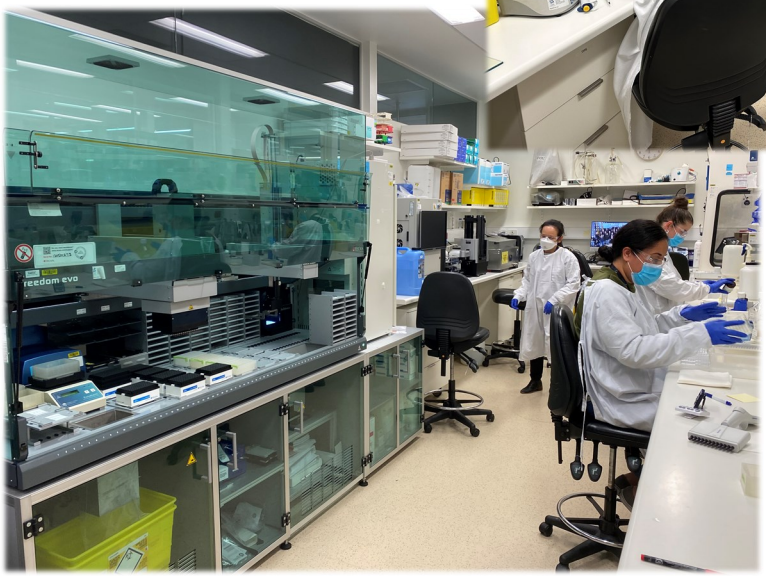

Annual Report 2022

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

Contents

About the Centre

The WHO Collaborating Centre for Reference and Research on Influenza at the Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne is part of the World Health Organisation Global Influenza Surveillance and Response System (WHO GISRS). The network was established in 1952 to monitor the frequent changes in influenza viruses with the aim of reducing the impact of influenza through the use of vaccines containing currently circulating strains. Together with WHO Collaborating Centres in Atlanta, Beijing, London and Tokyo, the Centre is responsible for analysing influenza viruses currently circulating in the human population in different countries around the world. The Centre in Melbourne was first designated as a Collaborating Centre in 1992, the third such Centre in the world.

Terms of Reference

Under its designation as a WHO Collaborating Centre for Reference and Research on Influenza, the Centre's Terms of Reference (for 2019-2023) are:

1. To obtain, isolate and preserve representative viruses from outbreaks and sporadic cases of influenza, and characterise their antigenic, genetic and drug sensitivity properties as requested by the WHO.
2. To collect epidemiological information on the prevalence of influenza, especially in countries and areas in the Region, under WHO's leadership.
3. To exchange information and materials (including viruses and antisera) with other WHO Collaborating Centres for Influenza, with Essential Regulatory Laboratories and with Veterinary Laboratories to assist WHO in developing recommendations on viruses to be included in seasonal and potential pandemic influenza vaccines (according to the Pandemic Influenza Preparedness Framework requirements).
4. To provide training and laboratory support to WHO National Influenza Centres and other laboratories, especially those in the developing world, in specialised techniques for diagnosis, isolation and characterisation of influenza viruses, according to their needs.
5. To undertake research to improve the detection, prevention and treatment of influenza and to assist WHO and national health authorities in developing and implementing plans for responding to pandemic influenza.
6. To implement activities defined in the Annex 5 of the PIP Framework under the Terms of Reference for WHO Collaborating Centres for Influenza (https://www.who.int/influenza/resources/pip_framework

Governance

The Centre is supported by the Australian Government Department of Health and Aged Care through a funding agreement between the Commonwealth and Melbourne Health, and reports directly to the Department as well as to WHO.

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Highlights of 2022

Surveillance

The Centre received and processed an unprecedented number of samples during 2022. A total of **12285 samples** was received, of which **98.9% were tested**. Of viruses tested, approximately **60.1%** were **A(H3N2) viruses.**

Research, publications and grants

The Centre further developed its research program during 2022, with Centre staff involved as authors on **71 papers** in peer-reviewed journals. Centre staff were awarded several research grants and funding, including **$998,339** from the **National Health and Medical Research Council (NHMRC)** and **USD $1,277,429** from the **National Institute of Health (NIH)**.

