

Recommended composition of influenza virus vaccines for use in the 2017 southern hemisphere influenza season

September 2016

The World Health Organization (WHO) convenes technical consultations¹ in February and September each year to recommend viruses for inclusion in influenza vaccines² for the northern and southern hemisphere influenza seasons, respectively. This recommendation relates to the influenza vaccines for use in the forthcoming southern hemisphere 2017 influenza season. A recommendation will be made in February 2017 relating to vaccines that will be used for the northern hemisphere 2017-2018 influenza season. For countries in equatorial regions, epidemiological considerations influence which recommendation (February or September) individual national and regional authorities consider appropriate.

Seasonal influenza activity, January 2016 – August 2016

Between January and August 2016, low to widespread influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania predominantly due to the circulation of influenza A(H1N1)pdm09 and B with some outbreaks of A(H3N2) viruses. In the northern hemisphere, influenza activity was high from January until April/May and declined thereafter with the exception of several countries in the Americas and Asia. In the southern hemisphere, activity remained low until March after which moderate to high activity was reported by a number of countries.

Northern hemisphere temperate region

Regional and widespread influenza activity was reported until April/May with influenza A(H1N1)pdm09 and B viruses co-circulating in most countries of Europe and several countries in Asia. In addition, a few countries in Europe and Asia, including China, reported regional outbreaks of A(H3N2) influenza virus in the early part of the year. North America reported high influenza activity caused by A(H1N1)pdm09 from January until May, type B viruses from January until June and A(H3N2) from March until May.

Southern hemisphere temperate region

Influenza activity was low in the early part of the year. Regional and widespread activity was reported from May onwards in southern Africa with early predominance of influenza B viruses, followed by the circulation of influenza A(H3N2) and A(H1N1)pdm09 viruses. Regional to widespread activity was reported in the southern cone of the Americas from March onwards with influenza B virus co-circulating with A(H1N1)pdm09 and regional A(H3N2) activity was reported in May. Oceania reported low circulation of viruses until March. High A(H1N1)pdm09 activity was reported in Papua New Guinea in March and in Fiji A(H3N2) activity was high in May. Australia reported high activity of A(H3N2) with co-circulation of influenza B virus from June to September.

