Recommended composition of influenza virus vaccines for use in the 2019 southern hemisphere influenza season

September 2018

WHO convenes technical consultations[1] in February and September each year to recommend viruses for inclusion in influenza vaccines[2] for the northern and southern hemisphere influenza seasons, respectively. This recommendation relates to the influenza vaccines for use in the southern hemisphere 2019 influenza season. A recommendation will be made in February 2019 relating to vaccines that will be used for the northern hemisphere 2019-2020 influenza season. For countries in tropical and subtropical regions, WHO recommendations on influenza vaccine composition (northern hemisphere or southern hemisphere) are available on the WHO Global Influenza Programme website[3].

Seasonal influenza activity

Between February and September 2018, influenza activity was reported globally, with influenza A(H1N1)pdm09, A(H3N2) and influenza B viruses co-circulating.

In the temperate zone of the northern hemisphere, influenza activity declined from February to April and remained at inter-seasonal levels in most countries. Influenza A(H1N1)pdm09 was the predominant type A in most countries in Europe, northern and western Africa and Asia. Influenza A(H3N2) was the predominant type A in northern Europe, North America and some countries in Asia. Influenza B viruses circulated in higher proportions than influenza A viruses in many countries in Europe. Influenza activity in northern Africa was high in several countries in February and March with widespread A(H1N1)pdm09 outbreaks in Algeria and A(H3N2) in Morocco.

Influenza activity in the tropical and subtropical region of Asia was high with regional/widespread outbreaks reported in South-East Asia. Influenza activity in tropical regions of South America was generally high with A(H1N1)pdm09, A(H3N2) and B outbreaks reported.

In the temperate zone of the southern hemisphere, influenza activity increased from March to June. In the southern cone of South America there was co-circulation of influenza A and B viruses, and in South Africa A(H1N1)pdm09 virus predominated with regional activity of influenza B virus reported later in the winter season. Influenza activity was low in Australia and New Zealand throughout this period.

