

## Questions and Answers

### Recommended composition of influenza virus vaccines for use in the southern hemisphere 2021 influenza season and development of candidate vaccine viruses for pandemic preparedness

**25 September 2020**

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## **1. What is the WHO Global Influenza Surveillance and Response System (GISRS)?**

GISRS is a global system of public health institutions coordinated by WHO, currently consisting of 146 National Influenza Centres (NICs) in 122 WHO Member States, 6 WHO Collaborating Centres for Influenza (CCs), 4 WHO Essential Regulatory Laboratories (ERLs) and 13 WHO H5 Reference Laboratories.

GISRS monitors the evolution of influenza viruses of public health concern, including seasonal, zoonotic and potential pandemic viruses, and recommends and implements risk assessment and response measures. In the 2019-2020 influenza season, NICs collected and tested over four million clinical specimens and shared more than 8000 representative influenza viruses with the WHO CCs for further analyses. Virus characterisation and other analyses, complemented with other available epidemiologic and disease information, form the evidence base for public health decisions on epidemic response and pandemic preparedness including seasonal vaccine virus selection and zoonotic influenza candidate vaccine virus (CVV) development. GISRS also provides guidance to countries and support for activities such as training, risk assessment, outbreak response, development of diagnostic tests, testing for antiviral drug resistance and scientific interpretation of important findings.

## **2. What is the purpose of WHO recommendations on the composition of influenza virus vaccines?**

These WHO recommendations provide a guide to national public health and regulatory authorities and vaccine manufacturers for the development and production of influenza vaccines for the next influenza season. In contrast to many other vaccines, the viruses in influenza vaccines need to be evaluated and updated regularly because circulating influenza viruses evolve continuously. Recommendations are usually made in February for the following influenza season in the northern hemisphere and in September for the following influenza season in the southern hemisphere. This timeframe is applied due to the fact that approximately 6-8 months are needed to produce, approve and distribute manufactured vaccines.

## **3. How are influenza vaccine recommendations made?**

Data and information from the GISRS network, which includes NICs, WHO CCs, WHO ERLs and WHO H5 Reference Laboratories, and from other sources are used to determine the recommended vaccine viruses, including:

- ***Surveillance data:***

Virus surveillance data from the GISRS network, complemented with epidemiologic and clinical findings inform the vaccine virus selection process.

- ***Antigenic characterisation of viruses:***  
GISRS laboratories, in particular WHO CCs, conduct testing to evaluate the antibody or immune response triggered by the proteins on the surface of influenza viruses. Antigenic cartography is used to visualize relatedness of viruses based on the data provided by WHO CCs.
- ***Human serology studies with influenza virus vaccines:***  
WHO CCs and WHO ERLs test how well antibodies from vaccinated people react with recently circulating influenza viruses.
- ***Genetic characterisation of viruses:***  
GISRS laboratories conduct testing to compare virus gene sequences of circulating influenza viruses to the sequences of vaccine viruses to identify genetic changes that might influence protection conferred by a given vaccine.
- ***Virus fitness forecasting:***  
Virus fitness relates to the likelihood of any emerging groups of viruses becoming more prevalent in coming months. Information from modelling studies, based on genetic and antigenic information, is therefore considered.
- ***Antiviral resistance:***  
GISRS laboratories test influenza viruses to determine if they have resistance to the antiviral drugs used to treat influenza infection. This information is taken into consideration when specific viruses are selected as CVVs.
- ***Vaccine effectiveness:***  
The Global Influenza Vaccine Effectiveness (GIVE) Collaboration, made up of many different studies conducted in countries in both the northern and southern hemispheres, provides information on vaccine performance in previous and current influenza seasons.
- ***Availability of Candidate Vaccine Viruses (CVVs):***  
The vast majority of vaccines produced globally use egg-based manufacturing processes. This requires CVVs which replicate well in eggs. CVVs are essential for production of egg-based vaccines in a timely manner for the next influenza season. Separate recommendations are made for CVVs used in cell-based manufacturing. Influenza vaccines using recombinant technology do not require CVVs for manufacturing.

These data, and other findings made available by GISRS, are evaluated during WHO Consultations usually in February and September of each year. The Consultation includes experts from WHO CCs, WHO ERLs, WHO H5 Reference Laboratories, NICs, the OIE/FAO Network of expertise on animal influenza (OFFLU), academic institutions, and other national and regional institutions. Further information about GISRS is available at

[http://www.who.int/influenza/gisrs\\_laboratory/en/](http://www.who.int/influenza/gisrs_laboratory/en/).

