World Health Organization

Questions and Answers

Recommended composition of influenza virus vaccines for use in the southern hemisphere 2024 influenza season and development of candidate vaccine viruses for pandemic preparedness

29 September 2023

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 151 National Influenza Centres (NICs) in 129 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 characterizations 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 animals.

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 characterization of viruses:***
  GISRS laboratories, in particular WHO CCs, use post-infection ferret antisera and pooled post-vaccination human sera to evaluate antibody reactivity with the surface proteins (antigens) of circulating and vaccine 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 sequences available in databases and antigenic information provided by the WHO CCs is considered.

- ***Antiviral resistance:***
  GISRS laboratories analyse 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:***
  CVVs are essential for production of vaccines in a timely manner for the next influenza season. Most vaccines produced globally use egg-based manufacturing processes which require CVVs that replicate well in eggs while cell-based vaccines require CVVs that replicate well in cell culture. Separate recommendations are made for egg- and cell-based CVVs because of the differing replication and manufacturing processes. 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 consultations include experts from WHO CCs, WHO ERLs, WHO H5 Reference Laboratories, NICs, the WOAH/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.

5. Which viruses are recommended by WHO to be included in influenza vaccines for use in the 2024 southern hemisphere influenza season?

The WHO recommends that trivalent vaccines for use in the 2024 southern hemisphere influenza season contain the following:

Egg-based vaccines

- **an A/Victoria/4897/2022 (H1N1)pdm09-like virus;**
- **an A/Thailand/8/2022 (H3N2)-like virus; and**
- **a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.**

Cell culture- or recombinant-based vaccines

- **an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;**
- **an A/Massachusetts/18/2022 (H3N2)-like virus; and**
- **a B/Austria/1359417/2021 (B/Victoria lineage)-like virus**

For quadrivalent egg- or cell culture-based or recombinant vaccines for use in the 2024 southern hemisphere influenza season, the WHO recommends inclusion of the following as the B/Yamagata lineage component:

- **a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.**

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 may not replicate equally well in the egg- and cell-based vaccine production systems. Therefore, different viruses with similar antigenic properties are sometimes recommended for the two production systems.

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

8. Are the vaccine viruses in this recommendation different from those in the previous southern hemisphere recommendations announced in September 2022?

The following updates to the vaccine have been recommended:

For the A(H1N1)pdm09 vaccine component, replacement of the A/Sydney/5/2021-like virus with A/Wisconsin/67/2022-like virus for cell culture-based or recombinant vaccines and A/Victoria/4897/2022-like virus for egg-based vaccines.

For the A(H3N2) vaccine component, replacement of the A/Darwin/6/2021-like virus with A/Massachusetts/18/2022-like virus for cell culture-based or recombinant vaccines and A/Darwin/9/2021-like virus with A/Thailand/8/2022-like virus for egg-based vaccines.

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 recommendations announced in February 2023?

The viruses recommended for production of 2024 southern hemisphere vaccines differ from the recommendation for the 2023-2024 northern hemisphere vaccine for the A(H3N2) vaccine virus component. A/Darwin/6/2021-like and A/Darwin/9/2021-like viruses were recommended for the 2023-2024 northern hemisphere A(H3N2) cell and egg-based vaccine components, respectively. The 2024 southern hemisphere vaccine recommendation for the A(H3N2) vaccine component is an A/Massachusetts/18/2022-like virus for cell-based and recombinant vaccines and A/Thailand/8/2022-like virus for egg-based vaccines.

10. What is the difference between quadrivalent and trivalent vaccines?

Currently licenced 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 and a B/Yamagata lineage virus). Currently licenced trivalent vaccines include two subtypes of influenza A viruses (an A(H1N1)pdm09 virus and an A(H3N2) virus) and one type B virus (either a B/Victoria or a B/Yamagata lineage virus). The WHO recommends which B lineage virus should be considered for inclusion in the trivalent vaccine.

As in previous years, national or regional authorities approve the composition and formulation of vaccines used in each country. It is a matter for the national or regional health and regulatory agencies to consider the relative benefit(s) and recommend the use of a trivalent or a quadrivalent influenza vaccine.

11. Should B/Yamagata lineage antigens continue to be included in the vaccine?

There has been no WHO CC confirmed detection of naturally occurring B/Yamagata-lineage influenza viruses since March 2020. Recent reports of very few B/Yamagata detections could not be confirmed as naturally occurring B/Yamagata-lineage viruses. It is unlikely that B/Yamagata-lineage viruses are circulating in the population. Therefore, it is the opinion of the WHO influenza vaccine composition advisory committee that the inclusion of B/Yamagata-lineage antigens in influenza vaccines is no longer warranted.

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. These countries should consider their epidemiologic and virologic surveillance data in selecting which vaccine formulation to use and deciding when to start vaccination.

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

The WHO recommended CVVs for vaccine development and production for the 2024 southern hemisphere influenza season are listed on the WHO website.

The available CVVs, including those for pandemic preparedness purposes (zoonotic viruses), and corresponding potency test reagents are posted by type/subtype 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. Human infections with influenza viruses from birds and pigs continue to be detected and these viruses remain a public health 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.

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 influenza vaccines. The selection and development of CVVs against zoonotic/potentially pandemic strains 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.

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

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