WHO vaccine strains isolated by the Centre

One new candidate vaccine virus that was originally isolated in eggs by the Centre was selected for **inclusion in the WHO recommended influenza vaccine strains.**

Ongoing COVID-19 work

While influenza case numbers have bounced back significantly since the easing of various COVID-19 restrictions, many members of the Centre have continued to participate in various COVID-19 related projects, seminars, and workshops during 2022.

Director’s report

I present the 2022 Annual Report of the WHO Collaborating Centre for Reference and Research on Influenza, a year that featured a return of regional influenza activity after a gap of two years. The Centre has continued to fulfil its commitments to the WHO, National Influenza Centres in the region, and the Commonwealth Government, and participated in training and research activities. Centre staff have worked with the WHO to adapt influenza sentinel surveillance systems to include COVID-19.

The influenza season in Australia began earlier than usual, with a large peak in June that ended somewhat abruptly in July. The Centre received and processed more than 12,000 influenza samples from laboratories in Australia and 15 other countries. The largest proportion of the samples analysed were influenza A(H3N2) viruses. The Centre continued to conduct antigenic and genetic characterisation of viruses and noted an increase in genetic diversification of the H1, H3, and B/Vic HA genes. Notably however, B/Yamagata lineage viruses have not been isolated since 2020. The Centre also continued routine testing of viruses for reduced susceptibility to neuraminidase inhibitors and the polymerase inhibitor baloxavir marboxil.

During 2022 the Centre continued to work on isolation of cell-based and egg-based viruses for vaccine production. A new vaccine candidate virus that was originally isolated in eggs by the Centre were selected for inclusion in the WHO recommended influenza vaccine strains for the Southern Hemisphere during 2023. Three of the four vaccine strains recommended for the 2023 Southern Hemisphere influenza vaccine were derived at the Centre. The ongoing spread of highly pathogenic avian influenza A(H5) viruses has now affected all continents except Australia and Antarctica. The Centre continues to monitor potential pandemic influenza viruses and seeks to obtain new viruses as they are detected, to check reagents and prepare virus and RNA stocks.

With COVID-19 vaccines and the reopening of international borders, Centre staff participated in in-person training in several countries including the Pacific Islands, Cambodia, Thailand, Mongolia, Timor -Leste and Ethiopia. The Centre hosted visitors from Cambodia and New Zealand for training in serologic and molecular techniques.

Centre staff contributed to a total of 71 original research papers, reviews and reports in 2022. Centre staff were successful in obtaining grant funding to support their research from a variety of sources including MRFF, Victorian Department of Health and Human Services, and NIH (USA) for work on influenza and SARS-CoV-2/COVID-19.

We are very grateful to Prof Deb Williamson, the Director of VIDRL and many other members of VIDRL staff, especially Jane Brewster, Anna Ayres and Dallas Wilson, for their support of the Centre’s work at every level during 2022. The continuing support and counsel of the Office of Health Protection in the Australian Government Department of Health and Aged Care are deeply appreciated. Finally, I would like to thank all the staff and students of the Centre for their excellent work through 2022, with the return of influenza activity globally. It is a privilege to work with the Centre staff and I look forward to working with our partners in 2022 and onwards.

