Questions and Answers

Recommended composition of influenza virus vaccines for use in the
Northern hemisphere 2021-2022 influenza season and development of
candidate vaccine viruses for pandemic preparedness

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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 147 National Influenza Centres (NICs) in 123 WHO Member States, 6 WHO Collaborating Centres for Influenza (CCs), 4 WHO Essential Regulatory Laboratories (ERLs) and 13 WHO H5 Reference Laboratories. The GISRS laboratories function year-round under the WHO Terms of Reference, sharing surveillance findings and virus materials in a timely fashion to inform risk assessment and mitigation measures including updates of seasonal influenza vaccines.

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. Virus characterization 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.

More information can be found at: https://www.who.int/influenza/gisrs_laboratory/en/

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 as approximately 6-8 months are needed to produce, approve and distribute manufactured vaccines. In addition, surveillance for zoonotic events, infection of a human with an influenza virus normally restricted to a non-human host, is continuous, as is monitoring of influenza activity in the animal sector and decisions are taken at least twice a year regarding the need to develop CVVs for pandemic preparedness purposes.

3. 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.
4. 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 make vaccine virus recommendations. This includes:

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

- **Antigenic characterization 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 characterization of viruses:**
  GISRS laboratories conduct gene sequencing to compare the sequences of circulating influenza viruses with those 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 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 held 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/.

5. What viruses are recommended by WHO to be included in influenza vaccines for use in the 2021-2022 northern hemisphere influenza season?

The WHO recommends that quadrivalent vaccines for use in the 2021-2022 northern hemisphere influenza season contain the following:

**Egg-based Vaccines**
- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Cambodia/e0826360/2020 (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/Cambodia/e0826360/2020 (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 to be used in the 2021-2022 northern hemisphere influenza season, the WHO recommends the use of A(H1N1)pdm09, A(H3N2) and B/Victoria lineage viruses as listed above for use in quadrivalent vaccines.

6. 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.

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

The following updates to the vaccine have been recommended:


For the A(H3N2) vaccine virus component, replacement of the A/Hong Kong/2671/2019-like virus for egg-based production and the A/Hong Kong/45/2019-like virus for cell culture-based production with an A/Cambodia/e0826360/2020-like virus, is recommended for both production systems.

The other viruses recommended for production of trivalent and quadrivalent 2021-2022 northern hemisphere vaccines are the same as recommended for the 2020-2021 northern hemisphere vaccine.

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/

8. Are the vaccine viruses in this recommendation different from those in the southern hemisphere recommendations announced in September 2020?

The following updates to the vaccine have been recommended:

For the A(H3N2) vaccine virus component, replacement of the A/Hong Kong/2671/2019-like virus for egg-based production and the A/Hong Kong/45/2019-like virus for cell culture-based production with an A/Cambodia/e0826360/2020-like virus, is recommended for both production systems.

The other viruses recommended for production of trivalent and quadrivalent 2021-2022 northern hemisphere vaccines are the same as recommended for the 2021 southern hemisphere vaccine.
9. Is the vaccine composition for the 2021 southern hemisphere influenza season still appropriate?

The best protection against influenza is vaccination. Every year influenza vaccination prevents millions of cases and consequently hundreds of thousands of hospitalizations and deaths. Trivalent and quadrivalent influenza vaccines protect against three and four very different groups of viruses that circulate in humans, respectively. Changes to vaccine components are made based on the best available data at the time of the WHO meeting on the composition of influenza virus vaccines. The influenza A(H1N1)pdm09 and influenza B recommendations for the 2021 southern hemisphere and 2021-2022 northern hemisphere influenza vaccines are the same. The 2021-2022 northern hemisphere vaccine has an updated component to address recent changes in circulating influenza A(H3N2) viruses. It is too early to know which influenza viruses will predominate in the southern hemisphere and there are often regional differences that dictate whether the vaccine composition is optimal or not.

10. 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.

11. What vaccine formulation (i.e. recommendation for northern or southern hemisphere influenza season) should countries in tropical and subtropical regions consider for use in vaccination programmes?

Influenza viruses circulate at varying times through the year in tropical and subtropical 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 subtropical regions in choosing between the northern or southern hemisphere formulations and published at:

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

The WHO recommended CVVs for vaccine development and production for the 2021-2022 northern hemisphere influenza season are listed at:
The availability of CVVs by type/subtype, including zoonotic viruses, and corresponding potency test reagents is posted and updated on the WHO website: [http://www.who.int/influenza/vaccines/virus/en/](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 GISRS influenza surveillance?

Influenza surveillance was disrupted in most countries during the early stages of the COVID-19 pandemic but has since recovered in many, with some countries testing even more samples than in previous years. In the 2019/2020 influenza season, NICs collected and tested over four million clinical specimens worldwide and shared more than 8000 representative influenza viruses with the WHO CCs for further analyses; while more clinical specimens were tested globally in 2020-2021, there were vastly reduced numbers of influenza detections and consequently far fewer viruses were available to be shared.

In the context of the current influenza vaccine composition meeting, 139 countries, areas, or territories reported data to the global influenza surveillance platform FluNet from 1 September
2020 to 31 January 2021; 161 countries, areas, or territories reported data over the same period of 2019/2020.


16. What impact has the COVID-19 pandemic had on seasonal 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 2020, influenza activity decreased sharply, concomitant with the spread of SARS-CoV-2 viruses, and global influenza activity has remained low in many countries and regions. Implementation of mitigation strategies (e.g. travel restrictions, social-distancing and increased personal hygiene measures) have contributed to decreased influenza activity but other factors may also be involved. The impact of this current low influenza virus circulation on influenza activity in coming seasons is unknown. Due to this uncertainty, it is imperative to maintain continuous global influenza surveillance.

17. What impact has the COVID-19 pandemic had on zoonotic influenza activity and pandemic risk?

The COVID-19 pandemic has been a stark reminder of the public health threat posed by viruses circulating in animal reservoirs. Zoonoses with influenza viruses from birds and swine have continued to be detected and remain a threat to public health. As such, GISRS continues to update the list of available CVVs for pandemic preparedness purposes and conducts risk assessments when zoonotic events are identified. [Access the influenza monthly risk assessment summary.](#)

18. How has the COVID-19 pandemic impacted the 2021-2022 northern hemisphere influenza vaccine recommendation?

The volume of data available from recently circulating influenza viruses and the geographic representation have been significantly lower for this northern hemisphere vaccine recommendation meeting than is typical. The reduced number of viruses available for characterization raises uncertainties regarding the full extent of the genetic and antigenic diversity of circulating influenza viruses and those likely to pose a threat in forthcoming
seasons. Nevertheless, new groups of A(H3N2) viruses were identified, some of which had spread internationally. Consequently, the A(H3N2) component recommendation has been updated.

19. Will the COVID-19 vaccine provide any protection against influenza and vice versa?

Vaccines provide protection against groups of related pathogens. SARS-CoV-2 (a coronavirus) and influenza (an orthomyxovirus) belong to different virus families that are not closely related: vaccines against one are not designed to protect against infection by the other virus.

For more information, please contact the WHO Global Influenza Programme at gisrs-whohq@who.int