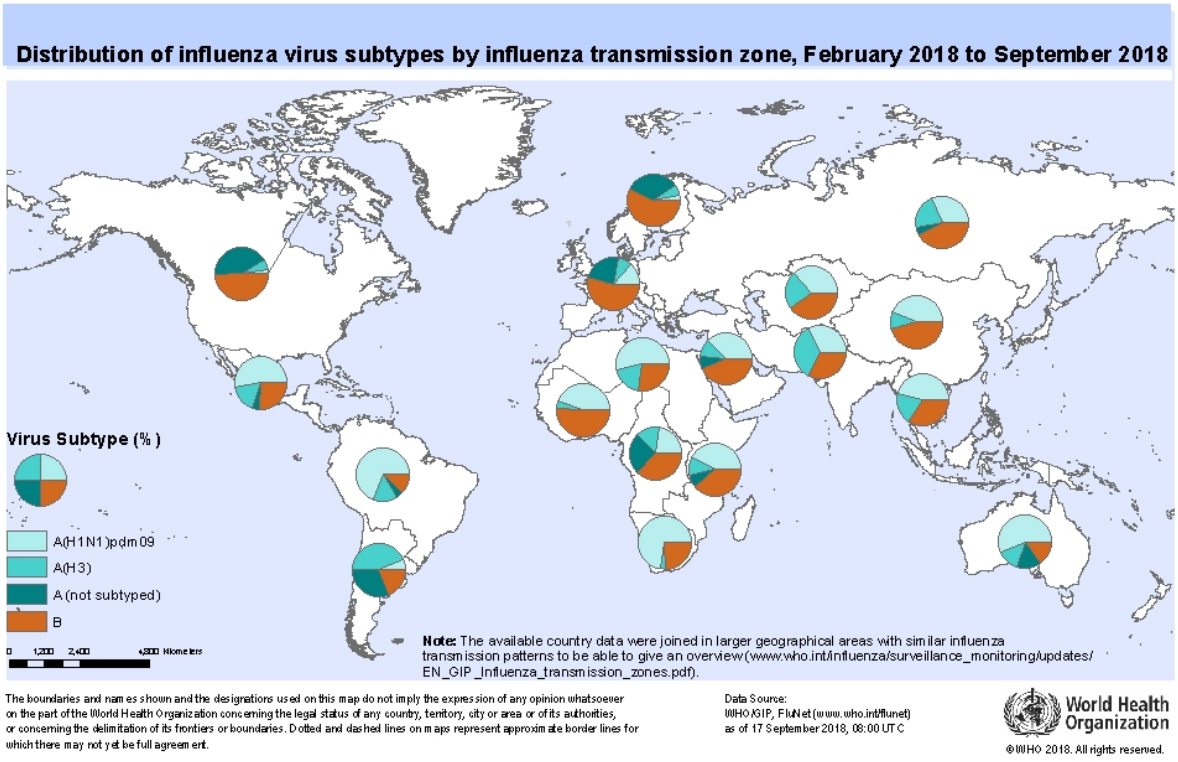
Influenza A

Influenza A viruses were predominant in most countries during this period, including countries in Africa, North America, central America, temperate and tropical South America and Oceania. Globally, co-circulation of both A(H1N1)pdm09 and A(H3N2) viruses was evident in all countries, areas and territories. Influenza A(H1N1)pdm09 viruses circulated in higher proportions in most countries in Africa, central, south-eastern and western Asia, tropical South America, central America, Oceania and the Caribbean. Influenza A(H3N2) viruses circulated in higher proportions in some countries in temperate regions of South America, southern Asia, North America and northern Europe.

[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
[3] Influenza in the tropics and sub-tropics: http://www.who.int/influenza/vaccines/tropics/en/

Influenza B

Influenza B viruses circulated in a higher proportion than influenza A viruses in most countries in Europe and western Asia, and in Canada. Globally, influenza B/Yamagata/16/88 lineage viruses predominated and B/Victoria/2/87 lineage viruses also circulated during this period.



Detailed information by country of the extent and type of seasonal influenza activity worldwide is available on the WHO website: http://www.who.int/influenza/resources/charts/en/

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

From 20 February to 24 September 2018, one human case of highly pathogenic avian influenza A(H5N6) virus infection was reported by China, where the virus is present in poultry. Since December 2003 a total of 880 human cases of avian influenza A(H5) virus infection with 460 deaths have been confirmed in 16 countries. To date there has been no evidence of sustained human-to-human transmission.

During this period, no human cases of avian influenza A(H7N9) virus infection were reported. Since February 2013, a total of 1567 cases with 615 deaths have been reported.

One human case of avian influenza A(H9N2) virus infection was reported by China during this period.

During this period, 13 cases of A(H1N2)v virus infection and one case of A(H3N2)v virus infection were reported by the United States of America.

Antigenic and genetic characteristics of recent seasonal influenza viruses

Influenza A(H1N1)pdm09 viruses

The vast majority of A(H1N1)pdm09 viruses had HA gene sequences that belonged to phylogenetic subclade 6B.1 and encoded the additional HA1 amino acid substitutions S74R, S164T and I295V. There is increasing genetic diversification of the HA genes of 6B.1 viruses with several genetic subgroups emerging, including those with HA1 amino acid substitutions of S183P, T120A or H138Y. The antigenic characteristics of A(H1N1)pdm09 viruses were assessed with post-infection ferret antisera in haemagglutination inhibition (HI) assays, which indicated that almost all recent A(H1N1)pdm09 viruses were antigenically indistinguishable from the vaccine virus, egg-propagated A/Michigan/45/2015, and its cell culture-propagated equivalent.

Human serology studies used serum panels from children, adults and elderly adults who had received trivalent or quadrivalent inactivated vaccines, either of the composition recommended for the northern hemisphere 2017-2018 season (A/Michigan/45/2015 (H1N1)pdm09-like, A/Hong Kong/4801/2014 (H3N2)-like and B/Brisbane/60/2008-like viruses in trivalent vaccines, with B/Phuket/3073/2013-like viruses included in quadrivalent vaccines) or that recommended for the southern hemisphere 2018 season (A/Michigan/45/2015 (H1N1)pdm09-like, A/Singapore/INFIMH-16-0019/2016 (H3N2)-like and B/Phuket/3073/2013-like viruses in trivalent vaccines, with B/Brisbane/60/2008-like viruses included in quadrivalent vaccines).

