Questions and Answers

Recommended composition of influenza virus vaccines for use in the southern hemisphere 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)? ........2
2. What is the purpose of WHO recommendations on the composition of influenza virus vaccines? ................................................................. 2
3. What are candidate vaccine viruses (CVVs)? ......................................................... 2
4. How are influenza vaccine recommendations made? ........................................ 3
5. What viruses are recommended by WHO to be included in influenza vaccines for use in the 2023 southern hemisphere influenza season? ......................................................... 4
6. What does the term “-like virus” mean in the vaccine recommendation? .......... 4
7. Why are different viruses sometimes recommended for egg- and cell-based vaccines? ......4
8. Are the vaccine viruses in this recommendation different from those in the previous southern hemisphere recommendations announced in September 2021? .......................5
9. Are the vaccine viruses in this recommendation different from those in the northern hemisphere recommendations announced in February 2022? ......................5
10. What is the difference between quadrivalent and trivalent vaccines? .............5
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? .............................................. 5
12. What CVVs are available for use in influenza vaccines? ........................................5
13. Why does GISRS continue to update the list of available CVVs for pandemic preparedness? ........................................................................ 6
14. What happens after the WHO recommendations are made? ......................... 6
15. What impact has the COVID-19 pandemic had on GISRS influenza surveillance? .........6
16. What impact has the COVID-19 pandemic had on seasonal influenza activity? ........7
17. Has the COVID-19 pandemic had an impact on zoonotic influenza activity and pandemic risk? ........................................................................... 7
18. How has the COVID-19 pandemic impacted the 2023 southern hemisphere influenza vaccine recommendation? ......................................................... 7
19. Is the avian origin A(H3N8) virus that caused two human infections in China related to human seasonal A(H3N2) viruses? ......................................................... 8
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 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, 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 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 therefore 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:**
  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 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. What viruses are recommended by WHO to be included in influenza vaccines for use in the 2023 southern hemisphere influenza season?

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

**Egg-based Vaccines**
- an A/Sydney/5/2021 (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/Sydney/5/2021 (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 2023 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 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 new 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 2021?

The following update to the vaccine has been recommended:


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

Previous and present WHO influenza vaccine composition recommendations can be found on the WHO Global Influenza Programme [website](https://www.who.int).

9. Are the vaccine viruses in this recommendation different from those in the northern hemisphere recommendations announced in February 2022?

The viruses recommended for production of trivalent and quadrivalent 2023 southern hemisphere vaccines differ from the recommendation for the 2022-2023 northern hemisphere vaccine for the A(H1N1)pdm09 vaccine virus component. The A/Victoria/2570/2019-like virus and A/Wisconsin/588/2019-like virus are recommended to be replaced with A/Sydney/5/2021-like viruses for egg- and cell-based production.

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 subtropical 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 2023 southern hemisphere influenza season are listed on the [WHO website](https://www.who.int).
The available CVVs, including zoonotic viruses, and corresponding potency test reagents are posted by type/subtype 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 influenza pandemic preparedness, 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 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.

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 during the early stages of the COVID-19 pandemic but has since recovered in most countries. In the 2019-2020 influenza season, over four 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 2020 and 2021, there were reduced numbers of influenza detections and consequently fewer viruses were available to be shared. In 2022, influenza virus detections have returned to pre-COVID-19 pandemic levels in many countries in the southern hemisphere. A(H3N2), A(H1N1)pdm09, and B/Victoria-lineage influenza B viruses have been detected in several countries. A sufficient number of influenza viruses have been available for characterization to support WHO recommendations for vaccine composition for the southern hemisphere.

In the context of the current influenza vaccine composition consultation, 157 countries, areas, or territories reported data to the global influenza surveillance platform (FluNet) from 1 February to 31 August 2022. During the same period in 2021, 129 countries, areas, or territories reported data.
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 updated 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. Starting in mid-March 2020, influenza activity decreased sharply, concomitant with the spread of SARS-CoV-2. Global influenza activity remained low in many countries and regions until the end of 2021. Implementation of mitigation strategies (e.g. travel restrictions, social-distancing and increased personal hygiene measures) contributed to decreased influenza activity though other factors may also have been involved.

Since February 2022, A(H3N2), A(H1N1)pdm09 and influenza B viruses have been detected in multiple countries and influenza activity has returned to pre-pandemic levels in some cases. Maintaining continuous global influenza surveillance and encouraging influenza vaccination is imperative to reduce the potential public health impact of seasonal influenza.

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

The COVID-19 pandemic has not had a direct impact on zoonotic influenza activity. However, 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 2023 southern hemisphere influenza vaccine recommendation?

In 2022, influenza virus detections have been close to pre-COVID-19 pandemic levels in many countries in the southern hemisphere. A sufficient number of influenza viruses were available for characterization to support WHO recommendations for vaccine composition for the southern hemisphere.
19. Is the avian origin A(H3N8) virus that caused two human infections in China related to human seasonal A(H3N2) viruses?

No, the A(H3N8) viruses are of avian origin and are antigenically and genetically distinct from A(H3N2) human seasonal influenza viruses.

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