Recommended composition of influenza virus vaccines for use in the 2021 southern hemisphere influenza season

September 2020

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 southern hemisphere 2021 influenza season. A recommendation will be made in February 2021 relating to vaccines that will be used for the northern hemisphere 2021-2022 influenza season. For countries in tropical and subtropical regions, WHO recommendations for influenza vaccine composition (northern hemisphere or southern hemisphere) are available on the WHO Global Influenza Programme website\(^3\).

Seasonal influenza activity

Public health and laboratory responses to the COVID-19 pandemic, caused by the coronavirus SARS-CoV-2, led to reduced influenza surveillance and/or reporting activities in many countries. Additionally, travel restrictions, mitigation strategies and social-distancing measures in several countries resulted in decreased influenza activity. Overall, fewer viruses were available for characterisation during the 2020 April to August time-period than in recent years.

**Between February and September 2020**, influenza A(H1N1)pdm09, A(H3N2) and influenza B viruses co-circulated although the proportions of the viruses circulating varied by region. Between February and March, influenza activity was elevated in most countries in the northern hemisphere; however, starting in mid-March, influenza activity rapidly decreased globally. Since April, very low levels of influenza have been reported globally, including countries in the temperate zone of the southern hemisphere.

**In the temperate zone of the northern hemisphere**, influenza activity was evident between February and March in most countries. In Europe overall, similar proportions of A(H1N1)pdm09, A(H3N2) and B/Victoria/2/87 lineage viruses were reported, while the relative proportions differed among countries. Influenza A(H1N1)pdm09 was predominant in most countries in Asia, North America, the Caribbean and Central America, followed by influenza B/Victoria/2/87 lineage and A(H3N2), with low numbers of B/Yamagata/16/88 lineage viruses reported. In some countries in Asia, such as Afghanistan, Cambodia and China, influenza A(H3N2) was predominant followed by influenza B and A(H1N1)pdm09, while in Mongolia, influenza A(H3N2) was the only type A detected. From mid-March, influenza activity sharply declined, and remained below inter-seasonal levels. Between April and September, influenza A viruses were more frequently detected than influenza B viruses in most reporting countries.

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\(^1\) [http://www.who.int/influenza/vaccines/virus/en/](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/pls/pdf_files/Fluvaccevirusselection.pdf](http://www.who.int/gb/pls/pdf_files/Fluvaccevirusselection.pdf)

\(^3\) Influenza in the tropics and sub-tropics: [http://www.who.int/influenza/vaccines/tropics/en/](http://www.who.int/influenza/vaccines/tropics/en/)
Influenza activity in tropical and subtropical countries was generally low. In Africa, South America, the Caribbean, Central America and tropical countries of Asia, influenza A(H1N1)pdm09 was predominant followed by influenza B/Victoria/2/87 lineage and A(H3N2), with low numbers of B/Yamagata/16/86 lineage viruses reported. Of note, in Mexico influenza activity was high in February and March and decreased in April. In most reporting countries in the tropics and subtropics, there were very few or no detections of influenza viruses between April and September. Of the very few detections reported, influenza B viruses were detected more often than influenza A viruses, and A(H1N1)pdm09 was the dominant subtype. In South East Asia, influenza A(H3N2) detections were higher than those of A(H1N1)pdm09.

In the temperate zones of the southern hemisphere, very few influenza virus detections were reported and detection rates remained below seasonal epidemic thresholds despite continued or even increased testing for influenza in some countries.

In the southern cone of South America, influenza A viruses predominated, with the majority being A(H1N1)pdm09, followed by influenza B, with the great majority being B/Victoria/2/87 lineage viruses. In Southern Africa, influenza A(H1N1)pdm09 viruses were predominant, followed by influenza B viruses, with no detection of A(H3N2) viruses. Influenza activity was very low in reporting countries in Oceania with co-circulation of influenza A and influenza B viruses and predominance of influenza A(H1N1)pdm09.

Influenza A

During this period influenza A viruses were predominant in most countries. Globally, co-circulation of both A(H1N1)pdm09 and A(H3N2) viruses was reported by most countries, areas and territories, with A(H1N1)pdm09 being dominant in most reporting countries. In Southern Africa, A(H1N1)pdm09 was the only subtype reported. However, A(H3N2) viruses circulated in higher proportions in some countries in Africa, Asia and Europe, notably in Burkina Faso, Mali and Mongolia, where it was the only A subtype reported.