#### **4. What viruses are recommended by WHO to be included in influenza vaccines for use in the 2021 southern hemisphere influenza season?**

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.**

For trivalent influenza vaccines for use in the 2021 southern hemisphere influenza season, the WHO recommends that the A(H1N1)pdm09, A(H3N2) and B/Victoria lineage viruses recommended above for the quadrivalent vaccines be used.

#### **5. Why are different viruses sometimes recommended for egg- and cell-based vaccines?**

In some instances, the same virus is not optimal for both production systems. In such cases different viruses with similar properties are selected as the prototypes to facilitate timely vaccine production.

For non-egg-based production platforms, vaccine manufacturers should consider the best choice of vaccine virus. In general, the use of the cell-based vaccine virus would be recommended for cell- or recombinant-based vaccines.

#### **6. Are the vaccine viruses in this recommendation different from those in the previous southern hemisphere recommendations announced in September 2019?**

There have been the following updates to the vaccine recommendations:

For the A(H1N1)pdm09 vaccine virus component, replacement of the A/Brisbane/02/2018-like virus with an A/Victoria/2570/2019-like virus for egg-based production and an A/Wisconsin/588/2019-like virus for cell-based production, is recommended.

For the A(H3N2) vaccine virus component, replacement of the A/South Australia/34/2019-like virus with an A/Hong Kong/2671/2019-like virus for egg-based production and an A/Hong Kong/45/2019-like virus for cell-based production, is recommended.

Previous and present WHO influenza vaccine composition recommendations can be found on the WHO Global Influenza Programme website at:

<http://www.who.int/influenza/vaccines/virus/recommendations/en/>

## **7. Are the vaccine viruses in this recommendation different from those in the previous northern hemisphere recommendations announced in February 2020?**

There have been the following updates to the vaccine recommendations:

For the A(H1N1)pdm09 vaccine virus component, replacement of the A/Guangdong-Maonan/SWL1536/2019-like virus with an A/Victoria/2570/2019-like virus for egg-based production and replacement of the A/Hawaii/70/2019-like virus with an A/Wisconsin/588/2019-like virus for cell-based production, is recommended.

The other viruses recommended for production of trivalent and quadrivalent 2021 southern hemisphere vaccines are the same as recommended for the 2020-2021 northern hemisphere vaccine.

## **8. Is the vaccine composition for the 2020-2021 northern hemisphere influenza season still appropriate?**

The influenza A(H3N2), B/Victoria-lineage and B/Yamagata-lineage virus components have not changed since the WHO recommendation for the composition of the vaccine for the 2020-2021 northern hemisphere influenza season was made in February 2020. The 2020-2021 northern hemisphere vaccine cannot accommodate updates to address recent changes in circulating influenza A(H1N1)pdm09 viruses due to vaccine manufacturing time constraints. Changes to vaccine components are made based on the best available data at the time of the WHO vaccine composition meeting. It is challenging to predict which viruses will be circulating in the forthcoming seasons and whether the chosen vaccine components will optimally cover the circulating influenza viruses.

## **9. What is the difference between quadrivalent and trivalent vaccines?**

Quadrivalent vaccines include two subtypes of influenza A viruses (an A(H1N1)pdm09 virus and an A(H3N2) virus) and two lineages of influenza B viruses (a B/Victoria lineage virus and a B/Yamagata lineage virus). Trivalent vaccines include two subtypes of influenza A viruses (an A(H1N1)pdm09 virus and an A(H3N2) virus) and one type B virus.

## **10. What vaccine formulation (i.e. recommendation for northern or southern hemisphere influenza season) should countries in tropical and subtropical regions consider for use in vaccines?**

Influenza viruses circulate at varying times through the year in tropical and sub-tropical countries. In selecting which vaccine formulation to use, these countries should consider their epidemiologic and virologic surveillance data to decide when to start vaccination and whether to use the formulation recommended for the northern or southern hemisphere influenza season. WHO has developed guidance to support countries in tropical and sub-tropical regions in choosing between the northern or southern hemisphere formulations (<http://www.who.int/influenza/vaccines/tropics/en/>).

## **11. What are candidate vaccine viruses (CVVs)?**

A CVV is a virus prepared for potential use in vaccine manufacturing that is antigenically similar to the virus that has been recommended for use in vaccines.

