses. In southern Asia, A(H1N1)pdm09 viruses were predominant. In South East Asia, increased activity was reported from September to October with A(H3N2) viruses in Cambodia, Lao People's Democratic Republic and Viet Nam and A(H1N1)pdm09 viruses in Thailand and Indonesia. Singapore reported increased activity with mainly B (Yamagata) viruses in January.

[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
[3] Influenza in the tropics and sub-tropics: http://www.who.int/influenza/vaccines/tropics/en/
[4] Influenza transmission zones: http://www.who.int/csr/disease/swineflu/transmission_zones/en/

In East Africa, influenza activity with B (Yamagata lineage) viruses was reported from Mozambique in November and increasing detection of influenza A(H1N1)pdm09 viruses was reported from Madagascar since December. Countries in West and Central Africa reported increased influenza activity with mainly influenza A(H1N1)pdm09 viruses during October-December, as did countries in North Africa from December.

In Central America and the Caribbean, influenza activity was generally low with some influenza A(H3N2) virus activity reported by Costa Rica in November, with other countries reporting influenza B virus activity. In tropical South America, influenza B virus activity was reported from Brazil and A(H3N2) viruses from Colombia in September-October. Since January, high A(H1N1)pdm09 virus activity was reported from Ecuador.



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/resources/charts/en/

Zoonotic influenza infections caused by A(H5), A(H7N4), A(H7N9), A(H9N2), A(H1)v and A(H3N2)v viruses

From 26 September 2017 to 19 February 2018, two human cases of highly pathogenic avian influenza A(H5N6) virus infection were reported by China, where the virus is present in poultry. Since December 2003, a total of 879 human cases of avian influenza A(H5) virus infection with 460 deaths have been confirmed in 16 countries. To date there has been no evidence of sustained human-to-human transmission.

During this period, three additional human cases of avian influenza A(H7N9) virus infection have been reported by China. Since February 2013, a total of 1567 cases with 613 deaths have been reported. One human case of low pathogenicity avian influenza A(H7N4) virus infection was reported by China. Five human cases of avian influenza A(H9N2) virus infection were reported by China

during this period. The viruses from two of these cases were recovered and belonged to the A/chicken/Hong Kong/Y280/97 genetic lineage.

During this period, two cases of confirmed A(H1)v virus infection were reported: one A(H1N2)v and one A(H1N1)v by the United States of America. One case of suspected A(H1N1)v virus infection was reported by Switzerland. Thirty-one 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

The vast majority of A(H1N1)pdm09 viruses had HA gene sequences that belonged to phylogenetic subclade 6B.1 and encoded the additional amino acid substitutions S74R, S164T and I295V. 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 viruses were antigenically indistinguishable from the vaccine virus, egg-propagated A/Michigan/45/2015.

Human serology studies used serum panels from children, adults and elderly adults who had received either trivalent or quadrivalent inactivated vaccines of the composition recommended for the northern hemisphere 2017-2018 season (A/Michigan/45/2015 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like, B/Brisbane/60/2008-like viruses in trivalent vaccines, with B/Phuket/3073/2013-like viruses included in quadrivalent vaccines). Geometric mean HI titres of antibodies against recent representative cell-propagated A(H1N1)pdm09 viruses were somewhat reduced compared to HI titres to the cell-propagated reference virus A/Michigan/45/2015; however, reductions were more pronounced when measured against the egg-propagated vaccine virus.

Influenza A(H3N2) viruses

Almost all A(H3N2) viruses belonged to the HA phylogenetic clade 3C.2a. There continued to be considerable genetic diversification of the HA and neuraminidase (NA) genes within this clade. Viruses from multiple subclades have co-circulated during this period. Viruses from subclade 3C.2a2 have predominated in North, Central and South America. A small number of clade 3C.3a viruses were detected, mostly in the Americas.

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 NA. 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, A/Michigan/15/2014 and A/Singapore/INFIMH-16-0019/2016. In contrast, a significantly lower proportion of A(H3N2) viruses was inhibited well by ferret antisera raised against egg-propagated 3C.2a reference virus A/Hong Kong/4801/2014. 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 recent egg-propagated A(H3N2) viruses.

In serology studies using the same human serum panels as described above for A(H1N1)pdm09 serology analysis, geometric mean HI titres of antibodies against cell culture-propagated A(H3N2) viruses were reduced significantly compared to HI titres against the egg-propagated vaccine virus. When compared to cell culture-propagated A/Hong Kong/4801/2014 (H3N2)-like viruses, the majority of cell culture-propagated viruses tested did not show significant reductions in geometric mean titres. Microneutralisation tests using the same serum panels showed similar results.

Influenza B viruses

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated but those of the B/Yamagata lineage predominated. All available HA gene sequences of B/Yamagata/16/88 lineage viruses belonged to genetic clade 3. In HI assays the vast majority of 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.

The HA gene sequences of the smaller number of B/Victoria/2/87 lineage viruses characterised belonged to genetic clade 1A, but an increasing proportion encoded an HA with deletions of either two or three amino acids. While the majority of recent viruses were inhibited well by post-infection ferret antisera raised against B/Brisbane/60/2008-like cell culture-propagated viruses in HI assays, a substantial proportion of viruses were poorly inhibited by these antisera. The great majority of these poorly reacting viruses, the circulation of which has expanded in the Americas and Europe, had a two-amino acid deletion (amino acids 162 and 163) in the HA and were well inhibited by antisera raised against B/Colorado/06/2017. Viruses with the three-amino acid HA deletion (amino acids 162-164) were detected in China and China Hong Kong Special Administrative Region (SAR). In addition, viruses with amino acid substitutions K165N and T221I in the HA were also poorly recognised by antisera raised against B/Brisbane/60/2008 and have been detected in China and Singapore.

