Questions and Answers

Recommended composition of influenza virus vaccines for use in the southern hemisphere 2018 influenza season and development of candidate vaccine viruses for pandemic preparedness

28 September 2017

1. What is the WHO Global Influenza Surveillance and Response System (GISRS)?
2. What is the purpose of WHO recommendations on the composition of influenza virus vaccines?
3. What viruses are recommended by WHO to be included in influenza vaccines for use in the 2018 southern hemisphere influenza season?
4. Are the vaccine viruses in this recommendation different from those in previous recommendations?
5. What are candidate vaccine viruses (CVVs)?
6. How are influenza vaccine recommendations made?
7. Why was the H3 component of the vaccine changed from A/Hong Kong/4801/2014 to A/Singapore/INFIMH-16-0019/2016?
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 A/Hong Kong/4801/2014 (H3N2)-like virus is in the vaccine?
9. Why was the influenza B virus component for trivalent vaccines changed from the B/Brisbane/60/2008-like virus (B/Victoria lineage) to a B/Phuket/3073/2013-like virus (B/Yamagata lineage)?
10. What are the implications of changing the influenza B component of the southern hemisphere vaccine for the upcoming northern hemisphere influenza season where the B/Brisbane/60/2008-like virus (B/Victoria lineage virus) is in the vaccine?
11. Could a B/Victoria lineage virus still be considered for use as a vaccine component in trivalent vaccines?
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 campaigns?
13. What CVVs are available for use in influenza vaccines?
14. What happens after the WHO recommendations are made?
15. Why does GISRS continue to update the list of available CVVs for pandemic preparedness?
1. **What is the WHO Global Influenza Surveillance and Response System (GISRS)?**

GISRS is a global public health laboratory network coordinated by WHO, currently consisting of 143 National Influenza Centres (NICs) in 113 WHO Member States, 6 WHO Collaborating Centres for Influenza (CCs), 4 WHO Essential Regulatory Laboratories (ERLs) and 13 WHO H5 Reference Laboratories.

This network conducts numerous public health activities including assessment of influenza viruses of public health concern, such as viruses with pandemic potential. In the previous completed surveillance year, NICs collected and tested more than three million clinical specimens from patients and shared representative influenza viruses with the WHO CCs for detailed analyses and for making recommendations for vaccine composition. The network 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 made in February/March for the following influenza season in the northern hemisphere and in September for the following influenza season in the southern hemisphere because approximately 6-8 months are needed to produce and approve vaccines.

3. **What viruses are recommended by WHO to be included in influenza vaccines for use in the 2018 southern hemisphere influenza season?**

WHO recommends that influenza vaccines for use in the 2018 southern hemisphere influenza season contain the following viruses:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; and
- a B/Phuket/3073/2013-like virus.

Among circulating influenza B viruses, there are two distinct lineages: B/Victoria and B/Yamagata lineages. Viruses from both lineages have circulated in various proportions in different countries during this period. The B/Phuket/3073/2013-like viruses are from the influenza B/Yamagata lineage. It is recommended that quadrivalent vaccines contain the above three viruses and a B/Brisbane/60/2008-like virus, a B/Victoria lineage virus.
4. Are the vaccine viruses in this recommendation different from those in previous recommendations?

The influenza B virus for trivalent vaccines and the A(H3N2) virus have been updated compared to the viruses recommended for the 2017 southern hemisphere and 2017-2018 northern hemisphere influenza seasons. The update is as follows:

- replacement of the A/Hong Kong/4801/2014 (H3N2)-like virus with an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus.
- replacement of the B/Brisbane/60/2008-like virus with a B/Phuket/3073/2013-like virus.

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

5. 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 egg-based or cell culture-based vaccines.

6. 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 use tests to determine 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 19 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 laboratories, are evaluated during WHO Consultations in February/March and September of each year. The consultation includes Advisers from WHO CCs and WHO ERLs, as well as Observers 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), and other national and regional institutions. Further information about GISRS is available at [http://www.who.int/influenza/gisrs_laboratory/en/](http://www.who.int/influenza/gisrs_laboratory/en/).

