Influenza Updates

The newsletter of the WHO Collaborating Centre for Reference and Research on Influenza in Melbourne

@WHOCCFluMelb

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Preparation for the upcoming influenza season

Winter and the influenza season is fast approaching over the next few months across many southern hemisphere countries. In fact, in Australia, the 2022 influenza season has started earlier than usual, with a big increase in cases in April and early May. Most of these cases are influenza A(H3N2), along with many A(H1N1)pdm09 infections seen in children. This means that any sample you are able to send to us will be vital in our continued surveillance efforts.

With this in mind, please note the following points:

- Please send us your samples as soon as possible after collection, as they are most useful when they have been collected recently
- We accept both viral isolates and/or original clinical specimens
- We need to receive samples by the end of August at the very latest (and preferably earlier) in order to process them in time for the Consultation.
- The WHO Shipping Fund Project (SFP) is available to assist National Influenza Centres in covering the cost of shipping samples to WHO Collaborating Centres up to four times per year. It is recommended that one of the shipments be in July to mid-August. If you have any questions about shipping samples or would like information about accessing the WHO Shipping Fund, please contact us at whoflu@influenzacentre.org.

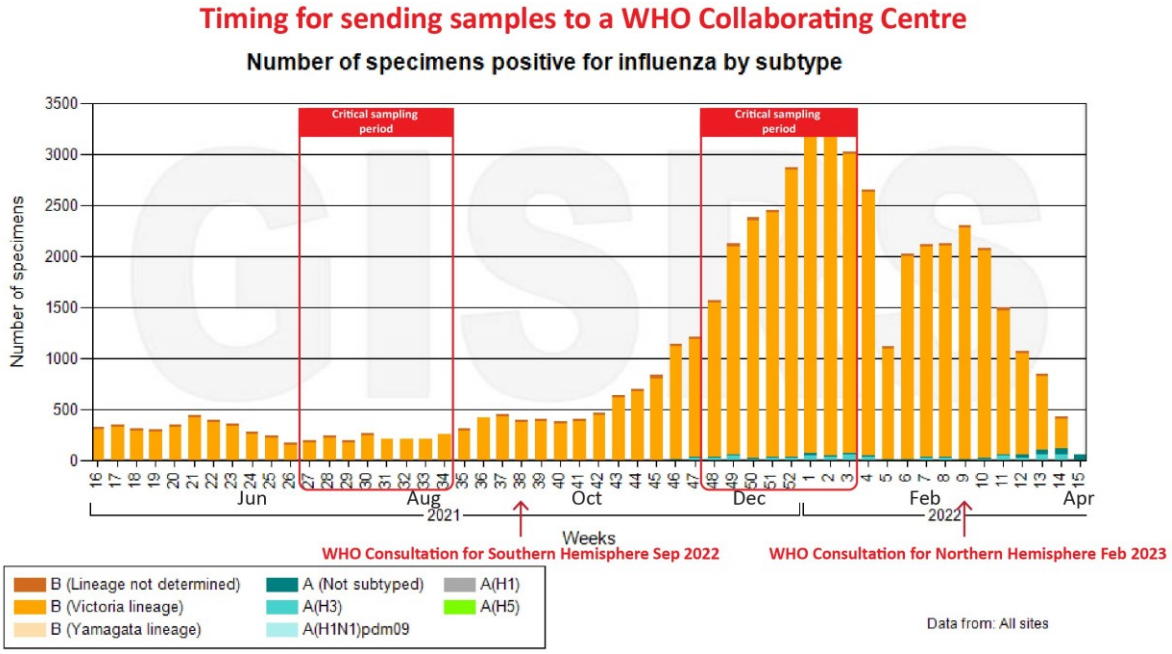


Figure adapted from FluNet: https://apps.who.int/flumart/Default?ReportNo=3&WHORegion=

WHO Collaborating Centre for Reference and Research on Influenza VIDRL

Doherty Institute

The University of Melbourne

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Recommendations for Northern Hemisphere 2022-2023 vaccine announced

The WHO Consultation on the Composition of Influenza Vaccines for the northern hemisphere 2022-2023 was held as a hybrid Consultation on 25 February 2022. Following the Consultation, WHO made the following recommendation:

It is recommended that **quadrivalent** vaccines for use in the 2022-2023 northern hemisphere influenza season contain the following:

Egg-based:

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Cell– or recombinant-based:

- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Darwin/6/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

