

Questions and Answers

Recommended composition of influenza virus vaccines for use in the southern hemisphere 2019 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 144 National Influenza Centres (NICs) in 114 WHO Member States, 6 WHO Collaborating Centres for Influenza (CCs), 4 WHO Essential Regulatory Laboratories (ERLs) and 13 WHO H5 Reference Laboratories.

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. In 2017, NICs collected and tested more than three million clinical specimens from patients and shared more than 10,000 representative influenza viruses with the WHO CCs for further analyses. Virus characterisation and other analysis, complemented with other available epidemiological 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 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. In contrast to many other vaccines, the viruses in influenza vaccines have to be evaluated and updated regularly because circulating influenza viruses continuously evolve. Recommendations are often 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 decided by the fact that approximately 6-8 months are needed to produce and approve vaccines.

3. How are influenza vaccine recommendations made?

Many different sources of data and information are used to determine the recommended vaccine viruses, including:

- ***Surveillance data from the GISRS network, which includes NICs, WHO CCs, WHO ERLs and WHO H5 Reference Laboratories:***
Virus surveillance data, complemented with epidemiologic and clinical findings inform the vaccine virus selection process.
- ***Antigenic characterization of viruses:***
GISRS laboratories, in particular the WHO CCs, also conduct testing to evaluate the antibody or immune response triggered by the proteins on the surface of influenza viruses. Antigenic cartography is used as a way to visualize relatedness of viruses.
- ***Human serology studies with inactivated 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 testing to compare virus gene sequences of circulating influenza viruses to the sequences of vaccine viruses to identify genetic changes that might influence protection conferred by a given vaccine.
- **Virus fitness forecasting:**
Information from modelling studies, based on genetic and antigenic information, is also considered.
- **Antiviral resistance:**
GISRS laboratories test influenza viruses to determine if they have any 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 18 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 potential CVVs:**
The vast majority of vaccines produced globally use egg-based manufacturing processes. This requires CVVs which grow well in eggs. These viruses must be available in order to produce vaccine and make the vaccine available in time for the next influenza season.

These data, and other findings made available by GISRS, are evaluated during WHO Consultations often in February and September of each year. The consultation includes Advisers from WHO CCs and WHO ERLs, and other experts from WHO CCs, WHO ERLs, WHO H5 Reference Laboratories, NICs, the University of Cambridge, the OIE/FAO Network of expertise on animal influenza (OFFLU), modelling groups, and other national and regional institutions. Further information about GISRS is available at http://www.who.int/influenza/gisrs_laboratory/en/.

4. What viruses are recommended by WHO to be included in influenza vaccines for use in the 2019 southern hemisphere influenza season?

WHO recommends that egg-based quadrivalent influenza vaccines for use in the 2019 southern hemisphere influenza season contain the following viruses:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Switzerland/8060/2017 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus; and
- a B/Phuket/3073/2013-like virus.

WHO recommends that egg-based trivalent influenza vaccines for use in the 2019 southern hemisphere influenza season contain the following:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Switzerland/8060/2017 (H3N2)-like virus; and
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage).

WHO recommends that the A(H3N2) component of non-egg based vaccines for use in the 2019 southern hemisphere influenza season be an A/Singapore/INFIMH-16-0019/2016-like virus together with the other components as indicated above.

5. Are the vaccine viruses in this recommendation different from those in the previous southern hemisphere recommendations?

There have been the following updates to the vaccine recommendations:

- for egg-based vaccines: replacement of the A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus with an A/Switzerland/8060/2017 (H3N2)-like virus.
- For both egg- and non-egg based vaccines:
 - replacement of the B/Brisbane/60/2008-like virus with a B/Colorado/06/2017-like virus.
 - for trivalent vaccines, a B/Colorado/06/2017-like virus is recommended as the influenza B component.

All previous WHO recommendations can be found on the WHO Global Influenza Programme website at: <http://www.who.int/influenza/vaccines/virus/recommendations/en/>

6. Why was the A(H3N2) component for egg-based vaccines changed from an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus to an A/Switzerland/8060/2017 (H3N2)-like virus?

Most recent A(H3N2) viruses were well inhibited by ferret antisera raised against cell culture propagated A/Singapore/INFIMH-16-0019/2016 (H3N2)-like viruses. However, ferret antisera raised against egg-propagated A/Singapore/INFIMH-16-0019/2016-like viruses inhibited a smaller proportion of recently circulating viruses. The majority of viruses tested from the currently predominating subclade 3C.2a2 were better inhibited by ferret antiserum raised against egg-propagated A/Switzerland/8060/2017.