## **12. What CVVs are available for use in influenza vaccines?**

The WHO recommended CVVs for vaccine development and production for the 2021 southern hemisphere influenza season are listed at:

[https://www.who.int/influenza/vaccines/virus/candidates\\_reagents/home/en/](https://www.who.int/influenza/vaccines/virus/candidates_reagents/home/en/)

The availability of CVVs by type/subtype, including zoonotic viruses, and corresponding potency test reagents is posted and updated on the WHO web site:

<http://www.who.int/influenza/vaccines/virus/en/>

## **13. Why does GISRS continue to update the list of available CVVs for pandemic preparedness?**

Influenza viruses circulate widely in some animals and may transmit sporadically to humans, resulting in zoonotic infections. As part of an influenza pandemic preparedness program, the WHO GISRS, in collaboration with animal health partners, analyses a range of zoonotic and potentially pandemic influenza viruses as they emerge and evolve and develops relevant CVVs as a first step in the production of some influenza vaccines. The selection and development of a zoonotic CVV is done to maintain a bank of viruses suitable for the immediate development of vaccines, for example during a pandemic, and also to assist those who may want to make pilot lots of vaccines, conduct clinical trials, or perform other pandemic preparedness tasks. The decision to use these materials for vaccine development should be based on the assessment of public health risk and needs in consultation with national regulatory and public health authorities.

#### **14. What happens after the WHO recommendations are made?**

Approval of the composition and formulation of vaccines that will be used in each country is the responsibility of national or regional regulatory authorities. It is the responsibility of the vaccine manufacturers to obtain the appropriate CVVs and to obtain approval from the local regulatory agencies. WHO publishes and updates a list of CVVs for selection by the manufacturers and regulatory agencies:

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

#### **15. What impact has the COVID-19 pandemic had on the GISRS influenza surveillance?**

Influenza surveillance was disrupted during the early stages of the COVID-19 pandemic resulting in substantial decreases in the numbers of specimens tested for influenza and subsequent shipments of viruses to WHO CCs of GISRS compared with the corresponding period in previous years. Reporting directly or indirectly to FluNet by some countries was also delayed or stopped. Some countries were less affected and maintained strong influenza surveillance as demonstrated by the detection of human cases of zoonotic influenza.

In order to address the persistent public health threat from influenza and maintain global influenza surveillance and response capabilities while responding to the COVID-19 pandemic, an interim WHO guidance document was published to prepare GISRS for the upcoming influenza seasons ([https://apps.who.int/iris/bitstream/handle/10665/332198/WHO-2019-nCoV-Preparing\\_GISRS-2020.1-eng.pdf?ua=1](https://apps.who.int/iris/bitstream/handle/10665/332198/WHO-2019-nCoV-Preparing_GISRS-2020.1-eng.pdf?ua=1)). From June 1 to August 30 of this year, 107 countries, areas, or territories reported data to the global influenza surveillance platform FluNet – 132 countries, areas, or territories reported data over the same period in 2019. In addition, countries are exploring the use of influenza surveillance systems for COVID-19 sentinel surveillance.

#### **16. What impact has the COVID-19 pandemic had on influenza activity?**

The COVID-19 pandemic has had a major impact on influenza activity. Between February and March 2020, influenza activity was elevated in most countries in the northern hemisphere consistent with a typical influenza season. Starting in mid-March, influenza activity decreased sharply, concomitant with the spread of SARS-CoV-2. Implementation of travel restrictions, mitigation strategies and social-distancing measures is likely the reason for decreased influenza activity. Correspondingly, very low levels of influenza detection have been reported globally, including from countries in the temperate zone of the southern hemisphere.

## **17. How has the COVID-19 pandemic impacted the 2021 southern hemisphere influenza vaccine recommendation?**

The amount of genetic and antigenic data available from recently circulating viruses has been significantly lower for this southern hemisphere vaccine recommendation meeting than is typical due to the COVID-19 pandemic. Influenza activity had started in several northern hemisphere countries prior to the emergence of the COVID-19 pandemic, providing a source of viruses collected in 2020, mainly from February and March. While the overall numbers were lower, recent viruses from every WHO region were characterized and the recommendations are based on viruses that are likely to be a fair representation of those that may continue to circulate. Nevertheless, due to the reduced number of recent viruses circulating and available for characterization, there are uncertainties regarding the full extent of genetic and antigenic diversity. It is unknown what impact the low level of influenza activity will have on forthcoming influenza seasons and which influenza virus types and subtypes will begin to circulate widely when social interactions resume.

**For more information, please contact the WHO Global Influenza Programme at [gisrs-whohq@who.int](mailto:gisrs-whohq@who.int)**