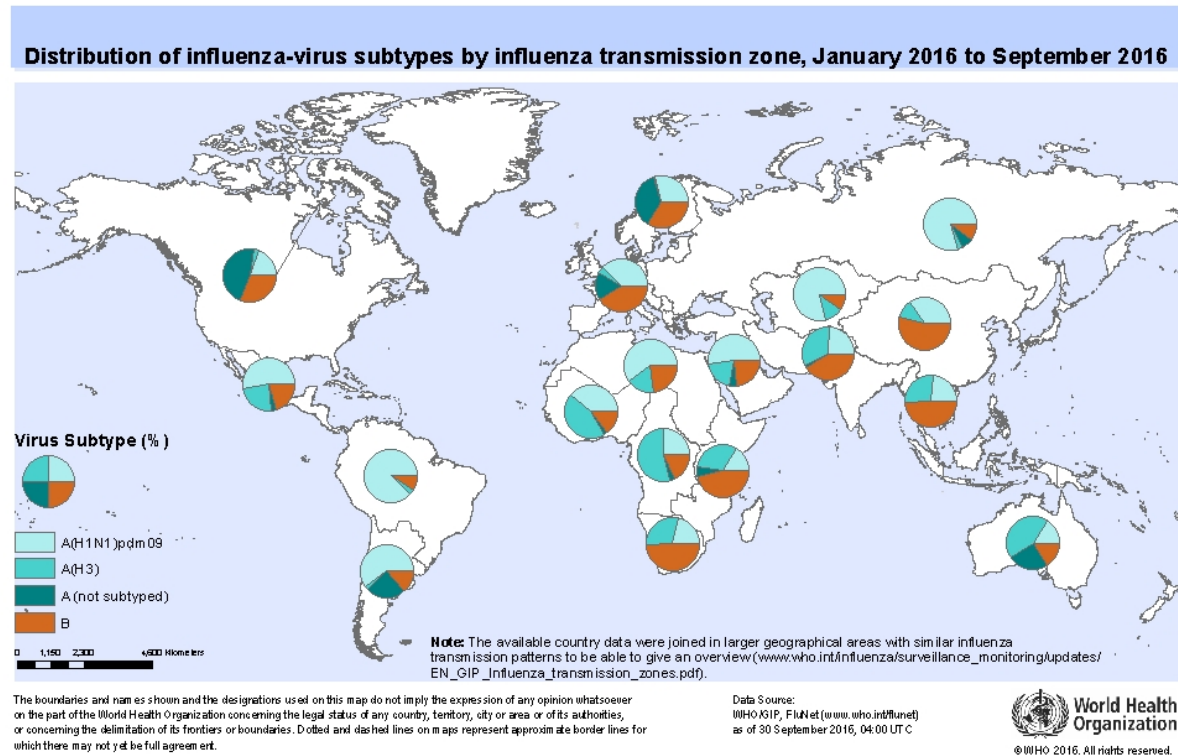
Tropical and subtropical regions

Influenza activity was variable but low overall in the tropical and subtropical regions of Africa. In Egypt there was an influenza B virus outbreak from March to May. In West Africa there was low influenza activity; however Ghana reported local to regional A(H3N2) activity from April to July. In Central Africa widespread activity was reported by the Democratic Republic of Congo from April to

¹ <http://www.who.int/influenza/vaccines/virus/en/>

² Description of the process of influenza vaccine virus selection and development available at: http://www.who.int/gb/pip/pdf_files/Fluvaccvirusselection.pdf

July and the Central African Republic from July to September. Influenza activity was variable in tropical America with a few countries reporting regional A(H1N1)pdm09 activity between March and June. Influenza activity was variable in tropical and subtropical Asia with regional outbreaks of A(H1N1)pdm09 followed by co-circulation of A(H3N2) and B viruses reported by several countries in tropical Asia and some countries in the Middle East from January until April.



Detailed information by country of the extent and type of seasonal influenza activity worldwide is available on the WHO website:

http://www.who.int/entity/influenza/vaccines/virus/recommendations/201609_influenzaactivitytable.pdf

Zoonotic influenza infections caused by A(H5), A(H7N9), A(H9N2), A(H1N2)v and A(H3N2)v viruses

From 23 February 2016 to 26 September 2016, four human cases of A(H5N6) infection were reported by China and ten human cases of A(H5N1) infection were reported by Egypt. The disease onset date for two of the cases from Egypt predated this reporting period. Highly pathogenic avian influenza A(H5) is present in poultry in both countries. Since December 2003, a total of 870 human cases of A(H5) infection with 458 deaths have been confirmed in 16 countries. To date there has been no evidence of sustained human-to-human transmission.

During this period 77 additional human cases of avian influenza A(H7N9) virus infection have been reported to WHO by China. Since February 2013, a total of 798 cases with 320 deaths have been reported.

Nine A(H9N2) human cases were reported during this period, eight in China and one in Egypt. Three of the cases from China, including a fatal case, had disease onset dates that predated the reporting period. Viruses from cases in China belong to the A/chicken/Hong Kong/Y280/97 genetic lineage. No data are available for the virus from Egypt where A/quail/Hong Kong/G1/97 lineage viruses circulate in poultry.

During this period, four cases of A(H1N2)v, three in the United States of America and one retrospective case in Brazil, and 19 cases of A(H3N2)v, 18 in the United States of America and one retrospective case in Viet Nam, were reported.

Antigenic and genetic characteristics of recent seasonal influenza viruses

Influenza A(H1N1)pdm09 viruses

The vast majority of A(H1N1)pdm09 viruses collected from February 2016 to August 2016 fell into the phylogenetic clade 6B. Most recently circulating viruses belonged to genetic subclade 6B.1. A small proportion of viruses circulating globally belonged to subclade 6B.2. Subclade 6B.2 viruses were detected most frequently in China, although 6B.1 viruses predominated. Antigenic characteristics of A(H1N1)pdm09 viruses were assessed with panels of post-infection ferret antisera and human paediatric, adult and older adult pre- and post-vaccination sera in haemagglutination inhibition (HI) assays. HI assays with ferret antisera indicated that almost all recent A(H1N1)pdm09 viruses were antigenically indistinguishable from the vaccine virus A/California/7/2009. However, representative 6B.1 and 6B.2 viruses were poorly inhibited by some post-vaccination adult human serum pools (Table 1). Furthermore, geometric mean post-vaccination HI titres of paediatric sera against some representative 6B.1 and 6B.2 A(H1N1)pdm09 viruses were reduced significantly compared to HI titres to the A/California/7/2009 vaccine virus, although this was not consistently observed for adult and older adult serum panels.