Prof Kanta Subbarao
Centre Director

Surveillance

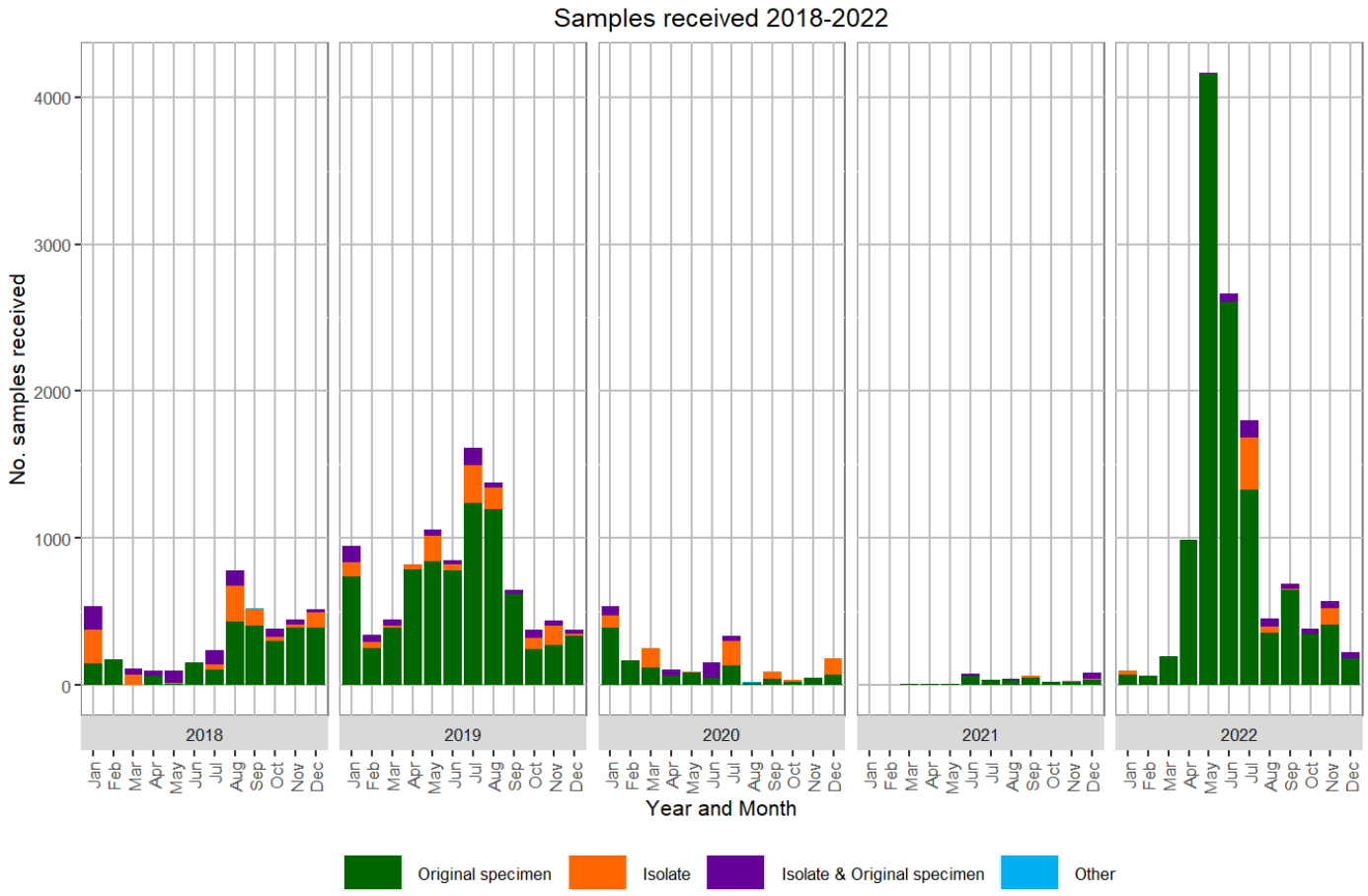
Introduction

The WHO Collaborating Centre for Reference and Research on Influenza at the Doherty Institute in Melbourne conducts human influenza surveillance for the WHO by analysing influenza samples submitted by WHO National Influenza Centres and other laboratories. There are four other such Collaborating Centres around the world, the others being in Atlanta, Beijing, London and Tokyo. Most of the samples received at the Centre in Melbourne are provided by laboratories in the Asia-Pacific region.

Twice a year (once each for the Northern and Southern Hemispheres), based on data and advice from the five Collaborating Centres and other experts, the WHO makes recommendations on suitable influenza strains to be included in the next seasonal vaccine.

There are two types of influenza virus, Type A and Type B, which cause significant disease in humans. The surface of influenza viruses is coated with two proteins, haemagglutinin (HA) and neuraminidase (NA). There are many subtypes of influenza A viruses, usually of avian origin, with various combinations of 18 antigenically different HA variants and 11 NA variants. Influenza B viruses are not classified into subtypes, however, there are two co-circulating lineages, B/Victoria and B/Yamagata. Currently there are three predominant families of influenza viruses circulating in the human population — influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B.