Haemagglutination inhibition geometric mean titres (GMTs) of post-vaccination antibodies against some recent representative cell culture-propagated A(H1N1)pdm09 viruses were significantly reduced compared to HI titres to the cell culture- or egg-propagated reference virus A/Michigan/45/2015; however, for the majority of viruses tested post-vaccination GMTs were not reduced significantly.

Influenza A(H3N2) viruses

The majority of A(H3N2) viruses collected from February to September 2018 belonged to the phylogenetic clade 3C.2a. There has continued to be considerable genetic diversification of the HA and NA genes of viruses within this clade. Viruses in subclades 3C.2a1b or 3C.2a2 were most common, with subclade 3C.2a2 predominating. Viruses in clade 3C.3a continued to be detected at low levels in several parts of the world.

Antigenic characterisation of clade 3C.2a viruses continued to be technically difficult because a large proportion of viruses did not agglutinate red blood cells, preventing HI analysis of such viruses. Virus neutralisation assays have become the preferred method for determining the antigenic characteristics of A(H3N2) viruses.

Most recent A(H3N2) viruses were well inhibited by ferret antisera raised against cell culture-propagated reference viruses in clade 3C.2a including A/Singapore/INFIMH-16-0019/2016. In contrast, a significantly lower proportion of A(H3N2) viruses was inhibited well by ferret antisera raised against egg-propagated A/Singapore/INFIMH-16-0019/2016. HI and virus neutralisation assays with ferret antiserum panels showed that viruses in clades 3C.2a and 3C.3a were antigenically distinguishable and those in subclades 3C.2a1b and 3C.2a2 were also antigenically distinct (Table 1).

Human serology studies, using the serum panels described above, showed that HI GMTs of post-vaccination antibodies against many cell culture-propagated and some egg-propagated A(H3N2) viruses were reduced significantly compared to GMTs against the egg-propagated vaccine virus A/Singapore/INFIMH-16-0019/2016. When compared to results for cell culture-propagated A/Singapore/INFIMH-16-0019/2016, cell culture-propagated viruses did not show significant reductions in HI GMTs. In virus neutralisation tests, using the same serum panels, all cell culture-propagated A(H3N2) viruses tested showed significant reductions in GMTs when compared to GMTs against egg-propagated A/Singapore/INFIMH-16-0019/2016. Some of these viruses also showed significant reductions in GMTs when compared to GMTs against cell culture-propagated A/Singapore/INFIMH-16-0019/2016.

Table 1. Antigenic analysis of influenza A(H3N2) viruses - Plaque Reduction Neutralisation (MDCK-SIAT)

Viruses	Passage history Ferret number Genetic group	Passage History	Neutralisation titre Post-infection ferret antisera A/Singapore/ INFIMH-16-0019/16 EGG 10^{-4} F41/17 3C.2a1 2-fold	A/Singapore/ INFIMH-16-0019/16 SIAT F45/17 3C.2a1 2-fold	A/Hong Kong/ 656/18 SIAT F25/18 3C.2a2 2-fold	A/Switzerland/ 8060/17 Egg F27/18 3C.2a2 2-fold
REFERENCE VIRUSES						
A/Singapore/INFIMH-16-0019/2016	3C.2a1	E5/E2 10^{-4}	2560	160	160	160
A/Singapore/INFIMH-16-0019/2016	3C.2a1	MDCK1/SIAT3/SIAT3	80	1280	160	80
A/Hong Kong/656/2018	3C.2a2	MDCK1/SIAT1 10^{-1}	40	640	2560	2560
A/Switzerland/8060/2017	3C.2a2	E6(Am2Al4)c57 10^{-5}	1280	320	5120	5120
TEST VIRUSES						
A/Belgium/S0846/2018	3C.2a1b	SIATx/SIAT1	<[1]	320	40	<
A/Vologda/RII-01/2018	3C.2a1b	MDCK1/SIAT1	40	160	40	<
A/Madrid/2172/2018	3C.2a1b	SIAT1	<	640	40	<
A/Iceland/90/2018	3C.2a1b	MDCK1/SIAT1	<	320	40	<
A/Belgium/S0428/2018	3C.2a2	SIATx/SIAT1	<	320	1280	1280
A/Belgium/G0278/2018	3C.2a2	SIATx/SIAT1	<	640	2560	2560
A/Lisboa/20/2018	3C.2a2	MDCK1/SIAT1	40	1280	2560	1280
A/Iceland/71/2018	3C.2a2	MDCK1/SIAT1	40	640	1280	1280
A/Mauritius/2263/2018	3C.2a2	SIAT1	80	1280	2560	2560
			Vaccine southern hemisphere 2018			

