Questions and Answers

Recommended composition of influenza virus vaccines for use in the northern hemisphere 2022-2023 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 148 National Influenza Centres (NICs) in 124 WHO Member States, 7 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 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 characterisations are combined with other available epidemiologic and disease information to 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 and for pandemic preparedness. 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. The recommendation dates are chosen to provide approximately 6-8 months for the production, regulatory approval and distribution of the manufactured vaccines.

For pandemic preparedness, CVV development is considered at least twice a year. The decisions are based on continuous surveillance for zoonotic events (human infection with an influenza virus normally restricted to a non-human host) and influenza activity in the animal sector.
3. What are candidate vaccine viruses (CVVs)?

Haemagglutinin (HA) is the primary antigen in influenza vaccines. A CVV is a virus prepared for potential use in vaccine manufacturing that possesses an HA which WHO CCs have determined to be 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 characterisation of viruses:**
  GISRS laboratories, in particular WHO CCs, conduct testing to evaluate the antibody or immune response triggered by the proteins (antigens) on the influenza virus surface. 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 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 sequences available in databases and antigenic information provided by the WHO CCs, is therefore considered.

- **Antiviral resistance:**
  GISRS laboratories test influenza viruses to determine if they remain susceptible to the antiviral drugs approved for treatment of influenza infections. 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 influenza seasons and interim reports on the current season.

• **Availability of CVVs:**
  The majority of vaccines produced globally use egg-based manufacturing processes which require CVVs that replicate well in eggs. CVVs are essential for production of egg-based vaccines in a timely manner for the next influenza season. CVVs perform a similar role for cell-based vaccine manufacturing processes and separate recommendations are made because of the cell replication requirement. Influenza vaccines comprised of recombinant influenza protein antigens 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 on the [WHO website](https://www.who.int).

5. **What viruses are recommended by WHO to be included in influenza vaccines for use in the 2022-2023 northern hemisphere influenza season?**

The WHO recommends that quadrivalent vaccines for use in the 2022-2023 northern hemisphere influenza season contain the following:

**Egg-based Vaccines**
- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021(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/Darwin/6/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (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 2022-2023 northern hemisphere influenza season, WHO recommends the use of A(H1N1)pdm09, A(H3N2) and B/Victoria lineage viruses as listed above for use in quadrivalent vaccines.
6. What does the term “-like virus” mean in the vaccine recommendation?

Recommended vaccine viruses are representative of the antigenic group of viruses anticipated to circulate widely in the forthcoming influenza season. Often multiple CVVs are available which possess HA antigens from other viruses that are antigenically similar to the recommended vaccine viruses. The term “-like virus” is included to allow for the use of these other CVVs for vaccine manufacturing.

7. Why are different viruses sometimes recommended for egg- and cell-based vaccines?

Influenza viruses do not always replicate equally well in the egg- and cell-based vaccine production systems. Different viruses which have similar antigenic properties are therefore recommended for the two production systems.

The use of the cell-based vaccine virus sequences is recommended for recombinant protein or other relevant new platforms of influenza vaccine production.

8. Are the vaccine viruses in this recommendation different from those in the previous northern hemisphere recommendations announced in February 2021?

The following updates to the vaccine have been recommended:

- For the A(H3N2) vaccine virus component, replacement of the A/Cambodia/e0826360/2020-like virus with A/Darwin/9/2021-like and A/Darwin/6/2021-like viruses for egg- and cell-based production, respectively.

- For the B/Victoria-lineage vaccine virus component, replacement of the B/Washington/02/2019-like virus with a B/Austria/1359417/2021-like virus is recommended for both production systems.

The other viruses recommended for production of trivalent and quadrivalent 2022-2023 northern hemisphere vaccines are the same as recommended for the 2021-2022 northern hemisphere vaccine.

Previous and present WHO influenza vaccine composition recommendations can be found on the WHO Global Influenza Programme website.
9. Are the vaccine viruses in this recommendation different from those in the southern hemisphere recommendations announced in September 2021?

The viruses recommended for production of trivalent and quadrivalent 2022-2023 northern hemisphere vaccines are the same as recommended for the 2022 southern hemisphere vaccines.

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?

WHO has developed guidance to support countries in tropical and sub-tropical regions in choosing between the northern and southern hemisphere formulations. In selecting which vaccine formulation to use and deciding when to start vaccination, these countries should consider their epidemiologic and virologic surveillance data.

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

The WHO recommended CVVs for vaccine development and production for the 2022-2023 northern hemisphere influenza season are listed on the WHO website.

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

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 CVV against zoonotic/potentially pandemic strains is done to maintain a bank of viruses suitable for the immediate development of vaccines in an emergency, for example 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 public health and regulatory 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 or protein sequences and to obtain approval from the local regulatory agencies. WHO publishes and updates a list of recommended CVVs and sequence accession numbers.

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, over 3.5 million clinical specimens worldwide were tested and reported to WHO, and more than 8000 representative influenza viruses were shared with the WHO CCs for further analyses. While more clinical specimens were tested globally during the 2020-2021 and 2021-2022 seasons, there were significantly reduced numbers of influenza detections and consequently fewer viruses were available for sharing.

In the context of the current influenza vaccine composition consultation, 119 countries, areas, or territories reported data to the global influenza surveillance platform (FluNet) from 1 September 2021 to 31 January 2022. During the same period of 2019-2020, prior to the COVID-19 pandemic, 161 countries, areas, or territories reported data.

To maintain influenza surveillance and monitor co-circulation of influenza and SARS-CoV-2 in the community in the context of the COVID-19 pandemic, WHO updated its interim guidance for GISRS for the end-to-end integration of influenza and SARS-CoV-2 surveillance. The revised interim guidance was published on 31 January 2022.

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. With the rapid spread and surge in SARS-CoV-2
circulation seen across the world from mid-March 2020, influenza activity decreased sharply and remained low in 2020 and most of 2021. 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. A(H3N2), A(H1N1)pdm09 and B/Victoria-lineage influenza B viruses have been detected in multiple countries since the southern hemisphere 2022 vaccine composition consultation, held in September 2021. Detections of B/Yamagata-lineage influenza viruses have been rare, and no samples were available for characterisation by WHO CCs. The impact of the current low influenza virus circulation on the influenza activity in coming seasons is unknown. Therefore, it is important to retain the B/Yamagata-lineage influenza viruses in quadrivalent vaccine formulation for the 2022-2023 northern hemisphere season.

Maintaining global influenza surveillance, if possible all-year round surveillance during the COVID-19 pandemic and encouraging influenza vaccination is imperative to reduce the potential public health impact of seasonal influenza.

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 animals. Zoonoses with influenza viruses from birds and pigs have continued to be detected and remain a threat. As such, GISRS continues to update the list of available CVVs for pandemic preparedness purposes and conducts risk assessments when zoonotic events are identified. The influenza monthly risk assessment summaries are published on the WHO website.

18. How has the COVID-19 pandemic impacted the 2022-2023 northern hemisphere influenza vaccine recommendation?

The volume of data available from recently circulating influenza viruses and the geographic representation have been lower for this northern hemisphere vaccine recommendation meeting than was typical prior to the COVID-19 pandemic. The reduced number of characterised viruses raises uncertainties regarding the full extent of the genetic and antigenic diversity of currently circulating influenza viruses and those likely to pose a threat in forthcoming seasons. Nevertheless, some groups of A(H3N2) and B/Victoria-lineage viruses have expanded and spread internationally during the current period. Consequently, the A(H3N2) and B/Victoria-lineage component recommendations have been changed from the previous northern hemisphere recommendation.

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