Influenza A(H3N2) viruses

A(H3N2) viruses collected from February to August 2016 fell into the phylogenetic clades 3C.2 and 3C.3. Viruses in subclade 3C.2a predominated in most regions of the world with the majority of these viruses having further changes in the haemagglutinin (HA) (N171K, I406V, G484E), now referred to as subclade 3C.2a1. Subclade 3C.3a has continued to circulate but represented a lower proportion of viruses circulating during this reporting period except in the United States of America where they predominated. Viruses in genetic subclade 3C.3b were rarely detected.

Antigenic characteristics of A(H3N2) viruses were assessed with panels of post-infection ferret antisera in HI and virus neutralisation assays. Antigenic characterization of 3C.2a viruses continued to be technically challenging because many viruses had low or undetectable haemagglutination activity in the presence of oseltamivir carboxylate, added to circumvent agglutination by the virus neuraminidase. Virus neutralisation assays supplemented HI assays for the antigenic characterization of viruses. Most recent A(H3N2) 3C.2a viruses were well inhibited by ferret antisera raised against cell culture-propagated reference viruses in subclade 3C.2a including A/Hong Kong/4801/2014 or A/Michigan/15/2014. These antisera also inhibited a majority of viruses in subclades 3C.2a1 (including those with an additional N121K HA substitution), 3C.3a and 3C.3b.

Egg propagation is known to introduce additional changes in HA that can affect antigenicity. Such changes have been particularly problematic for recent A(H3N2) viruses. Ferret antisera raised against egg-propagated 3C.2a viruses, including A/Hong Kong/4801/2014, generally inhibited recently circulating viruses better than antisera raised against egg-propagated A/Switzerland/9715293/2013 virus or other recent egg-propagated viruses.

Human serology studies were performed using serum panels from adults and older adults who had received seasonal quadrivalent inactivated vaccines with the composition recommended for the southern hemisphere 2016 season (A/California/7/2009 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like, B/Brisbane/60/2008-like and B/Phuket/3073/2013-like antigens). Geometric mean HI titres of antibodies against representative recent A(H3N2) viruses were somewhat reduced compared to HI titres against the cell-propagated vaccine virus. In microneutralisation tests with a subset of serum panels and viruses, geometric mean titres of antibodies against recent representative A(H3N2) viruses were similar to those against the cell-propagated vaccine virus.

Influenza B viruses

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated at equivalent levels in some countries, while viruses of the B/Victoria/2/87 lineage predominated in many countries.

Almost all of the HA gene sequences of B/Victoria/2/87 lineage viruses fell into genetic clade 1A. In HI assays, recent viruses were well inhibited by post-infection ferret antisera raised against either B/Brisbane/60/2008 or B/Texas/2/2013 cell culture-propagated viruses. B/Brisbane/60/2008 was recommended for use in vaccines for the 2016-2017 northern hemisphere influenza season.

The HA gene sequences of the vast majority of B/Yamagata/16/88 lineage viruses fell into genetic clade 3. In HI assays, recently circulating B/Yamagata/16/88 lineage viruses were well inhibited by post-infection ferret antisera raised against the cell culture-propagated B/Phuket/3073/2013 virus (clade 3). B/Phuket/3073/2013 was recommended for use in quadrivalent vaccines for the 2016-2017 northern hemisphere influenza season.