Influenza B

Globally, influenza B viruses generally circulated at lower levels than influenza A viruses. However, in some countries in the Americas (Belize, El Salvador, Nicaragua, Panama, Paraguay, and Trinidad and Tobago), Europe (Ireland), Africa (Niger and Senegal) and Asia (Azerbaijan, Iran(Islamic Republic of), Iraq, Israel and Kuwait), influenza B viruses predominated. Of the influenza B viruses, the B/Victoria/2/87 lineage predominated with very few B/Yamagata/16/88 lineage viruses detected.
Antigenic and genetic characteristics of recent seasonal influenza viruses, human serology and antiviral susceptibility

Influenza A(H1N1)pdm09 viruses

A(H1N1)pdm09 viruses that circulated since February 2020 have haemagglutinin (HA) genes that belong to phylogenetic clade 6B.1A, with subclades 5A, 5B and 7 detected. The vast majority belonged to subclade 5A encoding HA1 amino acid substitutions of N129D, T185I and N260D compared to A/Idaho/07/2018, an A/Brisbane/02/2018-like cell culture-propagated virus. The subclade 5A HA genes have continued to diversify and the majority of viruses circulating since February 2020 fell into three genetic groups: the progenitor 5A subclade (i.e. 6B.1A5A) and two recently designated groups, 5A-187A (encoding N129D, T185I, D187A, Q189E and N260D amino acid substitutions in HA1 compared to A/Idaho/07/2018) and 5A-156K (encoding HA1 substitutions N129D, K130N, N156K, L161I, T185I, V250A and N260D, and E179D in HA2 compared to A/Idaho/07/2018). Specific amino acid changes such as D187A and Q189E of the 5A-187A group are in HA antigenic site Sb, whereas N156K and L161I of the 5A-156K group are in antigenic site Sa. From December 2019 to April 2020 the global proportions of these three groups changed: 5A decreased, 5A-187A, which had shown rapid expansion, showed a slight increase, while the 5A-156K group increased rapidly in many countries simultaneously, notably in some of the countries that had A(H1N1)pdm09 epidemics.

The antigenic characteristics of A(H1N1)pdm09 viruses, assessed with post-infection ferret antisera in haemagglutination inhibition (HI) assays, indicated that the majority of A(H1N1)pdm09 viruses
circulating since February 2020 were antigenically like the vaccine reference viruses recommended for the 2020 southern hemisphere season (egg- and cell culture-propagated A/Brisbane/02/2018-like viruses). However, group 5A-156K viruses reacted poorly with these antisera and were antigenically distinct (Table 1). Ferret antisera raised against vaccine reference viruses recommended for the 2020-2021 northern hemisphere season (egg-propagated A/Guangdong-Maonan/SWL1536/2019-like viruses and cell culture-propagated A/Hawaii/70/2019-like viruses) showed the same pattern. Antisera raised against 5A-156K viruses such as egg-propagated A/Victoria/2570/2019 and cell culture-propagated A/Wisconsin/588/2019 inhibited viruses within this group well but poorly inhibited viruses without the HA1 N156K substitution (Table 1).

Table 1. Antigenic Analysis of A(H1N1)pdm09 - haemagglutination inhibition assay

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1 Pooled human post vaccination from Australia (SH 2020)
Human serology studies were conducted using several serum panels from children (6 months to 17 years), adults (18-64 years) and elderly adults (≥65 years) who had received the 2019-2020 northern hemisphere vaccines, and two serum panels from adults who had received the 2020 southern hemisphere vaccine. Both vaccines contained A/Brisbane/02/2018-like viruses as the A(H1N1)pdm09 vaccine component. Geometric mean titres (GMTs) against recent representative cell culture-propagated 6B.1A viruses were determined by HI assays. When compared to titres against egg- and cell culture- propagated A/Brisbane/02/2018-like vaccine viruses, post-vaccination GMTs against most viruses representing HA groups 5A-187A, 5A-156K and subclade 5B were significantly reduced. Notably, the 5A-156K viruses had the lowest GMTs among all the viruses tested across all serum panels.

Vaccine effectiveness (VE) estimates from the 2019-20 season in the United States of America indicated that vaccination was more effective against group 5A-187A viruses (41% (95% CI:25 to 54)) than against group 5A-156K viruses (7% (95% CI: -14 to 23)). A similar trend was observed in Europe.

Of 1382 influenza A(H1N1)pdm09 viruses tested for neuraminidase inhibitor (NAI) susceptibility, 11 showed highly reduced inhibition by one or more of the inhibitors. Ten of these viruses carried an H275Y substitution in neuraminidase (NA), which confers highly reduced inhibition by oseltamivir and peramivir, and one virus had an N295S substitution, which confers highly reduced inhibition by oseltamivir.

Of 821 A(H1N1)pdm09 viruses analysed for susceptibility to the endonuclease inhibitor baloxavir, none had amino acid substitutions in the PA protein known to be associated with reduced susceptibility to this inhibitor.

