Recommended composition of influenza virus vaccines for use in the 2019-2020 northern hemisphere influenza season

February 2019

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 forthcoming northern hemisphere 2019-2020 influenza season. A recommendation will be made in September 2019 relating to vaccines that will be used for the southern hemisphere 2020 influenza season. For countries in tropical and sub-tropical regions, WHO guidance for choosing between the northern and southern hemisphere formulations is available on the WHO Global Influenza Programme website[3].

Seasonal influenza activity, September 2018 – January 2019

Between September 2018 and January 2019, 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 remained at inter-seasonal levels until November, when it started to increase. In Europe overall influenza activity remained low in most countries, but started to increase sharply in several countries from mid to late January. Countries in eastern Asia (e.g. China, Japan, Mongolia and Republic of Korea) experienced high influenza activity which peaked mostly in January. In some countries in western Asia including Qatar and Saudi Arabia influenza activity was high between October and January with A(H1N1)pdm09 activity widespread. Influenza A viruses circulated in far greater numbers than influenza B viruses. Among subtyped influenza A viruses, A(H1N1)pdm09 was the predominant subtype in most reporting countries in Europe, North America, and eastern and western Asia. Influenza A(H3N2) was predominant in most countries in northern Africa and some countries in Europe and Asia.

Influenza activity in the tropical and subtropical regions of Asia was high in some countries, with regional outbreaks reported in Lao PDR and India, predominantly due to A(H1N1)pdm09. Influenza activity in most tropical countries of central America, the Caribbean and South America was generally low, with A(H1N1)pdm09, A(H3N2) and type B viruses co-circulating. High influenza A(H1N1)pdm09 activity was reported in Haiti and Nicaragua. For the countries in the tropical and subtropical zone of Africa, influenza A(H1N1)pdm09 was predominant in Senegal, while A(H3N2) was predominant in Burkina Faso, Cameroon, Central African Republic, Kenya, Mauritius, and Togo.

In the temperate zone of the southern hemisphere, influenza activity was generally low in most countries during this period and remained at inter-seasonal levels between late September and January. In countries in the temperate zone of South America there was co-circulation of influenza types A and B viruses. Influenza A(H1N1)pdm09 was predominant in Argentina, while A(H3N2) was predominant in Chile and Paraguay. In southern Africa influenza type B detections predominated, mostly of the B/Victoria/2/87 lineage. Influenza activity was generally low in Australia and New Zealand and below seasonal thresholds throughout this period with influenza A(H1N1)pdm09 viruses predominating. Some parts of Australia reported influenza A(H1N1)pdm09 and A(H3N2) activity at higher than usual inter-seasonal levels from November 2018 through January 2019.