Human serology studies were performed using serum panels from adults and older adults who had received seasonal quadrivalent inactivated vaccines of the composition recommended for the northern hemisphere 2015-2016 season (A/California/7/2009 (H1N1)pdm09-like, A/Switzerland/9715293/2013 (H3N2)-like, B/Phuket/3073/2013-like and B/Brisbane/60/2008-like antigens) or for the southern hemisphere 2016 season (A/California/7/2009 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like, B/Brisbane/60/2008-like and B/Phuket/3073/2013-like antigens). Geometric mean HI titres of antibodies against some representative recent B/Victoria/2/87 lineage viruses were reduced compared to HI titres against the cell-propagated vaccine virus B/Brisbane/60/2008. When tested against representative recent B/Yamagata/16/88 lineage viruses, geometric mean HI titres were reduced for some viruses compared to HI titres against the egg-propagated vaccine virus B/Phuket/3073/2013.

Resistance to influenza antiviral drugs

Neuraminidase inhibitors

The detection of viruses with reduced susceptibility to the neuraminidase inhibitors was very rare among the >9000 viruses tested during this reporting period.

Of >4000 influenza A(H1N1)pdm09 viruses tested for susceptibility to the neuraminidase inhibitors, 69 carried an H275Y amino acid substitution in neuraminidase which conferred highly reduced inhibition by oseltamivir and peramivir. Forty-one of these viruses were detected in Japan (41/1467; 2.8%) and sixteen were detected in the United States of America (16/2331; 0.7%). The majority of A(H1N1)pdm09 viruses carrying H275Y amino acid substitutions were from patients receiving oseltamivir treatment.

All of the A(H3N2) viruses tested were sensitive to neuraminidase inhibitors.

All but two influenza B/Yamagata/16/88 lineage viruses were sensitive to neuraminidase inhibitors. One virus carried an I221V amino acid substitution in neuraminidase that resulted in reduced peramivir inhibition, while the other contained an I348T amino acid substitution in neuraminidase that conferred reduced oseltamivir inhibition.

All but four of the influenza B/Victoria/2/87 lineage viruses were sensitive to neuraminidase inhibitors. Three viruses from Lao People's Democratic Republic carried an H134N amino acid substitution in neuraminidase and one virus from Malaysia carried a G104E amino acid substitution in

neuraminidase. Both substitutions conferred reduced or highly reduced inhibition by all four neuraminidase inhibitors – oseltamivir, zanamivir, peramivir and laninamivir.

M2 inhibitors

M gene sequencing of A(H1N1)pdm09 and A(H3N2) viruses revealed that all viruses analysed had S31N amino acid substitutions in their M2 proteins which is known to confer resistance to the M2 inhibitors, amantadine and rimantadine.

Recommended composition of influenza virus vaccines for use in the 2017 southern hemisphere influenza season

Influenza A(H1N1)pdm09 viruses, which predominated in many countries, co-circulated with A(H3N2) and influenza B viruses during the period February 2016 – August 2016.

Influenza A(H1N1)pdm09 viruses were associated with outbreaks in many countries. Influenza A(H1N1)pdm09 viruses were antigenically indistinguishable by post-infection ferret antisera but in studies with human post-vaccination sera representative 6B.1 and 6B.2 viruses were distinguishable from the A/California/7/2009 vaccine virus.

Influenza A(H3N2) viruses were associated with outbreaks in many countries. The majority of recent viruses were antigenically related to cell culture-propagated 3C.2a A/Hong Kong/4801/2014-like viruses.

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated, with viruses of the B/Victoria/2/87 lineage predominating in many countries. Most B/Victoria/2/87 lineage viruses were antigenically and genetically closely related to B/Brisbane/60/2008 and B/Texas/2/2013. The majority of recent B/Yamagata/16/88 lineage viruses were antigenically and genetically closely related to B/Phuket/3073/2013.

It is recommended that trivalent vaccines for use in the 2017 southern hemisphere influenza season contain the following:

- 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.

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

Lists of egg propagated candidate vaccine viruses (CVVs) suitable for use in vaccines produced in either eggs or cell culture, as well as cell culture-propagated CVVs suitable for use in vaccines produced in cell culture are available on the WHO website³. A list of reagents for vaccine standardization, including those for this recommendation, can also be found on the WHO website. CVVs for zoonotic influenza viruses are updated on the same website.