**Influenza A(H3N2) viruses**

HA phylogenetic analysis of A(H3N2) viruses collected from February to September 2020 showed regional heterogeneity, with clade 3C.3a viruses predominating in some countries in Europe and subclade 3C.2a1b viruses predominating in many countries globally. HA genes of viruses in subclade 3C.2a1b included groups with either T135K or T131K amino acid substitutions in HA1. Viruses within group 3C.2a1b+T135K fell into two major subgroups with additional HA1 substitutions: S137F, A138S and F193S, or A138S, G186D, D190N, F193S and S198P. Viruses within group 3C.2a1b+T131K fell into two major subgroups also with additional HA1 substitutions: Q197R and S219F, or K83E and Y94N (including recent viruses from Cambodia with an additional HA1 G186S substitution).

Antigenic characterisation of A(H3N2) viruses was performed by HI and virus neutralisation (VN) assays. Ferret antisera raised against egg-propagated A/South Australia/34/2019-like viruses (group 3C.2a1b+T131K) inhibited few recently circulating viruses well. However, the majority of viruses within subgroups of 3C.2a1b+T131K and 3C.2a1b+T135K were well inhibited by ferret antisera raised against cell culture-propagated A/Hong Kong/45/2019-like viruses, and less well by antisera raised against egg-propagated A/Hong Kong/2671/2019-like viruses. These viruses are in the 3C.2a1b+T135K subgroup, with S137F, A138S and F193S HA1 substitutions and are the recommended components of cell- and egg-based vaccines respectively for the 2020-2021 northern hemisphere influenza season. Ferret antisera raised against cell culture-propagated A/Kansas/14/2017 (3C.3a) inhibited clade 3C.3a viruses well, but inhibited viruses in subclade 3C.2a1b poorly.

Human serology studies using serum panels from adults who had received vaccine containing an A/South Australia/34/2019-like virus (southern hemisphere 2020 vaccine recommendation) in HI and
VN assays showed significant reductions in GMTs against most recent representative cell culture-propagated A(H3N2) viruses from clade 3C.3a and subclade 3C.2a1b when compared to titres against egg-propagated A/South Australia/34/2019-like reference viruses. VN GMTs against cell culture-propagated circulating viruses were reduced to varying degrees when compared to cell culture-propagated A/South Australia/34/2019-like reference viruses.

All 464 influenza A(H3N2) viruses tested were sensitive to NAIs. Of 428 A(H3N2) viruses examined, none showed evidence of reduced susceptibility to baloxavir by genetic or phenotypic analysis.

**Influenza B viruses**

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages accounted for 33% of the viruses typed, the vast majority of which were of the B/Victoria lineage in all regions.

HA gene sequences of B/Victoria lineage viruses characterised belonged to genetic clade 1A, but previously reported genetic and antigenic diversity has decreased. Compared to B/Brisbane/60/2008 (a former vaccine virus) the vast majority were viruses with a triple amino acid deletion in HA1 (positions 162-164); a very small minority were viruses with a double amino acid deletion (positions 162-163) and a few viruses with no amino acid deletion in the HA were detected in China. Of the triple amino acid deletion viruses, the vast majority possessed HA1 substitutions G133R and K136E, many with an additional E128K substitution. Amongst the triple deletion viruses with K136E, small numbers of viruses with additional substitutions have been identified. These include three groups with HA1 substitutions: N126K; D129N, many with N233S (resulting in loss of a potential glycosylation site); and N150K, G184E and R279K.

A large majority of viruses with the triple deletion were inhibited well by post-infection ferret antisera raised against both cell culture- and egg-propagated triple deletion viruses, such as B/Washington/02/2019. These viruses with the triple deletion were generally poorly inhibited by post-infection ferret antisera raised against both egg- and cell culture-propagated double deletion viruses (B/Colorado/06/2017-like, a former vaccine virus) and by antisera raised against B/Victoria lineage viruses with no amino acid deletion in the HA.

The few available HA gene sequences of B/Yamagata lineage viruses belonged to genetic clade 3. In HI assays the recently circulating B/Yamagata lineage viruses were inhibited well by post-infection ferret antisera raised against either cell culture- or egg-propagated B/Phuket/3073/2013.