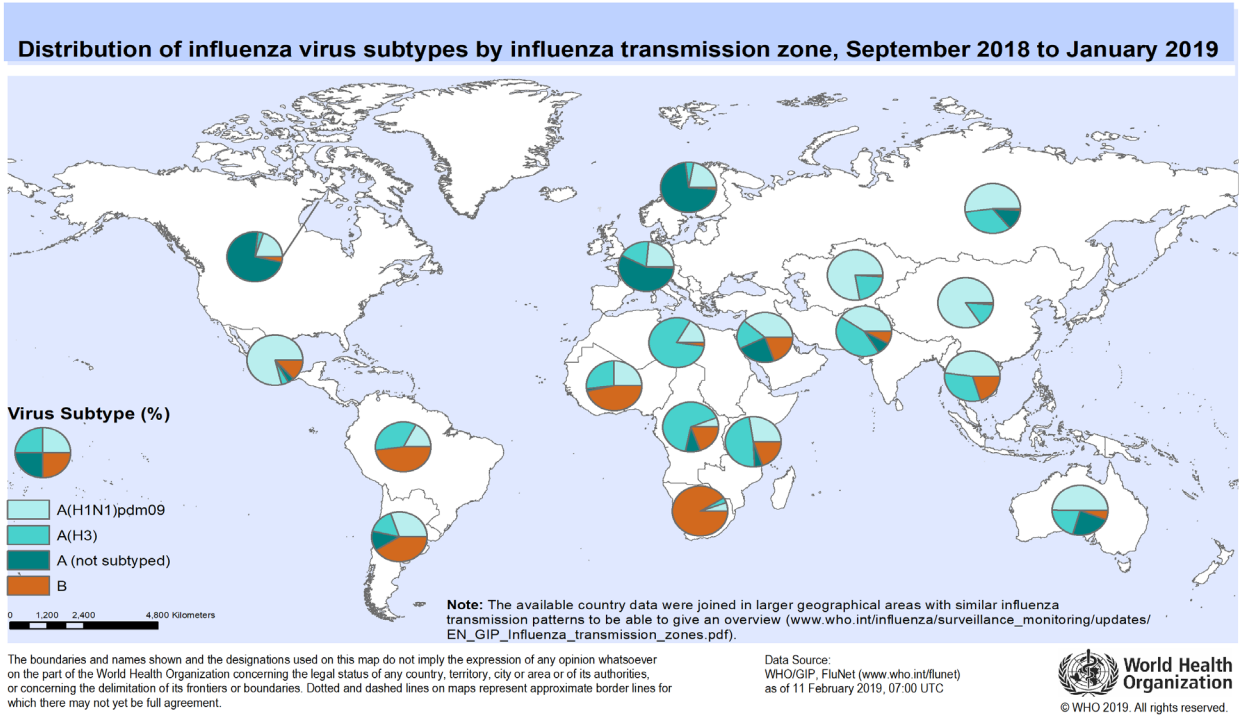
[1] http://www.who.int/influenza/vaccines/virus/en/
[2] Description of the process of influenza vaccine virus selection and development available at: http://www.who.int/gb/pip/pdf_files/Fluvaccvirusselection.pdf
[3] Influenza in the tropics and sub-tropics: http://www.who.int/influenza/vaccines/tropics/en/

Influenza A

Influenza A viruses were predominant in most countries and accounted for 95% of all influenza viruses detected. Globally, co-circulation of both A(H1N1)pdm09 and A(H3N2) viruses was evident in all countries, areas and territories. Influenza A(H1N1)pdm09 was predominant in most reporting countries in North America, Europe, Central America, Asia and Oceania. Influenza A(H3N2) viruses circulated in greater proportions compared to influenza A(H1N1)pdm09 in several countries in Africa and some countries in Asia (e.g. Islamic Republic of Iran). In Europe, A(H3N2) was predominant in Belgium, France, Lithuania, Luxembourg, Turkey, and Ukraine.

Influenza B

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated at low levels globally. Viruses of the two lineages were detected in similar numbers overall, but their relative proportions varied by region.



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) and A(H3N2)v viruses

From 25 September 2018 to 17 February 2019, three human cases of highly pathogenic avian influenza A(H5N6) virus infection were reported by China, where the virus is present in poultry. Since December 2003, a total of 883 human cases of avian influenza A(H5) virus infection with 462 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 March 2013, a total of 1567 cases of avian influenza A(H7N9) virus infection with 615 deaths have

been reported. Five human cases of avian influenza A(H9N2) virus infection were reported by China during this period and one case of A(H3N2)v virus infection was reported by Australia.