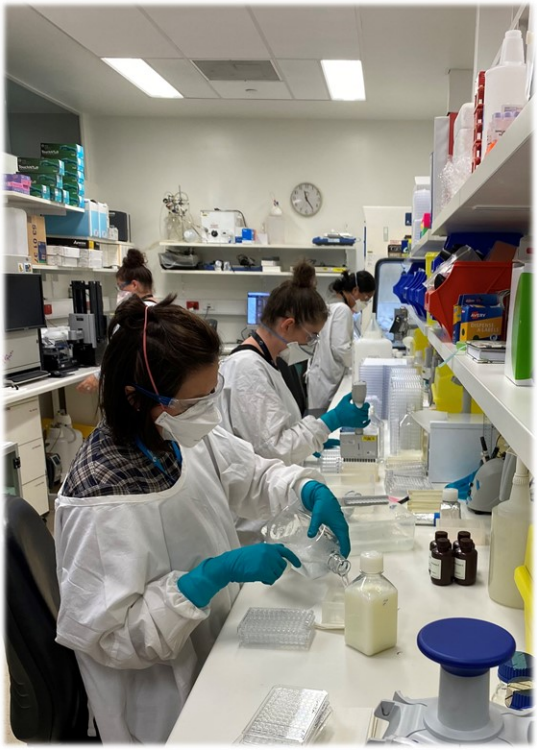
The composition of trivalent influenza vaccines is recommended to include the A(H1N1)pdm09, A(H3N2), and the B Victoria lineage viruses.

The recommendations for the northern hemisphere 2022-2023 vaccine remain the same as the recommendations for the 2022 southern hemisphere vaccine. More details about the most recent recommendations can be found here.

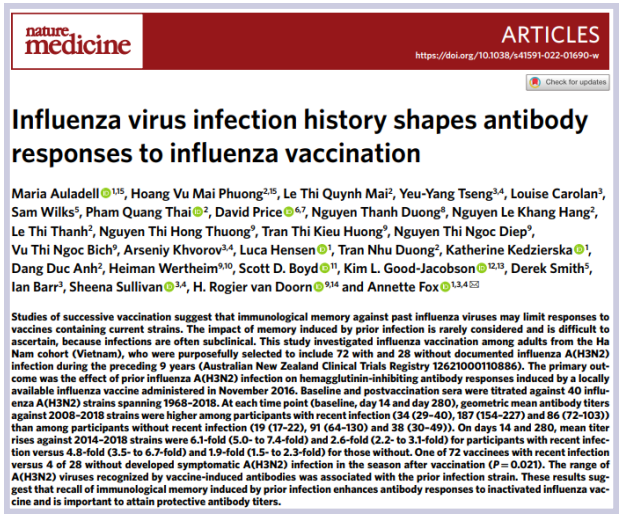
Contribution of National Influenza Centres to the vaccine recommendations

We thank everyone who has sent us influenza samples prior to the Consultation. Your viruses provide essential data on recently circulating strains and help to inform the choice of recommended vaccine strains.

In this context, we would like to acknowledge the contribution and critical role played by WHO National Influenza Centres and other submitting laboratories in providing influenza samples to WHO Collaborating Centres, not only for the purposes of analysis and surveillance, but also for the provision of potential vaccine candidates. Please continue to send us your samples. The need for constant surveillance remains as the influenza virus continues to circulate and evolve.



Featured Research Articles



nature medicine ARTICLES
https://doi.org/10.1038/s41591-022-01690-w

Check for updates

Influenza virus infection history shapes antibody responses to influenza vaccination

Maria Auladell[1,15], Hoang Vu Mai Phuong[2,15], Le Thi Quynh Mai[2], Yeu-Yang Tseng[3,4], Louise Carolan[3], Sam Wilks[5], Pham Quang Thai[2], David Price[6,7], Nguyen Thanh Duong[8], Nguyen Le Khang Hang[2], Le Thi Thanh[2], Nguyen Thi Hong Thuong[9], Tran Thi Kieu Huong[9], Nguyen Thi Ngoc Diep[9], Vu Thi Ngoc Bich[9], Arseniy Khvorov[3,4], Luca Hensen[1], Tran Nhu Duong[2], Katherine Kedzierska[1], Dang Duc Anh[2], Heiman Wertheim[9,10], Scott D. Boyd[11], Kim L. Good-Jacobson[12,13], Derek Smith[5], Ian Barr[3], Sheena Sullivan[3,4], H. Rogier van Doorn[9,14] and Annette Fox[1,3,4]✉