Four serum panels from adults (26-64 years of age), two that received vaccines containing B/Washington/02/2019-like (triple deletion) and B/Phuket/3073/2013-like viruses (southern hemisphere 2020 vaccine recommendation) and two that received vaccines with the northern hemisphere 2019-2020 formulation (B/Colorado/06/2017 (double deletion) and B/Phuket/3073/2013) were used in human serology studies. Post-vaccination HI GMTs against recent viruses of the B/Victoria lineage, representing the dominant HA1 triple deletion genetic group, were not significantly reduced when compared to titres against egg- or cell culture-propagated B/Washington/02/2019-like vaccine viruses. Post-vaccination HI GMTs against the great majority of recent representative B/Yamagata lineage viruses were not significantly reduced when compared to the cell culture-propagated B/Phuket/3073/2013 reference virus.
Of the 668 influenza B viruses screened for NAI susceptibility, all showed normal inhibition by oseltamivir and zanamivir. Of these, 445 were also tested against laninamivir and peramivir, and one virus showed reduced inhibition by peramivir. A total of 505 viruses were screened for susceptibility to baloxavir by genetic and/or phenotypic analysis, and none showed evidence of reduced susceptibility.

**Recommended composition of influenza virus vaccines for use in the 2021 southern hemisphere influenza season**

The HAs of currently circulating A(H1N1)pdm09 viruses belong to phylogenetic clade 6B.1A, falling within subclades 5A, 5B and 7, with HA subclade 5A viruses predominating. Globally, the majority of viruses in subclade 5A fell within two genetic groups 5A-187A and 5A-156K. Antigenic analyses using post-infection ferret antisera showed that antisera raised against viruses with 5A-187A HA (e.g., A/Hawaii/70/2019) inhibited most viruses well except for the emerging 5A-156K group which were poorly inhibited. The vast majority of group 5A-156K viruses were well inhibited by ferret antisera raised against reference viruses belonging to group 5A-156K, such as cell culture-propagated A/Wisconsin/588/2019 and egg-propagated A/Victoria/2570/2019. Serologic assays with human antisera showed reduced GMTs against recently circulating viruses in subclades 5A and 5B compared with titres against cell culture-propagated A/Brisbane/02/2018-like viruses, particularly for those representing the 5A-187A and the 5A-156K virus groups.

A(H3N2) viruses collected in the period February to September 2020 continued to show regional heterogeneity. Subclade 3C.2a1b viruses predominated in most countries globally but clade 3C.3a viruses were reported in Asia, Europe and Oceania. The great majority of these recently circulating viruses were poorly recognised by ferret antisera raised against A/South Australia/34/2019, the A(H3N2) vaccine component for the 2020 southern hemisphere influenza season. However, the majority of viruses in subclade 3C.2a1b with additional HA1 amino acid substitutions at T131K or T135K were well inhibited by ferret antisera raised against cell culture-propagated A/Hong Kong/45/2019, though less well by ferret antisera raised against egg-propagated A/Hong Kong/2671/2019, the recommended vaccine components for the 2020-2021 northern hemisphere influenza season.

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated, with the B/Victoria lineage being dominant in all regions. The vast majority of B/Victoria lineage viruses contained a triple amino acid deletion in HA1 (positions 162-164) and were inhibited well by post-infection ferret antisera raised against both cell culture- and egg-propagated triple deletion viruses, such as B/Washington/02/2019. The few circulating B/Yamagata lineage viruses were antigenically and genetically closely related to the egg-propagated vaccine virus B/Phuket/3073/2013 and its cell culture-propagated equivalent.
The WHO recommends that quadrivalent vaccines for use in the 2021 southern hemisphere influenza season contain the following:

**Egg-based vaccines**
- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/2671/2019 (H3N2)-like virus;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

**Cell- or recombinant-based vaccines**
- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/45/2019 (H3N2)-like virus;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

The WHO recommends that trivalent influenza vaccines for use in the 2021 southern hemisphere influenza season contain the following:

**Egg-based vaccines**
- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/2671/2019 (H3N2)-like virus; and
- a B/Washington/02/2019 (B/Victoria lineage)-like virus.

**Cell- or recombinant-based vaccines**
- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/45/2019 (H3N2)-like virus; and
- a B/Washington/02/2019 (B/Victoria lineage)-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\(^4\). A list of reagents for vaccine standardization, including those for this recommendation, can also be found on the WHO 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\(^5\).

CVVs (including reassortants) and reagents for use in the laboratory standardisation of inactivated vaccines may be obtained from:

- Biotherapeutics Section, 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; web site: [http://www.tga.gov.au](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,

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\(^4\) [http://www.who.int/influenza/vaccines/virus/candidates_reagents/home](http://www.who.int/influenza/vaccines/virus/candidates_reagents/home)

\(^5\) [https://www.who.int/immunization/policy/sage/en/](https://www.who.int/immunization/policy/sage/en/)
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 H17-5, 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.chinaivdc.cn/cnic/en).

WHO provides fortnightly updates\(^6\) of global influenza activity. Other information about influenza surveillance can be found on the WHO Global Influenza Programme website\(^7\).

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\(^7\) [http://www.who.int/influenza/gip](http://www.who.int/influenza/gip)