Figure 1. Samples received by the Centre, 2018-2022



Receipt of Influenza Viruses

During 2022 the Centre received 12285 clinical specimens and/or virus isolates from 44 laboratories in 16 countries (Figures 1 and 2, Table 1). This is significantly higher than the number of samples received by the Centre during 2021, and is consistent with the high number of influenza infections during the 2022 Australian influenza season. This can be attributed to the easing of various restrictions against the COVID-19 pandemic. Amongst samples received by the Centre for which the age of the patient was known, the largest number were from subjects aged between 10-19 years (Figure 3). 1 sample came from Australian general practitioner based surveillance systems (Table 2).

Isolation and analysis of viruses

Original clinical specimens received by the Centre can be genetically analysed by sequencing or real-time RT-PCR and are also required for recovery of egg isolates that may be potential vaccine strains. For more extensive analyses, viruses from original clinical specimens are cultured and isolated in Madin-Darby Canine Kidney (MDCK) cells.

Of the 12145 samples tested, a total of 8995 samples (74.1%) were successfully isolated by cell culture and/or analysed by real-time reverse-transcription polymerase chain reaction (RT-PCR). Samples for which a positive cell culture result was obtained with sufficient titre were further analysed by haemagglutination inhibition (HI) assay. For reporting purposes, subtypes and lineages are based on antigenic analysis of the HA and in some cases are confirmed by genetic analysis of NA. Of the samples for which results could be obtained, 60.1% were identified as A(H3N2) viruses, 27.8% were A unsubtyped, 10.0% were A(H1N1) pdm09 , and 1.9% were B/Victoria (Table 3).

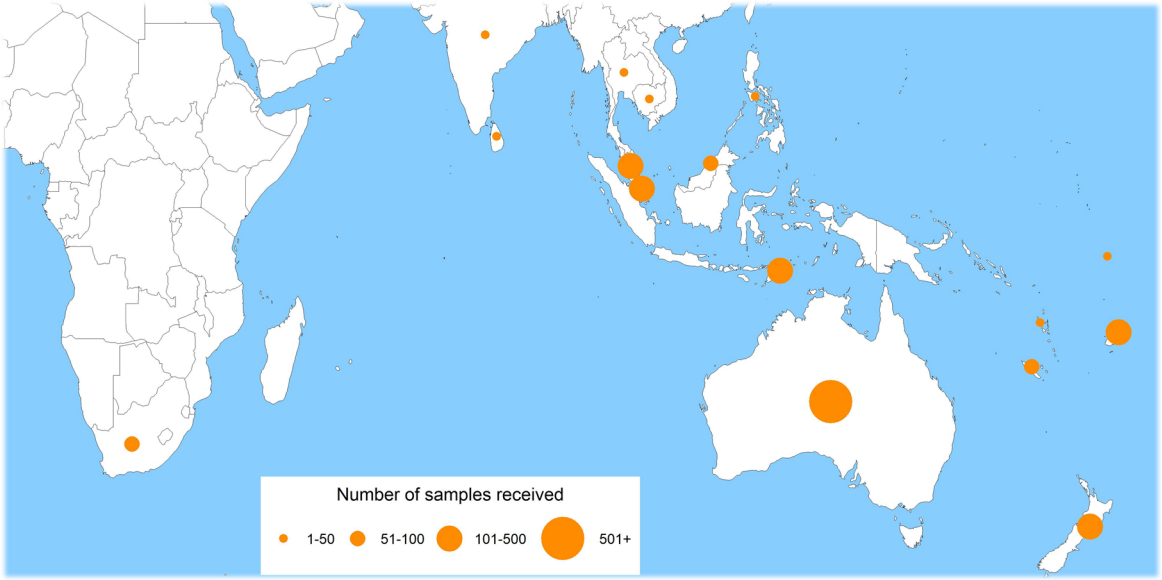


Figure 2. Geographic spread of influenza laboratories sending viruses to the Centre during 2022.