Studies of successive vaccination suggest that immunological memory against past influenza viruses may limit responses to vaccines containing current strains. The impact of memory induced by prior infection is rarely considered and is difficult to ascertain, because infections are often subclinical. This study investigated influenza vaccination among adults from the Ha Nam cohort (Vietnam), who were purposefully selected to include 72 with and 28 without documented influenza A(H3N2) infection during the preceding 9 years (Australian New Zealand Clinical Trials Registry 12621000110886). The primary outcome was the effect of prior influenza A(H3N2) infection on hemagglutinin-inhibiting antibody responses induced by a locally available influenza vaccine administered in November 2016. Baseline and postvaccination sera were titrated against 40 influenza A(H3N2) strains spanning 1968–2018. At each time point (baseline, day 14 and day 280), geometric mean antibody titers against 2008–2018 strains were higher among participants with recent infection (34 (29–40), 187 (154–227) and 86 (72–103)) than among participants without recent infection (19 (17–22), 91 (64–130) and 38 (30–49)). On days 14 and 280, mean titer rises against 2014–2018 strains were 6.1-fold (5.0- to 7.4-fold) and 2.6-fold (2.2- to 3.1-fold) for participants with recent infection versus 4.8-fold (3.5- to 6.7-fold) and 1.9-fold (1.5- to 2.3-fold) for those without. One of 72 vaccinees with recent infection versus 4 of 28 without developed symptomatic A(H3N2) infection in the season after vaccination ($P = 0.021$). The range of A(H3N2) viruses recognized by vaccine-induced antibodies was associated with the prior infection strain. These results suggest that recall of immunological memory induced by prior infection enhances antibody responses to inactivated influenza vaccine and is important to attain protective antibody titers.

Auladell M, Phuong HVM, Mai LTQ, Tseng YY, Carolan L, Wilks S, Thai PQ, Price D, Duong NT, Hang NLK, Thanh LT, Thuong NTH, Huong TTK, Diep NTN, Bich VTN, Khvorov A, Hensen L, Duong TN, Kedzierska K, Anh DD, Wertheim H, Boyd SD, Good-Jacobson KL, Smith D, Barr I, Sullivan S, van Doorn HR, Fox A. Influenza virus infection history shapes antibody responses to influenza vaccination. Nat Med. 2022 Feb;28(2):363-372. doi: 10.1038/s41591-022-01690-w. PubMed Link

'Influenza virus infection history shapes antibody responses to influenza infection'

And

'Opposing effects of prior infection versus prior vaccination on vaccine immunogenicity against influenza A(H3N2) viruses'

Featuring Annette Fox, Sheena Sullivan, Kanta Subbarao, Ian Barr, Louise Carolan, Vivian Leung, Ryan Tseng, and Arseniy Khvorov from the Centre

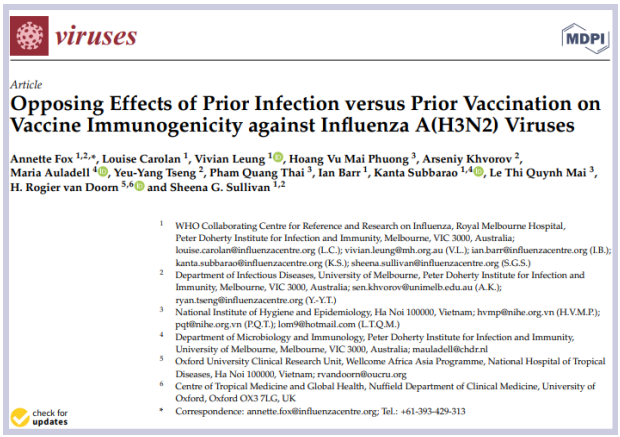
Two studies on immune responses elicited from influenza vaccination were published in February.

The first article, published in *Nature Medicine*, showed that individuals who had prior exposure to influenza infection were likely to produce a better immune response when given the seasonal influenza vaccine.

The study cohort for this nine year longitudinal study was established in Vietnam in collaboration with Oxford University and the National Institute of Hygiene and Epidemiology, Vietnam.

The second article, published in *Viruses*, combined data from this cohort in Vietnam with data from Australian healthcare workers.

Analysis of antibody responses from both cohorts showed that, while vaccination against A(H3N2) viruses following prior A(H3N2) infection resulted in increased antibody titres, this response was attenuated in those who had received prior influenza vaccination. This attenuation was further exacerbated in those who had received their vaccinations over the course of multiple years, with attenuation most prominent in those that had received vaccinations for three to five years prior. A prospective study to investigate the potential impact of repeat influenza vaccinations over the course of multiple years on vaccine effectiveness is underway.



viruses MDPI

Article

Opposing Effects of Prior Infection versus Prior Vaccination on Vaccine Immunogenicity against Influenza A(H3N2) Viruses

Annette Fox [1,2,*], Louise Carolan [1], Vivian Leung [1], Hoang Vu Mai Phuong [3], Arseniy Khvorov [2], Maria Auladell [4], Yeu-Yang Tseng [2], Pham Quang Thai [3], Ian Barr [1], Kanta Subbarao [1,4], Le Thi Quynh Mai [3], H. Rogier van Doorn [5,6] and Sheena G. Sullivan [1,2]