Antigenic and genetic characteristics of recent seasonal influenza viruses, serology and antiviral susceptibility

Influenza A(H1N1)pdm09 viruses

The vast majority of A(H1N1)pdm09 viruses had haemagglutinin (HA) gene sequences that belonged to phylogenetic subclade 6B.1 and encoded the additional HA1 amino acid substitutions of S74R, S164T and I295V, defining subclade 6B.1A. Within this subclade there has been increasing genetic diversity of the HA genes with several genetic subgroups emerging. Viruses with the HA1 amino acid substitution of S183P (such as A/Brisbane/02/2018) are currently predominating globally. The antigenic characteristics of A(H1N1)pdm09 viruses, assessed with post-infection ferret antisera in haemagglutination inhibition (HI) assays, indicated that almost all recent A(H1N1)pdm09 viruses were antigenically like the vaccine virus, egg-propagated A/Michigan/45/2015, and its cell culture-propagated equivalent. However, assays with some post-vaccination paediatric sera showed reduced HI titers against recent 6B.1A viruses with the HA1 amino acid substitution of S183P compared with titers against cell culture- and egg-propagated A/Michigan/45/2015 viruses (Table 1).

Human serology studies used serum panels from children, adults and elderly adults who had received either trivalent or quadrivalent inactivated vaccines with the composition recommended for the northern hemisphere 2018-2019 season (A/Michigan/45/2015 (H1N1)pdm09-like, A/Singapore/INFIMH-16-0019/2016 (H3N2)-like, B/Colorado/06/2017-like viruses in trivalent vaccines, with B/Phuket/3073/2013-like viruses included in quadrivalent vaccines). Geometric mean HI titres against many recent representative cell culture-propagated A(H1N1)pdm09 viruses with the HA1 amino acid substitution of S183P were reduced compared to HI titres to the cell culture-propagated reference virus A/Michigan/45/2015; reductions were more pronounced when measured against the egg-propagated vaccine virus.

Of 3192 influenza A(H1N1)pdm09 viruses tested for neuraminidase inhibitor (NAI) susceptibility, 16 showed reductions in susceptibility to one or more of the inhibitors. Fourteen viruses from seven countries carried an H275Y amino acid substitution in the NA, which conferred highly reduced inhibition by oseltamivir and peramivir. Two other A(H1N1)pdm09 viruses from the United States of America carried either S247N or I223M amino acid substitution in the neuraminidase (NA), which conferred reduced inhibition by oseltamivir. The NAI treatment status of the patients from which these 16 viruses were collected is unknown. One hundred and forty-seven A(H1N1)pdm09 viruses were tested for susceptibility to the endonuclease inhibitor baloxavir, with one virus from a treated child in Japan having a mixture of I38T and I38F amino acid substitutions in the PA protein that are known to confer reduced susceptibility to this inhibitor.

Table 1. Antigenic Analysis of A(H1N1)pdm09 - haemagglutination inhibition assay

		Ferret antisera		Post-vaccination human sera				
		6B.1		Individual paediatric post-vaccination serum				Pooled adult post-vacc. human sera
		EGG	MDCK	2018/2019 Season				
				6-35 month		9-16 year		
REFERENCE VIRUSES	HA subclade	MI/45	MI/45	3001539171	3001539098	3001539264	3001539653	
A/Michigan/45/2015 (egg)	6B.1	**2560**	2560	320	160	160	80	640
A/Michigan/45/2015 (MDCK)	6B.1	2560	**2560**	80	80	80	80	320
TEST VIRUSES								
A/Hawaii/56/2018	6B.1A	2560	2560	40	40	40	80	320
A/Montana/35/2018	6B.1A	2560	2560	40	20	40	40	320
A/Idaho/07/2018	6B.1A + 183P	2560	2560	40	20	40	40	320
A/Louisiana/18/2018	6B.1A + 183P	2560	2560	20	10	20	20	160
A/Maryland/46/2018	6B.1A + 183P	1280	2560	20	10	20	40	160
A/New Jersey/13/2018	6B.1A + 183P	1280	2560	20	10	20	40	160
A/El Salvador/589/2018	6B.1A + 183P	2560	2560	20	10	20	40	160
A/El Salvador/630/2018	6B.1A + 183P	1280	2560	20	10	10	20	160
A/Wisconsin/496/2018	6B.1A + 183P	2560	2560	20	10	20	40	160
A/Washington/182/2018	6B.1A + 183P	1280	2560	20	10	20	40	160
A/North Dakota/31/2018	6B.1A + 183P	1280	2560	20	10	10	20	160
A/South Dakota/45/2018	6B.1A + 183P	1280	2560	20	10	10	20	160
A/Utah/46/2018	6B.1A + 183P	2560	2560	20	10	20	20	160
A/Wisconsin/505/2018	6B.1A + 183P	2560	2560	20	20	20	40	160
A/Iowa/59/2018	6B.1A + 183P	1280	2560	10	10	20	20	160
A/Wisconsin/516/2018	6B.1A + 183P	2560	2560	10	10	20	20	160
A/California/76/2018	6B.1A + 183P	160	320	10	<10	10	10	160
A/Pennsylvania/511/2018	6B.1A + 183P	80	80	10	10	10	20	160