Serology studies using the same human serum panels as described above yielded geometric mean HI titres of antibodies against representative recent B/Victoria/2/87 lineage viruses that were somewhat reduced when compared to HI titres against egg- or cell culture-propagated B/Brisbane/60/2008-like reference viruses. Antibodies induced by B/Brisbane/60/2008-like vaccine viruses in very young children reacted with reduced titres against viruses of the B/Victoria/2/87 lineage with two- and three-amino acid deletions in the HA. 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 were similar to those against cell culture-propagated B/Phuket/3073/2013-like reference viruses.

Resistance to influenza antiviral drugs

NA inhibitors

The detection of viruses with reduced susceptibility to the NA inhibitors was very rare among the 5353 viruses tested by the WHO Collaborating Centres[5] during this reporting period.

Of 1431 influenza A(H1N1)pdm09 viruses tested, 14 showed reduced susceptibility. Twelve viruses from Australia, Japan or the United States of America carried an H275Y amino acid substitution in the NA, which conferred highly reduced susceptibility to oseltamivir and peramivir. One A(H1N1)pdm09 virus from France carried an I223R amino acid substitution in the NA, which conferred reduced susceptibility to both oseltamivir and zanamivir.

Of 2202 influenza A(H3N2) viruses tested, 8 showed reduced susceptibility. Two of these viruses had highly reduced susceptibility to oseltamivir, one was from Australia and carried a R292K amino acid substitution in the NA and the other was from England and contained a four amino acid deletion (residues 244-247) in the NA, which also conferred reduced zanamivir susceptibility.

Of the 1720 influenza B viruses tested, 6 of the B/Victoria/2/87 lineage and 8 of the B/Yamagata/16/88 lineage demonstrated reduced susceptibility to the NA inhibitors. Of the B/Victoria/2/87 lineage viruses, three from Malaysia carried an H273Y, E105K or a T146I amino acid substitution in the NA that conferred highly reduced susceptibility to peramivir. Two B/Victoria/2/87

[5] http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/

lineage viruses from Madagascar contained a D197N amino acid substitution and one virus from China Hong Kong SAR contained an A200T substitution in the NA.

Of the B/Yamagata/16/88 lineage viruses, three from Japan carried an I221T, I221V or an H134Y amino acid substitution in the NA that conferred reduced susceptibility to peramivir. Three B/Yamagata/16/88 lineage viruses from the United States of America had reduced susceptibility to the NA inhibitors; two viruses possessed a D197N amino acid substitution and one possessed a dual I221T/H273Y amino acid substitution in the NA.

M2 inhibitors

M gene sequencing revealed that all A(H3N2) viruses analysed, other than one 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 2018-2019 northern hemisphere influenza season

There was considerable variation in the predominant virus type circulating in different regions during the period September 2017 to January 2018. Influenza B viruses predominated in many countries, while A(H3N2) viruses predominated in some and A(H1N1)pdm09 viruses circulated widely in Africa, Asia, parts of Europe and in the Middle East.

The vast majority of influenza A(H1N1)pdm09 viruses belonged to genetic subclade 6B.1 and were antigenically indistinguishable from the vaccine virus A/Michigan/45/2015.

Influenza A(H3N2) viruses were associated with outbreaks in several countries. The majority of recent viruses were antigenically related to cell culture-propagated A/Hong Kong/4801/2014-like and A/Singapore/INFMH-16-0019/2016-like viruses; they reacted poorly with ferret antisera raised to many egg-propagated clade 3C.2a viruses but somewhat better to egg-propagated A/Singapore/INFMH-16-0019/2016-like viruses.

Influenza B viruses of the B/Yamagata/16/88 lineage predominated in most regions of the world. Recent B/Yamagata/16/88 lineage viruses were antigenically and genetically closely related to the vaccine virus B/Phuket/3073/2013. Influenza B viruses of the B/Victoria/2/87 lineage were detected in low numbers but a substantial and increasing proportion of these viruses, containing a two amino acid deletion in their HAs, were antigenically distinguishable from the vaccine virus B/Brisbane/60/2008 but closely related to B/Colorado/06/2017.

It is recommended that quadrivalent vaccines for use in the 2018-2019 northern 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;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

It is recommended that the influenza B virus component of trivalent vaccines for use in the 2018-2019 northern hemisphere influenza season be a B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage.

Lists of egg- or cell culture-propagated candidate vaccine viruses (CVVs) suitable for use in human vaccine production are available on the WHO website[6]. 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[7].

CVVs (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@health.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[8] of global influenza activity. Other information about influenza surveillance can be found on the WHO Global Influenza Programme website[9].

[6] http://www.who.int/influenza/vaccines/virus/candidates_reagents/home
[7] http://www.who.int/wer/2012/wer8747.pdf
[8] http://www.who.int/influenza/surveillance_monitoring/updates/en/
[9] http://www.who.int/influenza

Acknowledgements

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Annex 1

Declarations of interest

The WHO recommendation on composition of influenza vaccines for the northern hemisphere 2018-2019 season was made through a technical consultation with relevant WHO Collaborating Centres on Influenza (CCs) and Essential Regulatory Laboratories (ERLs).

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 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 (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 Dayan Wang	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 NA Variants, US 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	In 2016 received US$500 from HHS/BARDA US being its Scientific Advisor.
WHO CC and 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	Dr Mandvi Bharadwaj	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 an Adviser.