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5 Oxford University Clinical Research Unit, Wellcome Africa Asia Programme, National Hospital of Tropical Diseases, Ha Noi 100000, Vietnam; rvandoorn@oucru.org
6 Centre of Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford OX3 7LG, UK
* Correspondence: annette.fox@influenzacentre.org; Tel.: +61-393-429-313

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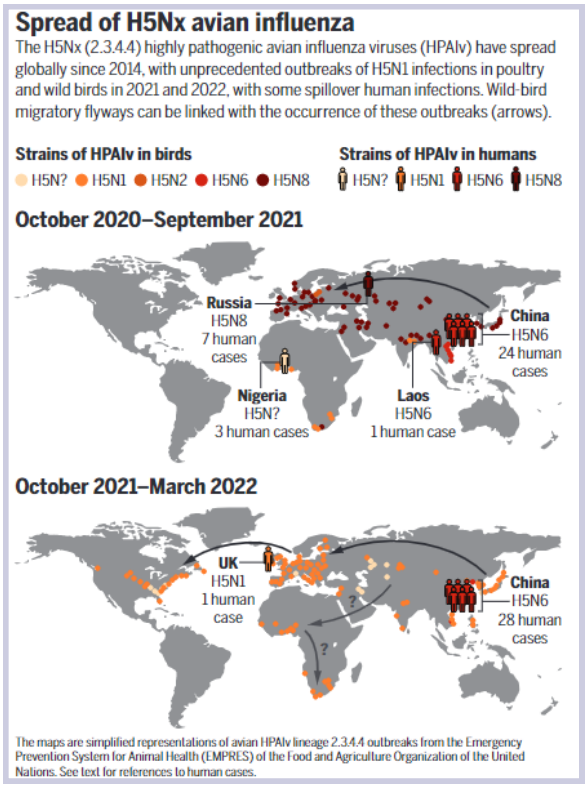
Fox A, Carolan L, Leung V, Phuong HVM, Khvorov A, Auladell M, Tseng YY, Thai PQ, Barr I, Subbarao K, Mai LTQ, van Doorn HR, Sullivan SG. Opposing Effects of Prior Infection versus Prior Vaccination on Vaccine Immunogenicity against Influenza A(H3N2) Viruses. Viruses. 2022 Feb 25;14(3):470. doi: 10.3390/v14030470. PubMed Link

Both studies were predominantly led by Dr Annette Fox, in collaboration with A/Prof Sheena Sullivan.

Featured Research Articles (continued)

'Resurgence of avian influenza virus'



This Science Perspective article written by Dr Michelle Wille and Deputy Director Ian Barr outlines the facets to the resurgence of H5N1 avian influenza virus.

Since October 2021, there have been >3000 outbreaks of avian influenza lineage 2.3.4.4 H5N1, including both outbreaks in poultry and wild birds. In North America, for example, ~35 million birds have been culled since November 2021 when the first cases were recorded. In wild birds, there have seen devastating outbreaks with thousands dying in mass mortality events. For example, the end of 2021 saw 8,000-10,000 Eurasian Cranes (*Grus grus*) die in Israel. Between November 2021 – March 2022, approximately 20% of Barnacle Geese (*Branta leucopsis*) died in the UK, and there is an ongoing outbreak in breeding Great Skuas (*Stercorarius skua*) due to this disease. Human cases of avian influenza are also of concern. While the risk for human transmission is low, this risk is higher for people who are in contact with poultry. To date, there have been cases in China, Laos, Russia, Nigeria, the UK, and the USA, for people who fall into this category.

Wille M, Barr IG. Resurgence of avian influenza virus. Science. 2022 Apr 29;376(6592):459-460. doi: 10.1126/science.abo1232. PubMed Link

Overall, H5Nx avian influenza is a One Health problem, that can likely only be solved with a One Health solution.

'Australia as a global sink for the genetic diversity of avian influenza A virus'

Tying in with the above publication, this new study featuring Dr Michelle Wille has investigated how or if avian influenza viruses move between Australia and the northern hemisphere, how these viruses move within Australia, and whether the evolutionary genetics of Australian viruses are consistent with patterns from the northern hemisphere.

The study found that, while introductions of avian influenza from Asia and North America do occur, they are infrequent in many viral subtypes. Incursions were more common in subtypes detected as infrequent in duck populations, which highlights the important role of long distance migratory shorebirds in viral introductions. We found that virus exportation events from Australia were rare, with only a single instance. Essentially, viruses are introduced to Australia, then circulate and become extinct within Australia, suggesting that this country is a global sink for avian influenza diversity. Within Australia, virus movement is most common between adjacent states, with no clear movement corridors or directions.

