

## Questions and Answers

### **Recommended composition of influenza virus vaccines for use in the southern hemisphere 2016 influenza season and development of candidate vaccine viruses for pandemic preparedness**

**24 September 2015 (*revised 13 October 2015*)**

- 1. What is the WHO Global Influenza Surveillance and Response System (GISRS)?**
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- 9. What happens after the WHO recommendations are made?**
- 10. Why does GISRS continue to update the list of available candidate vaccine viruses 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 142 National Influenza Centres (NICs) in 112 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. NICs collect and test clinical specimens from patients and share representative influenza viruses with the WHO CCs for detailed analysis, and for making recommendations for vaccine composition. This network also provides guidance to countries and support for activities such as training, outbreak response, development of diagnostic tests, testing for antiviral drug resistance and scientific interpretation of important findings.

## **2. What is the purpose of the 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 frequently because circulating influenza viruses continuously evolve. Recommendations are made in September for the following influenza season in the southern hemisphere and in February for the following influenza season in the northern 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 2016 southern hemisphere influenza season?**

WHO recommends that influenza vaccines for use in the 2016 southern hemisphere influenza season contain the following viruses:

- an A/California/7/2009 (H1N1)pdm09-like virus
- an A/Hong Kong/4801/2014 (H3N2)-like virus
- a B/Brisbane/60/2008-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.

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

The vaccine viruses recommended for the 2016 southern hemisphere influenza season are different from those used for the 2015 southern hemisphere and those recommended for the northern hemisphere 2015-2016 influenza seasons.

For **2016 southern hemisphere** influenza season, it is recommended that trivalent vaccines contain the following:

- an A/California/7/2009 (H1N1)pdm09-like virus;
- an A/Hong Kong/4801/2014 (H3N2)-like virus;
- a B/Brisbane/60/2008-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.

For **2015-2016 northern hemisphere** influenza season, it was recommended that trivalent vaccines contain the following:

- an A/California/7/2009 (H1N1)pdm09-like virus;
- an A/Switzerland/9715293/2013 (H3N2)-like virus;
- a B/Phuket/3073/2013-like virus.

It was recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus.

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

**5. What are the implications of the updated A(H3N2) and B components of the trivalent vaccines to the 2015-2016 northern hemisphere season?**

So far most A(H3N2) viruses characterized remain antigenically similar to A/Switzerland/9715293/2013 – the vaccine component for 2015-2016 northern hemisphere influenza season, and most influenza B viruses belong to the B/Yamagata-lineage, of which a B/Phuket/3073/2013-like virus is the recommended vaccine component for the upcoming northern hemisphere season. Therefore there are not likely to be major implications to the effectiveness of the 2015-2016 vaccines.

The updates for the 2016 southern hemisphere season were made with the intention of having the most suitable components for the influenza season at that time, taking into consideration virus antigenic properties and also genetic evolution epidemiological factors and vaccine production technology.

**6. How was the vaccine recommendation made for the 2016 southern hemisphere influenza season?**

Many different sources of information and factors were used to determine the recommended 2016 southern hemisphere vaccine viruses, including:

- **Surveillance data from the GISRS network, which includes NICs, WHO CCs, WHO ERLs and WHO H5 Reference Laboratories:**  
Laboratory testing at these designated laboratories identified the different influenza viruses that were circulating and predominant around the globe. These virologic 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 conducted testing to evaluate the antibody or immune response triggered by the proteins on the surface of influenza viruses. The most common of these tests is the haemagglutination inhibition assay, which works by measuring how well antibodies bind to (and thus inactivate) influenza viruses. Other tests used to see how well a particular virus might work as a vaccine candidate include microneutralization assays, plaque reduction neutralization tests, and focus reduction assays.
- **Human serology studies with inactivated influenza virus vaccines:**  
WHO CCs and ERLs use HI and microneutralization assays to determine how well antibodies in sera from vaccinated people cross-react with or neutralize recently circulating influenza viruses.
- **Genetic characterization of viruses:**  
GISRS laboratories conducted testing to compare genetic sequences of circulating

seasonal and zoonotic influenza viruses to determine how related influenza viruses are to one another and current vaccine viruses, how they are evolving, and how genetic changes might influence protection by a given vaccine.

- **Antiviral resistance:**

GISRS laboratories tested influenza viruses to determine if they have any resistance to the antiviral drugs used to treat influenza infection, such as oseltamivir, zanamivir, peramivir, and laninamivir.