7. **Why was the A(H3N2) component of the vaccine changed from A/Hong Kong/4801/2014 to A/Singapore/INFIMH-16-0019/2016?**

Influenza A(H3N2) viruses were associated with outbreaks in many countries. Although recent viruses remain antigenically related to cell-propagated A/Hong Kong/4801/2014, the majority of recent viruses reacted poorly with ferret antisera raised to egg-propagated A/Hong Kong/4801/2014-like viruses. Circulating A(H3N2) viruses were better inhibited by a ferret antiserum raised against the egg-propagated reference virus, A/Singapore/INFIMH-16-0019/2016, compared to ferret antisera raised against other egg-propagated A(H3N2) viruses.

Based on the above and other analysis, an A/Singapore/INFIMH-16-0019/2016-like virus is recommended for use in vaccines for the southern hemisphere 2018 influenza season.

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 A/Hong Kong/4801/2014 (H3N2)-like virus is in the vaccine?**

Influenza vaccines target either three or four influenza viruses that represent the circulating influenza types and subtypes of the virus. The effectiveness of vaccines containing A/Hong Kong/4801/2014 was suboptimal in the 2017 southern hemisphere season, in regions where A(H3N2) viruses predominated. If influenza A(H3N2) viruses predominate in the 2017/2018 northern hemisphere season, it is likely that vaccine effectiveness would be suboptimal for the A(H3N2) virus; however the vaccine should provide good protection for influenza A(H1N1)pdm09 and influenza B virus infection.
9. Why was the influenza B virus component for trivalent vaccines changed from the B/Brisbane/60/2008-like virus (B/Victoria lineage) to a B/Phuket/3073/2013-like virus (B/Yamagata lineage)?

Global influenza virus circulation data indicated that both B/Victoria/2/87 and B/Yamagata/16/88 lineages have co-circulated in the past year. However, in recent months, B/Yamagata/16/88 lineage viruses have become predominant in many countries.

The majority of recent viruses of the B/Yamagata/16/88 lineage were antigenically similar to the B/Phuket/3073/2013-like reference virus.

Based on the above analysis and knowledge accumulated through monitoring and analysing influenza B viruses of the two lineages in the past, the WHO’s expert group recommended that the influenza B component of the trivalent vaccines for the southern hemisphere 2018 season should be a B/Yamagata/16/88 lineage virus, antigenically similar to B/Phuket/3073/2013.

10. What are the implications of changing the influenza B component of the southern hemisphere vaccine for the upcoming northern hemisphere influenza season where the B/Brisbane/60/2008-like virus (B/Victoria lineage virus) is in the trivalent vaccine?

Of the influenza B viruses, B/Victoria lineage viruses predominated in 2016/2017 and therefore a B/Victoria lineage virus was recommended for trivalent vaccines for the 2017/2018 northern hemisphere. Global influenza virus circulation data indicate that both B/Victoria/2/87 and B/Yamagata/16/88 lineages have co-circulated in the past year. In recent months, B/Yamagata/16/88 lineage viruses have become predominant in many countries, leading to a change in the recommendation for the 2018 southern hemisphere trivalent vaccine. Trivalent vaccines containing B/Victoria/2/87 lineage viruses may provide some cross-protection against B/Yamagata/16/88 lineage viruses.

Quadrivalent vaccines contain both B/Victoria and B/Yamagata lineage vaccine viruses.

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

Countries or regions of the world that expect B/Victoria lineage viruses to predominate in 2018 may choose to use a B/Brisbane/60/2008-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. Quadrivalent influenza vaccines contain both a B/Yamagata and a B/Victoria lineage vaccine virus, of which a B/Phuket/3073/2013-like virus and a B/Brisbane/60/2008-like virus are currently recommended.

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 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/).

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

The WHO recommended CVVs for vaccine development and production for the 2018 southern hemisphere influenza season are listed at:
www.who.int/influenza/vaccines/virus/candidates_reagents/2018_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/

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 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)

15. 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.

Further information about zoonotic influenza CVVs can be found at:
http://www.who.int/influenza/vaccines/virus/characteristics_virus_vaccines/en/

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