Critically, this is the first holistic analysis of avian influenza genomes across Australia, comprising more than 300 unique genomes recovered from all states and most territories. This project relied on collaboration between national, state and university laboratories and research groups working together as part of the National Avian Influenza Wild Bird Program.

Wille M, Grillo V, Ban de Gouvea Pedroso S, Burgess GW, Crawley A, Dickason C, Hansbro PM, Hoque MA, Horwood PF, Kirkland PD, Kung NY, Lynch SE, Martin S, McArthur M, O'Riley K, Read AJ, Warner S, Hoye BJ, Lisovski S, Leen T, Hurt AC, Butler J, Broz I, Davies KR, Mileto P, Neave MJ, Stevens V, Breed AC, Lam TTY, Holmes EC, Klaassen M, Wong FYK. Australia as a global sink for the genetic diversity of avian influenza A virus. PLoS Pathog. 2022 May 10;18(5):e1010150. doi: 10.1371/journal.ppat.1010150. PubMed Link

Building COVID-19 diagnostic capacity in the Solomon Islands

A recent article by the Peter Doherty Institute for Infection and Immunity covered the work that Prof Patrick Reading and Jean Moselen had done in the Solomon Islands to assist with strengthening molecular testing for SARS-CoV-2.

They were predominantly based at the National Referral Hospital molecular laboratory in Honiara.

This work was funded by the Department of Foreign Affairs and Trade Indo-Pacific Centre for Health Security through the COMBAT-AMR project.

To read the full article, please click here.

Upcoming meetings and conferences

The 11th OPTIONS meeting for the Control of INFLUENZA will be held this year on 26-29 September in Belfast, UK as a hybrid meeting. The abstract deadline has been extended until 25 May 2022 , and early bird registration will close on 28 June 2022.

For more information, and to register for the event, please click here.

NRL Science of Quality

The 2022 NRL Asian Summit will be held this year on 23-24 May as a virtual event. The two day meeting will include regional speakers focusing on topics as they relate to quality in testing and provide a forum for interactive discussion by delegates.

Registration details and the full program can be accessed here.

Farewell and good luck

It is with sadness but good wishes that we announce the departure of two staff members from the Centre. We thank Gen and Ryan for their significant contributions to the Centre, and wish them all the very best for their future.

Ms Genevieve O'Neill had been a Medical Scientist with the Centre Epidemiology team for around 9 months. She has now taken on a role as an Epidemiologist in Lismore.

Dr Ryan Tseng had been a Post-Doctoral researcher with Dr Annette Fox's research group for around 2 years. He has now taken on a position with Oxford Nanopore.

Recent activities at the Centre (1 January — 30 April 2022)

Below is a summary of surveillance activities at the Centre during this current reporting period. We have seen a significant rise in influenza activity compared to this time in 2021. We anticipate that the next few months will continue to be busy as the southern hemisphere influenza season returns.

Samples received: The Centre received 1338 influenza samples from the laboratories and institutions listed below during the period 1 January—30 April 2022.

AUSTRALIA: Canberra Hospital, 4Cyte Pathology, Westmead Hospital, John Hunter Hospital, Royal Darwin Hospital, QLD Health Forensic and Scientific Services (QHFSS), SA Pathology, Royal Hobart Hospital, Alfred Hospital, Austin Pathology, Australian Clinical Labs, Dorevitch Pathology Heidelberg, Eastern Health Pathology, Monash Medical Centre, Royal Children's Hospital Molecular Microbiology Department (Bio21), Royal Melbourne Hospital, St Vincent's Hospital, VIDRL, PathWest Laboratory Medicine (QEII)

FIJI: Center for Communicable Disease Control

INDIA: National Institute of Virology

PHILIPPINES: Research Institute for Tropical Medicine

SINGAPORE: National Public Health Laboratory

SRI LANKA: Medical Research Institute

TIMOR-LESTE: Laboratório Nacional da Saúde

Isolation of viruses in eggs:
The Centre undertakes primary isolation of selected viruses in eggs to obtain potential vaccine strains. From 1 January to 30 April 2022, 3 A(H1N1)pdm09 and 3 A(H3N2) viruses were successfully isolated in eggs at the Centre.