Influenza A(H3N2) viruses

The majority of A(H3N2) viruses collected from September 2018 to January 2019 belonged to the phylogenetic subclade 3C.2a1b; however, the number of clade 3C.3a viruses has increased substantially since November 2018 in several geographic regions. There has continued to be considerable genetic diversification of the HA and NA genes, but viruses in subclade 3C.2a2 were much less prevalent than in the previous reporting period.

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 current A(H3N2) viruses.

Most recent A(H3N2) viruses in clade 3C.2a were well inhibited by post-infection 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 post-infection ferret antisera raised against both egg-propagated A/Singapore/INFIMH-16-0019/2016 (3C.2a1) and A/Switzerland/8060/2017 (3C.2a2) viruses. HI and virus neutralisation assays with post-infection 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. 3C.3a viruses were well inhibited by ferret antisera raised against recent 3C.3a cell culture-propagated reference viruses, but were antigenically distinct from previously circulating 3C.3a viruses, such as A/Switzerland/9715293/2013.

Human serology studies, using the serum panels described above, showed that geometric mean HI titres of antibodies against egg-propagated A(H3N2) viruses were similar to HI titres against the egg-propagated vaccine virus A/Singapore/INFIMH-16-0019/2016 with the exception of viruses from clade 3C.3a which showed significant reductions in HI titres. In virus neutralisation tests, geometric mean neutralisation titres against all cell culture-propagated A(H3N2) viruses were reduced significantly compared to egg-propagated A/Singapore/INFIMH-16-0019/2016. When compared to cell culture-propagated A/Singapore/INFIMH-16-0019/2016, only clade 3C.3a viruses showed significant reductions in neutralisation titres.

Of 1039 influenza A(H3N2) viruses tested, one virus from the Republic of Korea, from a patient with unknown treatment status, showed reduced inhibition by oseltamivir due to a S331R amino acid substitution in the NA. One hundred and sixteen A(H3N2) viruses were assessed for susceptibility to baloxavir by genetic and phenotypic analysis, with five viruses from treated children in Japan containing either I38T or I38T/M amino acid substitutions in the PA which are known to confer reduced baloxavir susceptibility.

Influenza B viruses

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages were detected in small numbers overall and their relative proportions varied between reporting countries.

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- or egg-propagated B/Phuket/3073/2013 viruses.

The HA gene sequences of the B/Victoria lineage viruses characterised belonged to genetic clade 1A, but there was a significant increase in their diversity. Viruses without HA amino acid deletions, viruses with a two amino acid deletion in HA (amino acids 162 and 163) and an increasing proportion of viruses with a three amino acid deletion in HA (amino acids 162-164) were detected in many countries. The great majority of viruses with the deletion of two amino acids in HA reacted well with post-infection ferret antisera raised against both egg- and cell culture-propagated B/Colorado/06/2017-like viruses.

However, recent viruses with the three amino acid deletion in HA and those without HA amino acid deletions were less well inhibited by these antisera.