Based on the above and other analyses, an A/Switzerland/8060/2017 (H3N2)-like virus is recommended for use in egg-based vaccines for the southern hemisphere 2019 influenza season.

7. Why is the recommendation for the A(H3N2) component of egg-based vaccines different from non-egg based vaccines?

Recent A(H3N2) viruses from all sub-clades of 3C.2a were well inhibited by ferret antisera raised against cell culture-propagated A/Singapore/INFIMH-16-0019/2016 (H3N2)-like viruses. Therefore, an update to the A(H3N2) component of non-egg-based vaccines was not warranted.

8. What are the implications of changing the influenza A(H3N2) component of the southern hemisphere vaccine for the upcoming northern hemisphere influenza season, where the egg-based vaccine includes an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus?

From the recently ended southern hemisphere 2018 season, there was insufficient circulation of A(H3N2) viruses to estimate the effectiveness of the egg-based A/Singapore/INFIMH-16-

0019/2016 (H3N2) component of the 2018 southern hemisphere vaccine. In the northern hemisphere, influenza activity to date is low and it is too early to tell which type or subtype influenza virus strain will be predominant. While the effectiveness of the A(H3N2) component in the upcoming northern hemisphere vaccines might be reduced, the overall effectiveness of vaccines depends on which types of viruses actually circulate. Importantly, the A(H1N1)pdm09 and influenza B vaccine viruses are expected to match the circulating viruses and provide good levels of protection. Moreover, research shows that the presence of neuraminidase (NA) in the vaccine – when antigenically matched with the NA of circulating viruses, may provide some protection. This is the case for the majority of recent A(H3N2) viruses.

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

Quadrivalent vaccines include two subtype A viruses (an A(H1N1)pdm09 virus and an A(H3N2 virus)) and two lineage B viruses (a B/Victoria lineage virus and a B/Yamagata lineage virus). Trivalent vaccines include two subtype A viruses (an A(H1N1)pdm09 virus and an A(H3N2) virus) and one type B virus.

10. Why was the influenza B/Victoria lineage virus vaccine component changed from a B/Brisbane/60/2008-like virus to a B/Colorado/06/2017-like virus?

While many recent B/Victoria lineage viruses were well inhibited by antisera raised against B/Brisbane/60/2008-like viruses, an increasing proportion of viruses were antigenically different from B/Brisbane/60/2008-like viruses and were more closely related to B/Colorado/06/2017-like viruses.

11. Why was the influenza B virus component for trivalent vaccines changed from the B/Phuket/3073/2013-like virus (B/Yamagata lineage) to a B/Colorado/06/2017-like virus (B/Victoria lineage)?

The increase in circulation of antigenically distinct B/Colorado/06/2017-like viruses within the B/Victoria lineage in many countries has led to a change in the recommendation for trivalent vaccines.

12. Could a B/Yamagata lineage virus still be considered for use as a vaccine component in trivalent vaccines?

Countries or regions of the world that expect B/Yamagata lineage viruses to predominate in 2019 may choose to use a B/Phuket/3073/2013-like virus in their trivalent influenza vaccines. Approval of the composition and formulation of vaccines to be used in each country is the responsibility of national or regional regulatory authorities.

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

Influenza viruses circulate at varying times through the year in tropical and sub-tropical countries. In selecting which vaccine formulation to use, these countries should consider their surveillance information, in particular epidemiological and virological data to decide when to start vaccination and whether to use the formulation recommended for the northern or

southern hemisphere influenza season. WHO has formulated guidance for countries in tropical and sub-tropical regions to assist them in choosing which vaccine composition (February/March or September) is most appropriate (<http://www.who.int/influenza/vaccines/tropics/en/>).

14. 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.

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

The WHO recommended CVVs for vaccine development and production for the 2019 southern hemisphere influenza season are listed at:
www.who.int/influenza/vaccines/virus/candidates_reagents/2019_south/en/

The availability of CVVs by type/subtype, including zoonotic viruses, and corresponding potency test reagents is posted and updated on the WHO web site:
<http://www.who.int/influenza/vaccines/virus/en/>

16. 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 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 an assessment of the public health risk and needs in consultation with national regulatory and public health authorities.

17. 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 manufacturer to obtain the appropriate CVVs and to obtain approval from the local regulatory agency. 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)

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