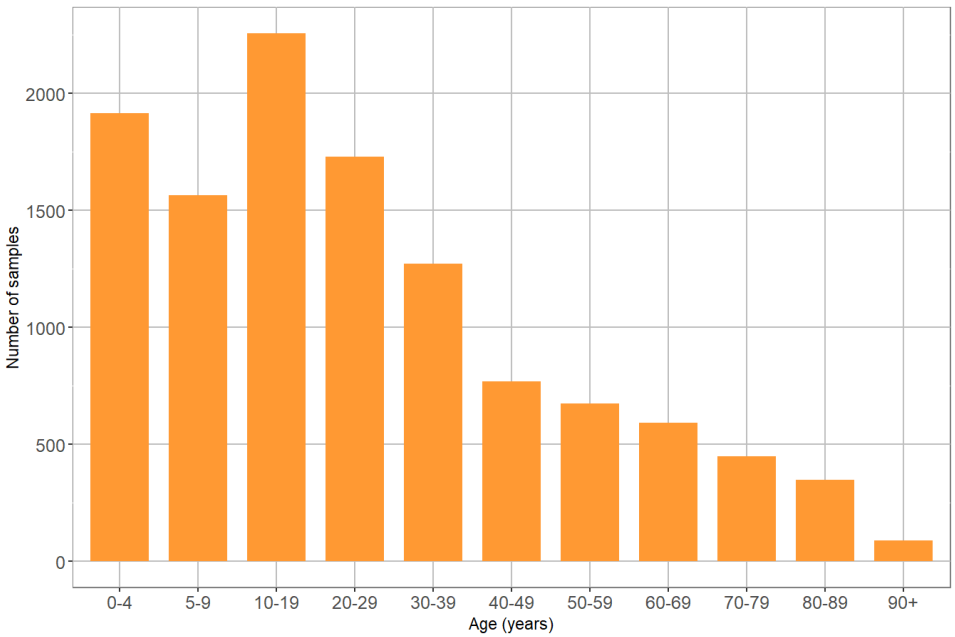


Figure 3. Age distribution of patients from whom samples were received at the Centre in 2022 and the age is known.

Table 1. Samples received by the Centre in 2022, by country.

Country	Samples received				% Samples tested
	Specimens	Isolates	Specimen + Isolate	Other (eg. RNA/ DNA/tissue)	
AUSTRALASIA					
Australia	10489	122	241	4	99%
New Zealand	1	149			100%
SOUTH EAST ASIA					
Brunei	88				100%
Cambodia		12			100%
Malaysia		209			100%
Philippines	35				100%
Singapore	62		53		100%
Thailand	9	1			100%
Timor-Leste	332				100%
SOUTH ASIA					
India		49			100%
Sri Lanka	19				100%
SOUTH PACIFIC					
Fiji	203				86.2%
New Caledonia	60				100%
Tuvalu	16				100%
Vanuatu	40				100%
AFRICA					
South Africa			90		100%
TOTAL	**11354**	**542**	**384**	**4**	**98.9%***

**These include samples that were culture or RT-PCR negative*

Table 2. Samples received from general from general practitioner-based surveillance systems, the Australian Sentinel Practices Research Network (ASPREN) and the Victorian Sentinel Practices Influenza Network (VicSPIN), and the hospital-based Influenza Complications Alert Network (FluCAN) in 2022

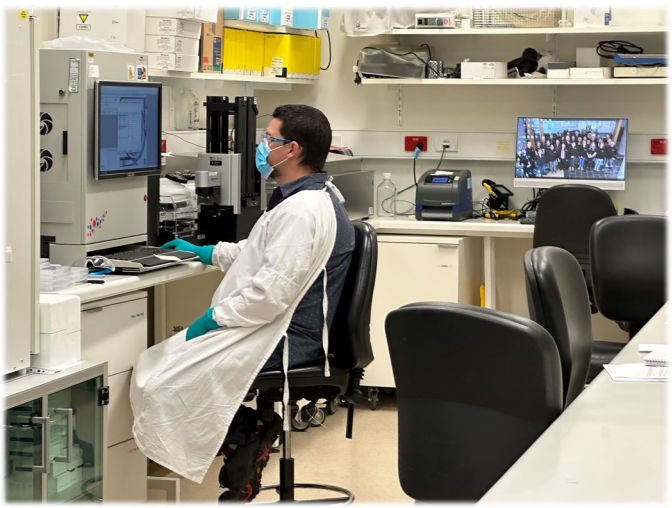
	No. samples received	No. isolates recovered*	Viruses analysed by HI assay
Australian Sentinel Practices Research (ASPREN) Network	153	38	37
Victorian Sentinel Practices Influenza Network (VicSPIN)	26	19	10
Influenza Complications Alert Network (FluCAN)	1747	912	846
TOTAL	**1926**	**969**	**893**

