Questions and Answers

Recommended composition of influenza virus vaccines for use in the northern hemisphere 2017-2018 influenza season and development of candidate vaccine viruses for pandemic preparedness

2 March 2017

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 2016, NICs collected and tested up to 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. This 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. 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/) .

3. What viruses are recommended by WHO to be included in influenza vaccines for use in the 2017-2018 northern hemisphere influenza season?

WHO recommends that influenza vaccines for use in the 2017-2018 northern hemisphere influenza season contain the following viruses:

– an A/Michigan/45/2015 (H1N1)pdm09-like virus;
– an A/Hong Kong/4801/2014 (H3N2)-like virus; and
– a B/Brisbane/60/2008-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/Brisbane/60/2008-like viruses are from the influenza B/Victoria lineage. It is recommended that quadrivalent vaccines contain the above three viruses and a B/Phuket/3073/2013-like virus, a B/Yamagata-lineage virus.

4. Are the vaccine viruses in this recommendation different from those in previous recommendations?

The A(H1N1)pdm09 virus has been updated compared to the virus recommended for northern hemisphere 2016-2017 influenza season. This updated recommendation is as follows:

- replacement of the A/California/7/2009 (H1N1)pdm09-like virus with an A/Michigan/45/2015 (H1N1)pdm09-like virus.

These recommendations are the same as those made for the 2017 southern hemisphere influenza vaccine.

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. Why are there recommendations for vaccines produced in cell culture as well as for vaccines produced in eggs?

Influenza vaccines are made in hens' eggs, cell culture or through recombinant protein expression. Generally, viruses used in egg-based vaccines are isolated and propagated in hens' eggs while those used in cell culture-based vaccines can be isolated and propagated either in hens' eggs or in an appropriate cell culture system.

6. What are candidate vaccine viruses (CVVs)?

A CVV is a virus prepared for potential use in vaccine manufacturing that is antigenically indistinguishable from the virus that has been recommended for use in egg-based or cell culture-based vaccines.

7. 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 determine how genetic changes 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 14 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 time 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/.

8. 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 2017-2018 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. 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.

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

The WHO recommended CVVs for vaccine development and production for the 2017-2018 northern hemisphere influenza season are listed at:
www.who.int/influenza/vaccines/virus/candidates_reagents/2017_18_north/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/

10. 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)

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 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 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/).

12. 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 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.

The most recent recommendations for A(H7N9) included two new CVVs because of the antigenic diversity and difference seen in the recently circulating low pathogenicity avian A(H7N9) viruses and the emergence of highly pathogenic avian influenza A(H7N9) viruses. Based on the available evidence these highly pathogenic avian influenza viruses do not cause increased disease severity in humans or increased transmissibility between humans. More information regarding a risk assessment of these viruses can be found on the WHO website: http://www.who.int/influenza/human_animal_interface/avian_influenza/riskassessment_AH7N9_201702/en/ .

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