World Health Organization

Questions and Answers

Recommended composition of influenza virus vaccines for use in the southern hemisphere 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 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 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 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 countries with guidance 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 the WHO recommendations for 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 seasonal influenza vaccines for the next influenza season. In contrast to many other vaccines, the viruses in influenza vaccines are 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 is antigenically similar to the virus 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 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 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 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 and current influenza seasons.

- ***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 more recent cell-based vaccine manufacturing processes and separate CVV 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 at WHO website.

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

WHO recommends that quadrivalent vaccines for use in the 2022 southern 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 southern 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 recommendations?

Recommended vaccine viruses are representative of the antigenic group of viruses anticipated to dominate in the upcoming 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 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 southern hemisphere recommendation 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 and the A/Hong Kong/45/2019-like viruses with A/Darwin/9/2021-like and A/Darwin/6/2021-like viruses for egg- and cell culture-based production, respectively, is recommended.

- 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 southern hemisphere vaccines are the same as recommended for the 2021 southern 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 northern hemisphere recommendation 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 culture-based production, respectively, is recommended.

- For the B/Victoria 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 southern hemisphere vaccines are the same as recommended for the 2021/2022 northern hemisphere vaccine.

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 lineage B virus.

11. Is the vaccine composition for the 2021/2022 northern hemisphere influenza season still appropriate?

Human seasonal influenza is caused by one of the four circulating types of virus. The best protection against influenza is vaccination using trivalent or quadrivalent influenza vaccines. 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 B/Yamagata-lineage viruses recommended for the 2022 southern hemisphere and 2021/2022 northern hemisphere influenza vaccines are the same. It is anticipated that the 2021/2022 northern hemisphere influenza vaccine will provide expected protection against viruses likely to circulate.

12. 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 subtropical regions in choosing between the northern and southern hemisphere formulations because influenza viruses circulate at varying times throughout the year in these regions. When 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.

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

The WHO recommended CVVs for vaccine development and production for the 2022 southern hemisphere influenza season are listed at 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.

14. 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 programme, 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 for the production of some influenza vaccines. The selection and development of a zoonotic/potentially pandemic CVV is done to maintain a bank of viruses suitable for the immediate production 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.

15. 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 use the relevant CVVs or protein sequences, as appropriate, and to obtain approval from the local regulatory agencies. WHO publishes and updates a list of recommended CVVs and sequence accession numbers.

16. 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. While more clinical specimens were tested globally in 2021 than in 2020, there were vastly reduced numbers of influenza detections and consequently far fewer viruses available for sharing with WHO CCs. From February through August 2021, NICs collected and tested over three million clinical specimens worldwide and shared more than 1500 of these with the WHO CCs for further analyses.

In the context of the current influenza vaccine composition consultation, 129 countries, areas, or territories reported data to the global influenza surveillance platform FluNet from 1 February to 31 August 2021; 157 countries, areas, or territories reported data over the same period of 2020.

To address the persistent public health threat from influenza and maintain global influenza surveillance and response capabilities, WHO published successive guidance documents to prepare GISRS for the forthcoming influenza seasons in the context of the COVID-19 pandemic. The guidance, *Maintaining surveillance of influenza and monitoring SARS-CoV-2 – adapting Global Influenza Surveillance and Response System (GISRS) and sentinel systems during the COVID-19 pandemic*, was updated in November 2020.

17. 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, and 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. A(H3N2), A(H1N1)pdm09 and B/Victoria-lineage influenza B viruses have been detected in multiple countries since the northern hemisphere 2021/2022 vaccine composition meeting, held in February 2021. B/Yamagata-lineage influenza viruses have been detected rarely and no samples were available for characterisation at WHO CCs. Due to the continued uncertainty relating to the COVID-19 pandemic and its effects on influenza activity, it is imperative to maintain continuous global influenza surveillance and encourage influenza vaccination.

18. 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 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.

19. How has the COVID-19 pandemic impacted the 2022 southern hemisphere influenza vaccine recommendation?

The volume of data available from recently circulating influenza viruses and the geographic representation have been significantly lower for this southern 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, new groups of A(H3N2) and B/Victoria-lineage viruses were identified that had spread internationally and showed antigenic changes compared to recently recommended vaccine viruses. Consequently, the A(H3N2) and B/Victoria-lineage component recommendations have been updated.

20. 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.

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