Antigenic analysis
212 viruses analysed by haemagglutination inhibition (HI) assay

Antiviral drug susceptibility
258 viruses analysed by neuraminidase inhibition (NAI) assay

Sequencing
282 viruses analysed
127 HA genes
82 NA genes
64 MP genes
55 NS genes

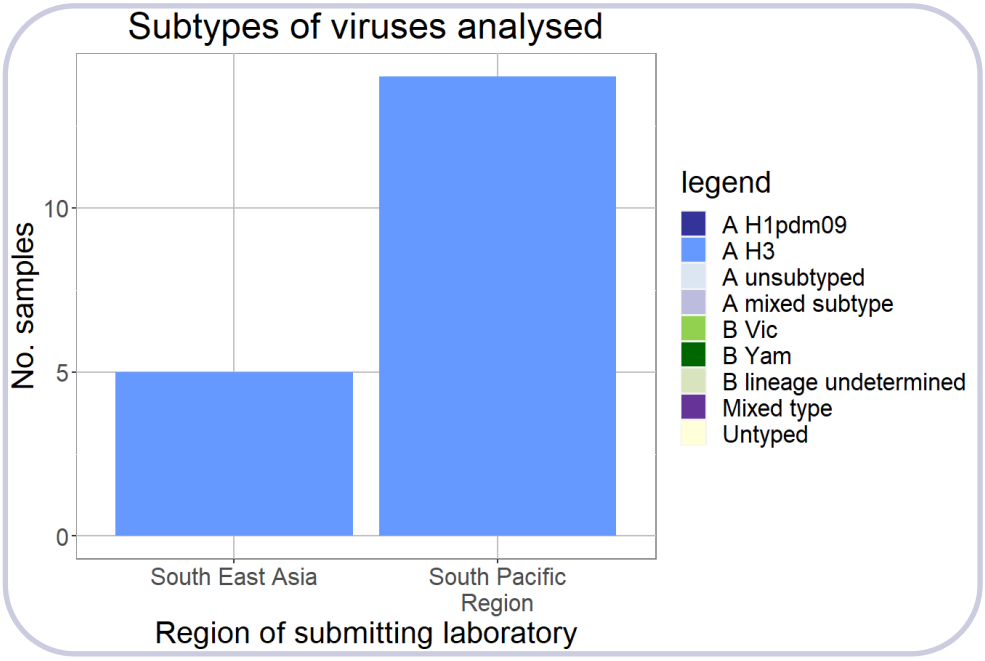
Country of submitting laboratory	No. of viruses analysed by HI assay*				No. of viruses tested by NAI assay*				No. of viruses sequenced by NGS or Sanger sequencing			
	A(H1N1)pdm09	A(H3N2)	B lineage undetermined	B/Victoria	A(H1N1)pdm09	A(H3N2)	B lineage undetermined	B/Victoria	A(H1N1)pdm09	A(H3N2)	B lineage undetermined	B/Victoria
Australia	35	186		2	15	160		2	14	59		1
Fiji		14				14				19		
India	3	10		15	3	10		15	3	4		8
Philippines		5		2		5		2		5		2
Singapore		3	1	25		1	1	25				
Sri Lanka										6	1	
Timor-Leste		5				5						
Total	**38**	**223**	**1**	**44**	**18**	**195**	**1**	**44**	**17**	**99**	**1**	**11**

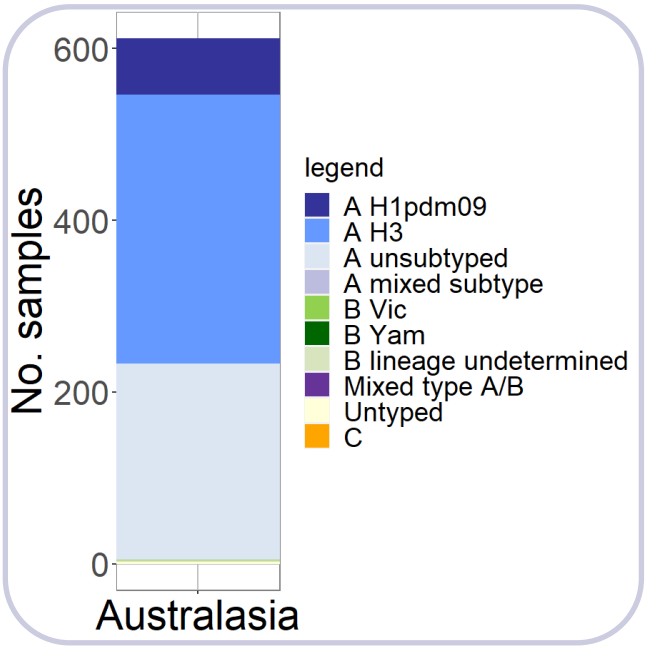
* *Subtypes and lineages are based on analysis of HA and in some cases confirmed by genetic analysis of NA.*

Surveillance update: Virus activity 1 January—30 April 2022

The data below are results for viruses collected or sampled between 1 January and 30 April 2022 that have been analysed at the Centre as of 3 May 2022.