Human serology studies, using the serum panels described above, showed only minor reductions in post-vaccination HI geometric mean titres against representative recent B/Yamagata lineage viruses when compared to the cell culture-propagated B/Phuket/3073/2013 reference virus. Post-vaccination HI geometric mean titres against recent viruses of the B/Victoria lineage representing the three major genetic groups with three, two or no amino acid deletions in the HA showed only small to medium reductions when compared to egg- or cell culture-propagated B/Colorado/06/2017 reference viruses.

Of the 437 influenza B viruses tested for NAI susceptibility, and the 40 tested for baloxavir susceptibility, none demonstrated reduced susceptibility.

Recommended composition of influenza virus vaccines for use in the 2019-2020 northern hemisphere influenza season

During the period of September 2018 to January 2019, influenza A viruses predominated globally. Influenza A(H1N1)pdm09 virus was predominant in North America, most countries of Europe, Central America, Asia and Oceania, while A(H3N2) virus was predominant in several countries in Africa and some Asian countries. Both subtypes of influenza A viruses co-circulated in some European countries. Among influenza B viruses, both lineages were detected but overall numbers were very low.

The vast majority of influenza A(H1N1)pdm09 viruses belonged to genetic subclade 6B.1A and were antigenically indistinguishable from the vaccine virus A/Michigan/45/2015 using post-infection ferret antisera but were distinguishable in studies with post-vaccination human sera.

Influenza A(H3N2) viruses circulated globally, predominating in most countries in Africa and some countries in Europe and Asia. The majority of recent viruses were inhibited well by post-infection 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 and egg-propagated A/Switzerland/8060/2017-like viruses inhibited a much smaller proportion of recently circulating viruses. 3C.3a viruses, which have been increasing in prevalence since November 2018, were poorly inhibited by post-infection ferret antisera raised to clade 3C.2a reference viruses but were well inhibited by ferret antisera raised against recent 3C.3a cell culture-propagated reference viruses.

Influenza B viruses of the B/Victoria/2/87 and the B/Yamagata/16/88 lineages co-circulated at low levels globally in similar numbers overall, though their relative proportions varied between reporting countries. Recent B/Yamagata/16/88 lineage viruses were antigenically and genetically closely related to the vaccine virus B/Phuket/3073/2013. Influenza B viruses of the B/Victoria/2/87 lineage containing no deletion in their HAs and viruses containing a two amino acid deletion or a three amino acid deletion in their HAs co-circulated in several countries. Most of the viruses with a deletion of two amino acids in the HA reacted well with post-infection ferret antisera raised against B/Colorado/06/2017, but viruses without a deletion in the HA and viruses with a deletion of three amino acids in the HA reacted less well with these antisera. In contrast, post-vaccination sera from humans vaccinated with B/Colorado/06/2017 reacted similarly with representative B/Victoria lineage viruses with three, two or no amino acid deletions in the HA.

It is recommended that quadrivalent vaccines for use in the 2019-2020 northern hemisphere influenza season contain the following:

- an A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- an A(H3N2) virus to be announced on 21 March 2019*;
- 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 the influenza B virus component of trivalent vaccines for use in the 2019-2020 northern hemisphere influenza season be a B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage.

*** In light of recent changes in the proportions of genetically and antigenically diverse A(H3N2) viruses, the recommendation for the A(H3N2) component has been postponed.**

Lists of egg- or cell culture-propagated candidate vaccine viruses (CVVs) suitable for use in human vaccine production are available on the WHO website[4]. 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[5].

CVVs (including reassortants) and reagents for use in the laboratory standardisation of inactivated vaccines may be obtained from:

- Biomedicines and Influenza Vaccines Section, 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

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

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 updates[6] of global influenza activity. Other information about influenza surveillance can be found on the WHO Global Influenza Programme website[7].

Acknowledgements

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

Annex 1

Declarations of interest

The WHO recommendation on the composition of influenza vaccines for use in the northern hemisphere influenza season 2019-2020 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 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 ceased in 2018. No benefit generated or expected from it.
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 London	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. Therefore, Dr Subbarao participated in the consultation 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.