[1] Titres <10

Influenza B viruses

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated but those of the B/Yamagata lineage predominated globally. All available HA gene sequences of B/Yamagata lineage viruses belonged to genetic clade 3. In HI assays the vast majority of recently circulating B/Yamagata lineage viruses were well inhibited by post-infection ferret antisera raised against cell culture- and egg-propagated B/Phuket/3073/2013 viruses.

The HA gene sequences of the B/Victoria lineage viruses characterised belonged to genetic clade 1A; a steadily increasing proportion of viruses from many countries had a two amino acid deletion in HA (amino acids 162 and 163). During this period, 13 viruses from five countries were identified with a three amino acid deletion in HA (amino acids 162-164). Recent viruses without HA amino acid deletions were well inhibited by post-infection ferret antisera raised against B/Brisbane/60/2008-like cell culture-propagated viruses in HI assays, but viruses with HA amino acid deletions were poorly inhibited by these antisera. The great majority of viruses with the deletion of two amino acids in HA reacted well with ferret antisera raised against both egg- and cell culture-propagated B/Colorado/06/2017-like viruses. However, viruses with the three amino acid deletion in HA reacted poorly with these ferret antisera.

Human serology studies, using the serum panels described above, showed moderate reductions in post-vaccination HI GMTs against representative recent viruses of the B/Victoria lineage with two or three amino acid deletions in HA when compared to egg- or cell culture-propagated B/Brisbane/60/2008-like reference viruses. Post-vaccination HI GMTs against most recent B/Yamagata lineage viruses were similar to, or somewhat reduced compared to those against cell culture-propagated B/Phuket/3073/2013-like reference viruses.

Resistance to influenza antiviral drugs

NA inhibitors

The detection of viruses with reduced susceptibility to the NA inhibitors was very rare among the 4801 viruses tested by the WHO Collaborating Centres[4] during this reporting period.

A(H1N1)pdm09
Of 1874 influenza A(H1N1)pdm09 viruses tested, 13 showed highly reduced inhibition (HRI) by one or more NA inhibitors. All 13 viruses, from Bosnia and Herzegovina, China, France, Mexico or the United States of America, carried an NA H275Y amino acid substitution.

A(H3N2)
Of 936 influenza A(H3N2) viruses tested, four showed reduced inhibition by one or more NA inhibitors. One was from Canada and carried an NA E119V amino acid substitution resulting in HRI by oseltamivir, one from Estonia showed an NA S334R substitution resulting in reduced inhibition (RI) by oseltamivir, one from Australia showed polymorphism at NA residue 224 (R224X: RI by four NA inhibitors) and another from Australia carried two substitutions in the NA (V303I, N342K) resulting in RI by oseltamivir and zanamivir.

Influenza B
Of the 485 influenza B/Victoria lineage viruses tested, seven viruses demonstrated reduced inhibition by NA inhibitors. One virus from Canada carried an NA A245T amino acid substitution that conferred HRI by zanamivir. Four viruses from the United States of America contained NA D197E or G247D amino acid substitutions and two viruses from Ukraine contained an NA D197N substitution, all of which conferred RI by one or more of the NA inhibitors.

[4] http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/

Of the 1506 B/Yamagata lineage viruses tested, eight viruses demonstrated RI by NA inhibitors. Three viruses from the United States of America and one each from Australia, Belgium, China, China Hong Kong Special Administrative Region and Russian Federation carried NA I221T, R154K, D197N, R150K or T436P amino acid substitutions, all of which conferred RI by one or more of the NA inhibitors.

Polymerase inhibitor

Sensitivity to baloxavir marboxil, now licensed for use in Japan, was assessed for representative viruses collected there. Of 10 influenza A(H1N1)pdm09, 15 A(H3N2), one B/Victoria lineage and 16 B/Yamagata lineage viruses, none showed reduced susceptibility to baloxivir marboxil.