Virus types/subtypes[†]	
The type and subtype/lineage of 631 viruses have been determined.	10.5% A(H1N1)pdm09 52.6% A(H3N2) 0.2% B/Victoria



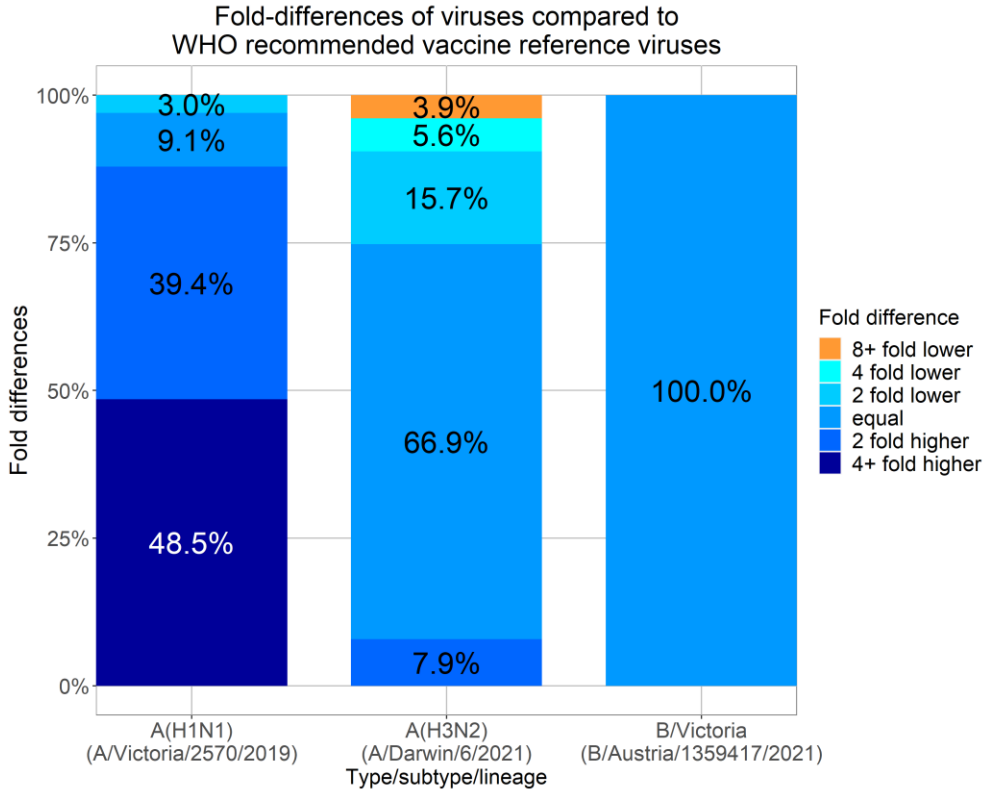


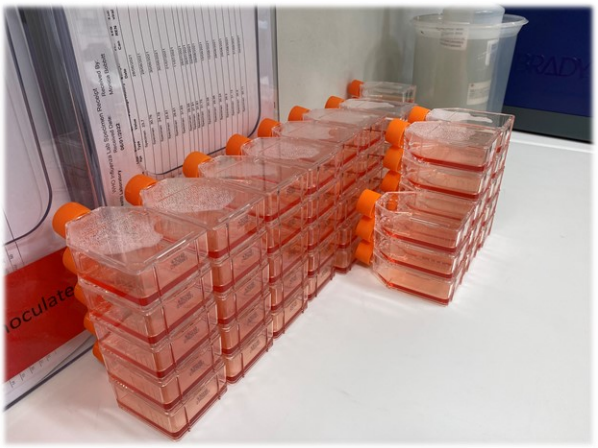
[†] *Subtypes and lineages are based on analysis of the HA and in some cases confirmed by genetic analysis of NA.*

Antigenic analysis*

A total of 212 viruses were tested using the haemagglutination inhibition (HI) assay.