- **Vaccine effectiveness:**

The Global Influenza Vaccine Effectiveness (GIVE) Collaboration, made up of 15 different studies conducted in countries in both the northern and southern hemispheres, provided information on vaccine effectiveness for northern and southern hemisphere seasons.

- **Availability of potential vaccine candidates:**

The vast majority of vaccines produced globally use egg-based manufacturing processes. This often requires 6 to 8 months in order to produce the hundreds of millions of doses available for the next influenza season. Selection of candidate vaccine viruses also considers the availability of adequate egg-grown viruses and/or virus reassortants used by vaccine manufacturers in order to produce large quantities of vaccine.

These data, and other findings made available by GISRS laboratories, were evaluated during a WHO Consultation from 21 to 23 September 2015. The consultation included 9 Advisers from WHO CCs and WHO ERLs, and was observed by 31 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).

Based on the findings presented at the consultation meeting, including thousands of antigenic and genetic test results comparing multiple circulating viruses, potential candidate vaccine viruses, and current vaccine viruses, two changes were recommended for the 2016 southern hemisphere vaccine composition.

The first change is an update for the influenza A(H3N2) component. Influenza A(H3N2) viruses collected from February 2015 to August 2015 fell into two groups based on gene sequencing (i.e., phylogenetic clades 3C.2 and 3C.3). Among these, there were three genetic sub-clades that circulated. Viruses in sub-clade 3C.2a are now predominant in all regions of the world. Sub-clade 3C.3a and 3C.3b viruses continue to circulate but represent a small minority of viruses in this reporting period.

Throughout the year, WHO evaluates thousands of *cell*-grown viruses to identify ones that best represent currently circulating viruses. Once identified, these viruses are grown in *eggs* to adapt them for optimal use in *egg*-based manufacturing processes. Previously, WHO selected a virus from sub-clade 3C.3a (an A/Switzerland/9715293/2013-like virus) for use in the vaccine. Recently, a representative virus from sub-clade 3C.2a (an A/Hong Kong/4801/2014-like virus) was identified and evaluated for possible use in the vaccine. A comparison of *cell*-grown A/Switzerland and A/Hong Kong viruses shows them to be antigenically similar; however, the *egg*-grown A/Hong Kong virus was antigenically and genetically more similar to the predominant, circulating 3C.2a viruses than the *egg*-propagated A/Switzerland virus. Therefore, an A/Hong Kong/4801/2014-like virus was

selected to replace the A/Switzerland/9715293/2013-like virus for updating the southern hemisphere A(H3N2) vaccine component.

For the second vaccine change, a B/Victoria lineage virus was selected for the influenza B component of trivalent vaccines. Epidemiologic and virologic data from February 2015 to August 2015 indicated an increasing number of B/Victoria lineage viruses at the end of the northern hemisphere season and through the southern hemisphere season. A change in the trivalent B component was made to account for this trend observed in several regions.

**7. 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 2016 may choose to use a B/Phuket/3073/2013-like virus in their trivalent influenza vaccines. Approval of the composition and formulation of vaccines that will be used in each country is the responsibility of national or regional regulatory authorities. Quadrivalent influenza vaccines typically 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.

**8. What candidate vaccine viruses (high-growth reassortants) are available for use in influenza vaccines?**

The WHO recommended candidate vaccine viruses for vaccine development and production for the 2016 southern hemisphere influenza season are listed at:  
[http://www.who.int/influenza/vaccines/virus/candidates\\_reagents/2016\\_south/en/](http://www.who.int/influenza/vaccines/virus/candidates_reagents/2016_south/en/)

The availability of high-growth reassortants by type/subtype, including A(H7N9) and A(H5N1) viruses, and corresponding potency test reagents is posted and updated on the WHO web site: <http://www.who.int/influenza/vaccines/virus/en/>

**9. 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 candidate vaccine viruses and to obtain approval from the local regulatory agency. WHO publishes and updates a list of candidate vaccine viruses for selection by manufacturers and regulatory agencies.  
([http://www.who.int/influenza/vaccines/virus/candidates\\_reagents/home](http://www.who.int/influenza/vaccines/virus/candidates_reagents/home))

**10. Why does GISRS continue to update the list of available candidate influenza vaccine viruses 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 candidate

vaccine viruses as a first step in the production of influenza vaccines. The selection and development of a zoonotic candidate vaccine virus is done for the purposes of having a bank of potential 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.

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