Recommended composition of influenza virus vaccines for use in the 2019 southern hemisphere influenza season

There was considerable variation in the predominant virus type circulating in different regions during the period February to September 2018. Influenza A(H1N1)pdm09 viruses predominated in many countries, while A(H3N2) viruses predominated in some and influenza B viruses circulated widely in most parts of the world.

The vast majority of influenza A(H1N1)pdm09 viruses belonged to genetic subclade 6B.1 and were antigenically indistinguishable from the vaccine virus A/Michigan/45/2015.

Influenza A(H3N2) viruses were associated with outbreaks in several countries. The majority of recent viruses were inhibited well by ferret antisera raised against cell culture-propagated A/Singapore/INFIMH-16-0019/2016-like viruses. In contrast, ferret antisera raised against egg-propagated A/Singapore/INFIMH-16-0019/2016-like viruses inhibited a smaller proportion of recently circulating viruses. Ferret antiserum raised against egg-propagated A/Switzerland/8060/2017 inhibited the majority of viruses tested from the predominating subclade 3C.2a2.

Influenza B viruses of the B/Yamagata lineage predominated in most regions of the world. Recent B/Yamagata lineage viruses were antigenically and genetically closely related to the vaccine virus B/Phuket/3073/2013. Influenza B viruses of the B/Victoria lineage were detected in low numbers but a substantial and increasing proportion of these viruses, containing a two amino acid deletion in the HA, were antigenically different from B/Brisbane/60/2008-like vaccine viruses but closely related to B/Colorado/06/2017-like viruses.

It is recommended that egg based quadrivalent 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;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

It is recommended that egg based trivalent 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).

It is recommended 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 vaccine components as indicated above.

Lists of egg- or cell culture-propagated candidate vaccine viruses (CVVs) suitable for use in human vaccine production are available on the WHO website[5]. A list of reagents for vaccine standardisation, including those for this recommendation, can also be found on the WHO website. CVVs for zoonotic influenza viruses are listed 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 influenza[6].

CVVs (including reassortants) and reagents for use in the laboratory standardisation of inactivated vaccines 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@health.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, 4-7-1 Gakuen, 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, 4-7-1 Gakuen, 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/).

[5] http://www.who.int/influenza/vaccines/virus/candidates_reagents/home
[6] http://www.who.int/wer/2012/wer8747.pdf

WHO provides fortnightly updates[7] of global influenza activity. Other information about influenza surveillance can be found on the WHO Global Influenza Programme website[8].

Acknowledgements

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[7] http://www.who.int/influenza/surveillance_monitoring/updates/en/
[8] http://www.who.int/influenza

Annex 1

Declarations of interest

The WHO recommendation on the composition of influenza vaccines for use in the southern hemisphere influenza season 2019 was made through a WHO Consultation with relevant WHO Collaborating Centres on Influenza (CCs) and Essential Regulatory Laboratories (ERLs).

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 for 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 Atlanta	Dr Jacqueline Katz	None
WHO CC Beijing	Dr Dayan Wang	None
WHO CC London	Dr John McCauley	None
WHO CC Melbourne	Dr Kanta Subbarao	• Being co-owner with NIH of a patent: Influenza Hemagglutinin and Neuraminidase Variants, US Patent Number: 7,504,109 B2, 17 March 2009. The patent is current, but being abandoned as agreed by all owners. No benefit generated or expected from it. • Received travel support and honorarium from BMGF/IMSSM, FLUCOP and BMGF/TSRI being as Member of their Scientific Advisory Boards on universal influenza vaccine development, development of assays for influenza vaccine correlates of protection and next generation vaccine immunogens. This is current. • Being Principle Investigator of a CRADA with MedImmune on the development of live attenuated vaccines against pandemic influenza. No funding received. It ceased in Nov 2016.
WHO CC Memphis	Dr Richard Webby	In 2016 received US$500 from HHS/BARDA US being its Scientific Advisor.
WHO CC and ERL NIID Tokyo	Dr Takato Odagiri	None
WHO ERL CBER Bethesda	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 Subbarao, it was concluded that with disclosure at the beginning of the consultation to all participants, Dr Subbarao should continue to serve as an Adviser.

The interest declared by Dr Webby was reviewed by WHO and determined not to present a conflict of interest with the objectives of the WHO consultation. Therefore Dr Webby participated in the consultation as an Adviser.