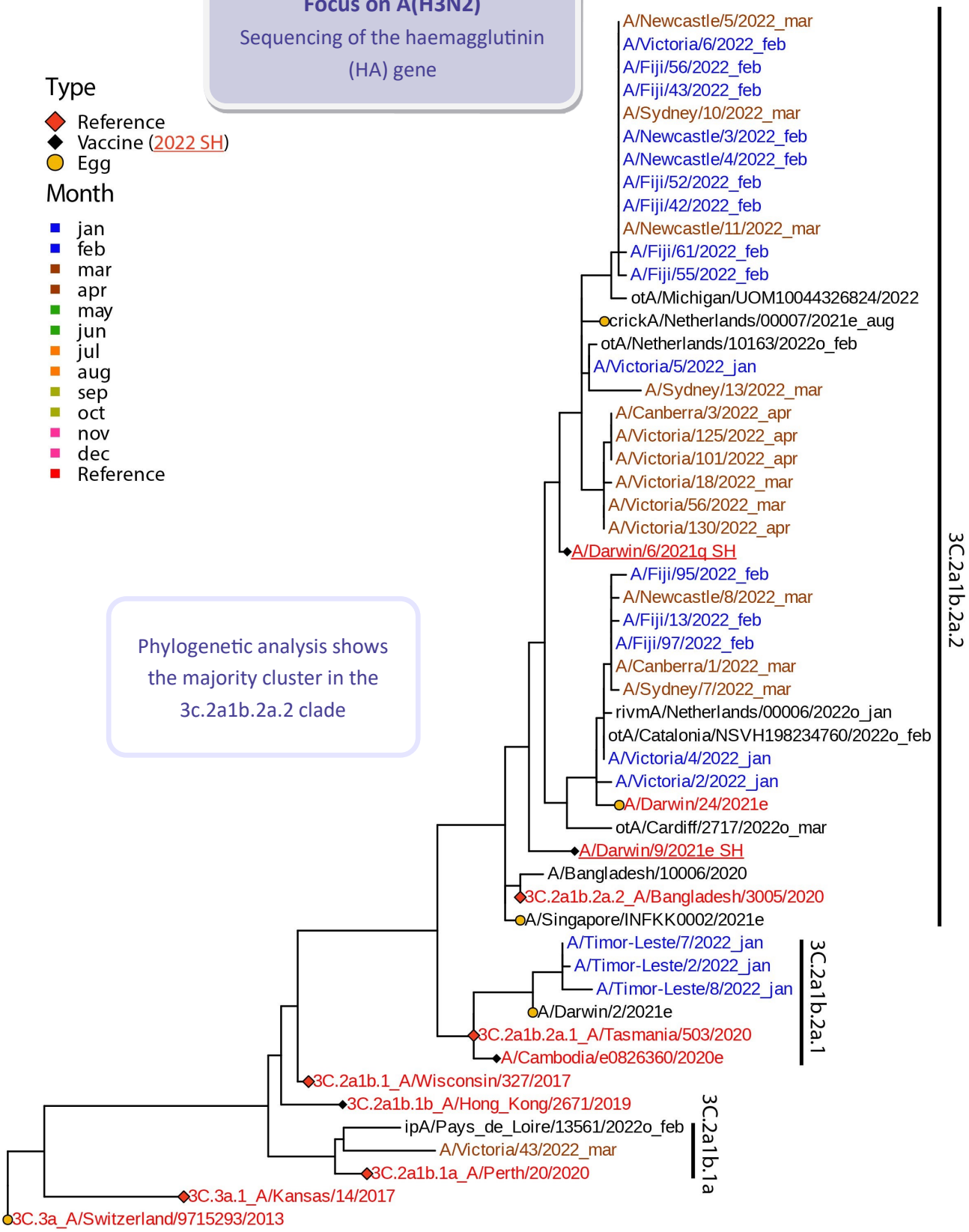
Viruses were identified as low-reactors if their titre against reference antiserum was at least 8-fold lower than the titre of the reference virus. All A(H1N1)pdm09 and B/Victoria viruses were antigenically similar to their respective reference strains. A small proportion (3.9%) of A (H3N2) viruses were low reactors to the reference strain, A/Darwin/6/2021.





† *Subtypes and lineages are based on analysis of the HA and in some cases confirmed by genetic analysis of NA.*

Genetic analysis:
Focus on A(H3N2)
Sequencing of the haemagglutinin (HA) gene



Phylogenetic analysis shows the majority cluster in the 3c.2a1b.2a.2 clade

Antiviral drug susceptibility testing:

187 viruses tested by neuraminidase inhibition (NAI) assay

Testing for susceptibility to the antiviral drugs oseltamivir (Tamiflu), zanamivir (Relenza), peramivir, and laninamivir showed that no viruses had highly reduced inhibition by one or more neuraminidase inhibitors (NAI).

Type/subtype/ lineage	Oseltamivir			Peramivir			Laninamivir			Zanamivir		
	Normal inhibition	Reduced inhibition	Highly reduced Inhibition	Normal inhibition	Reduced inhibition	Highly reduced Inhibition	Normal inhibition	Reduced inhibition	Highly reduced Inhibition	Normal inhibition	Reduced inhibition	Highly reduced Inhibition
A(H1N1)pdm09	15			15			15			15		
A(H3N2)	171			171			171			171		
B/Victoria	1			1			1			1		
Total	**187**			**187**			**187**			**187**		

Viruses with reduced inhibition by antiviral drugs in the NAI assay undergo genetic analysis of the neuraminidase gene to detect mutations associated with the functional change. The relationship between reduced inhibition and the clinical effectiveness of a neuraminidase inhibitor is not well understood. Further studies would be required to determine whether a virus with reduced inhibition in the NAI assay is clinically resistant.

WHO Collaborating Centre for Reference and Research on Influenza

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