As in previous years, national or regional authorities approve the composition and formulation of vaccines used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine. WHO has published recommendations on the prevention of influenza⁴.

³ http://www.who.int/influenza/vaccines/virus/candidates_reagents/home

⁴ <http://www.who.int/wer/2012/wer8747.pdf>

Candidate vaccine viruses (including reassortants) and reagents for use in the laboratory standardization of inactivated vaccine may be obtained from:

- Immunobiology, Laboratories Branch, Medical Devices and Product Quality Division, Therapeutic Goods Administration, P.O. Box 100, Woden, ACT, 2606, Australia (fax: +61262328564, email: influenza.reagents@tga.gov.au; web site: <http://www.tga.gov.au>)
- Division of Virology, National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QG UK (fax: +441707641050, e-mail: enquiries@nibsc.org, web site: http://www.nibsc.org/science_and_research/virology/influenza_resource.aspx)
- Division of Biological Standards and Quality Control, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, Maryland, 20993, USA (fax: +1 301 480 9748), email: cbershippingrequests@fda.hhs.gov)
- Influenza Virus Research Center, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashi-Murayama, Tokyo 208-0011, Japan (fax: +81425616156, email: flu-vaccine@nih.go.jp)

Requests for reference viruses should be addressed to:

- WHO Collaborating Centre for Reference and Research on Influenza, VIDRL, Peter Doherty Institute, 792 Elizabeth Street, Melbourne, Victoria 3000, Australia (fax: +61393429329, web site: <http://www.influenzacentre.org>, email: whoflu@influenzacentre.org)
- WHO Collaborating Centre for Reference and Research on Influenza, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashi-Murayama, Tokyo 208-0011, Japan (fax: +81425616149 or +81425652498, email: whocc-flu@nih.go.jp)
- WHO Collaborating Centre for Surveillance, Epidemiology and Control of Influenza, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop G16, Atlanta, GA 30329, United States (fax: +14046390080, web site: <http://www.cdc.gov/flu/>, email: influenzavirussurveillance@cdc.gov)
- WHO Collaborating Centre for Reference and Research on Influenza, The Francis Crick Institute, 1 Midland Road, London NW1 1AT, UK (Tel: +44 203 796 1520 or +44 203 796 2444) (website: <http://www.crick.ac.uk/research/worldwide-influenza-centre> email: whocc@crick.ac.uk)
- WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Viral Disease Control and Prevention, China CDC, 155 Changbai Road, Changping District, 102206, Beijing, P.R. China. (tel: +86 10 5890 0851, fax: +86 10 5890 0851, email: whocc-china@cnic.org.cn, website: <http://www.cnic.org.cn/eng/>).

WHO provides fortnightly updates⁵ of the global influenza activity. Other information of influenza surveillance can be found on the WHO Global Influenza Programme website⁶.

Acknowledgements

The WHO recommendation on vaccine composition is based on the year-round work of the WHO Global Influenza Surveillance and Response System (GISRS). We thank the National Influenza Centres (NICs) of GISRS, and non-GISRS laboratories including the OIE/FAO Network of Expertise on Animal Influenza (OFFLU), who contributed information, clinical specimens, viruses and associated data; WHO Collaborating Centres of GISRS for their in-depth characterization and comprehensive analysis of viruses; University of Cambridge for performing antigenic cartography and phylogenetic analysis; WHO Essential Regulatory Laboratories of GISRS for their complementary virus analyses and contributions from a regulatory perspective; and laboratories involved in the production of high growth/yield reassortants as candidate vaccine viruses. We also acknowledge the Global Initiative for Sharing All Influenza Data (GISAID) for the EpiFlu database and other sequence databases which were used to share gene sequences and associated information; modelling groups for virus fitness forecasting; and the Global Influenza Vaccine Effectiveness (GIVE) Collaboration for sharing estimates of influenza vaccine effectiveness on a confidential basis.

⁵ http://www.who.int/influenza/surveillance_monitoring/updates/en/

⁶ <http://www.who.int/influenza>

Table 1: Haemagglutination inhibition assays of A(H1N1)pdm09 viruses

STRAIN DESIGNATION	Genetic Clade	Passage history	POST-INFECTION FERRET SERA							POST-VACCINATION HUMAN SERA*					
			EGG	MDCK	MDCK	MDCK	MDCK	MDCK	MDCK	2011/12	2013/14	2014/15	2015/16		
			CA/7	CA/7	MD/13	DR/7293	BL/559	MI/45	IA/53	A	B	C	D	E	F
A/California/7/2009	H1pdm09	E3	2560	2560	2560	2560	2560	2560	1280	640	640	320	640	160	640
A/California/7/2009	H1pdm09	C3	2560	2560	2560	1280	1280	2560	1280	320	640	320	320	320	640
A/Maryland/13/2012	6A	M1/C2	5120	2560	2560	1280	1280	2560	1280	320	640	160	160	160	640
A/Dominican Rep/7293/201	6C	C2	2560	2560	2560	2560	1280	2560	1280	320	1280	320	320	320	640
A/Bolivia/559/2013	6B	E5	2560	2560	2560	1280	1280	2560	1280	20	20	40	40	20	640
A/Bolivia/559/2013	6B	C2	5120	5120	5120	2560	2560	5120	1280	10	10	40	20	20	640
A/Michigan/45/2015	6B.1	E3	2560	5120	5120	2560	2560	5120	2560	80	40	80	640	10	1280
A/Michigan/45/2015	6B.1	M1/C3	2560	2560	2560	2560	2560	5120	2560	10	10	40	40	40	1280
A/Panama/318595/2016	6B.1	C2	1280	1280	2560	2560	1280	5120	1280	10	10	40	20	20	640
A/Iowa/53/2015	6B.2	E4	1280	1280	1280	1280	640	2560	1280	10	10	20	40	20	320
A/Iowa/53/2015	6B.2	C3	1280	1280	640	1280	640	2560	1280	10	10	20	10	20	160
A/Minnesota/32/2015	6B.2	C3	640	640	1280	1280	640	1280	1280	10	10	20	10	20	320

* Post vaccination pooled sera (A-D, F) or a single serum (E) from adults (birth years, 1961-83) vaccinated with TTV or QIV from the indicated seasons

Annex 1

Declarations of interest

The WHO recommendation on composition of influenza vaccines for the southern hemisphere 2017 influenza season was made through a technical consultation with relevant WHO Collaborating Centres on Influenza (CCs) and Essential Regulatory Laboratories (ERLs) of the WHO Global Influenza Surveillance and Response System.

In accordance with WHO policy, Directors and Experts of the relevant WHO CCs and ERLs, in their capacity as representatives of their respective institutions ("Advisers") completed the WHO form of Declaration of Interests for WHO Experts before being invited to the consultation. At the start of the consultation, the interests declared by the Advisers were disclosed to all consultation participants.

The Advisers declared the following personal current or recent (within the past 4 years) financial or other interests relevant to the subject of work:

Institution	Representative	Personal interest
WHO CC, CDC, Atlanta	Dr Jacqueline Katz	None
WHO CC, CNIC, Beijing	Dr Yuelong Shu	None
WHO CC, The Francis Crick Institute, London	Dr John McCauley	None
WHO CC, VIDRL, Melbourne	Dr Ian Barr	Shareholdings in significant amount of the company CSL Limited.
WHO CC, St Jude Children's Hospital, Memphis	Dr Richard Webby	None
WHO CC and ERL, NIID, Tokyo	Dr Takato Odagiri	None
WHO ERL, CBER, Silver Spring	Dr Zhiping Ye	None
WHO ERL, NIBSC, Potters Bar	Dr Othmar Engelhardt	None
WHO ERL, TGA, Canberra	Dr Mandvi Bharadwaj	None

Based on the WHO assessment of the interest declared by Dr Barr, it was concluded that Dr Barr should continue to serve as an Adviser, considering that the interest was disclosed at the beginning of the consultation, and that, in accordance with the conditions required of all WHO CC Melbourne staff, Dr Barr has agreed to refrain from acquiring additional shares in companies involved in influenza vaccine manufacture.

In view of the foregoing, Dr Barr participated in the consultation as an Adviser.