** These numbers do not include samples from which isolates were recovered but did not have sufficient haemagglutination titres to be tested by HI assay.*

Table 3. Samples successfully isolated or analysed by cell culture and/or RT-PCR assay at the Centre in 2022, by country.

Country	Samples tested by cell culture and/or RT-PCR assay*				
	A (H1N1) pdm09	A (H3N2)	A unsubtyped	B/ Victoria	B lineage undetermined
AUSTRALASIA					
Australia	841	4682	2500	56	11
New Zealand	4	145			
SOUTH EAST ASIA					
Brunei		51			
Cambodia		11		1	
Malaysia		192			
Philippines	2	17		3	
Singapore		46		28	1
Thailand		9			
Timor-Leste		70		38	1
SOUTH ASIA					
India	17	14		17	
Sri Lanka		6		1	
SOUTH PACIFIC					
Fiji		84			
New Caledonia		50			
Vanuatu		12			
AFRICA					
South Africa	37	20		28	
TOTAL	**901**	**5409**	**2500**	**172**	**13**

**These do not include samples that were culture or RT-PCR negative*



Antigenic Analysis of Influenza Isolates

Background

The antigenic properties of influenza viral isolates are analysed using the HI assay, in which viruses are tested for their ability to agglutinate red blood cells in the presence of ferret antisera previously raised against reference viruses. A number of A(H3N2) viruses are also analysed antigenically using a microneutralisation assay known as the Focus Reduction Assay (FRA-MN). Subtypes are based on analysis of the HA and in some cases are confirmed by genetic analysis of the NA gene.

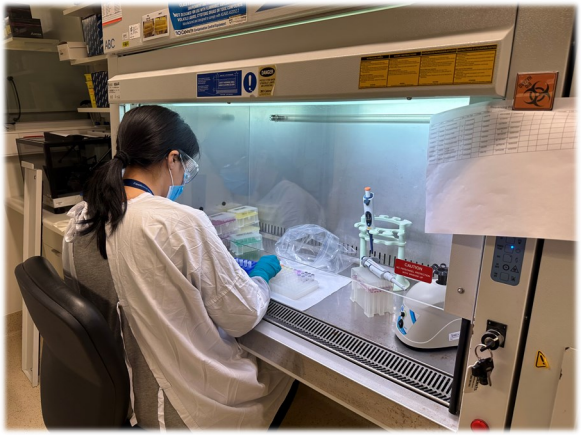
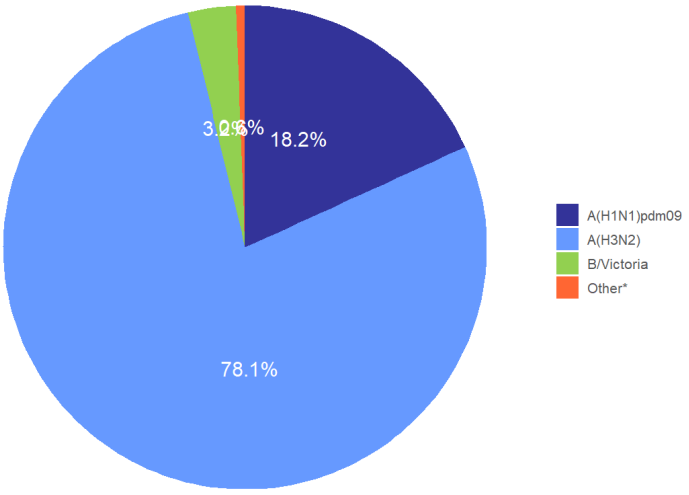


Figure 4. Influenza sub/types and lineages of samples received in 2022 and characterised by antigenic analysis.

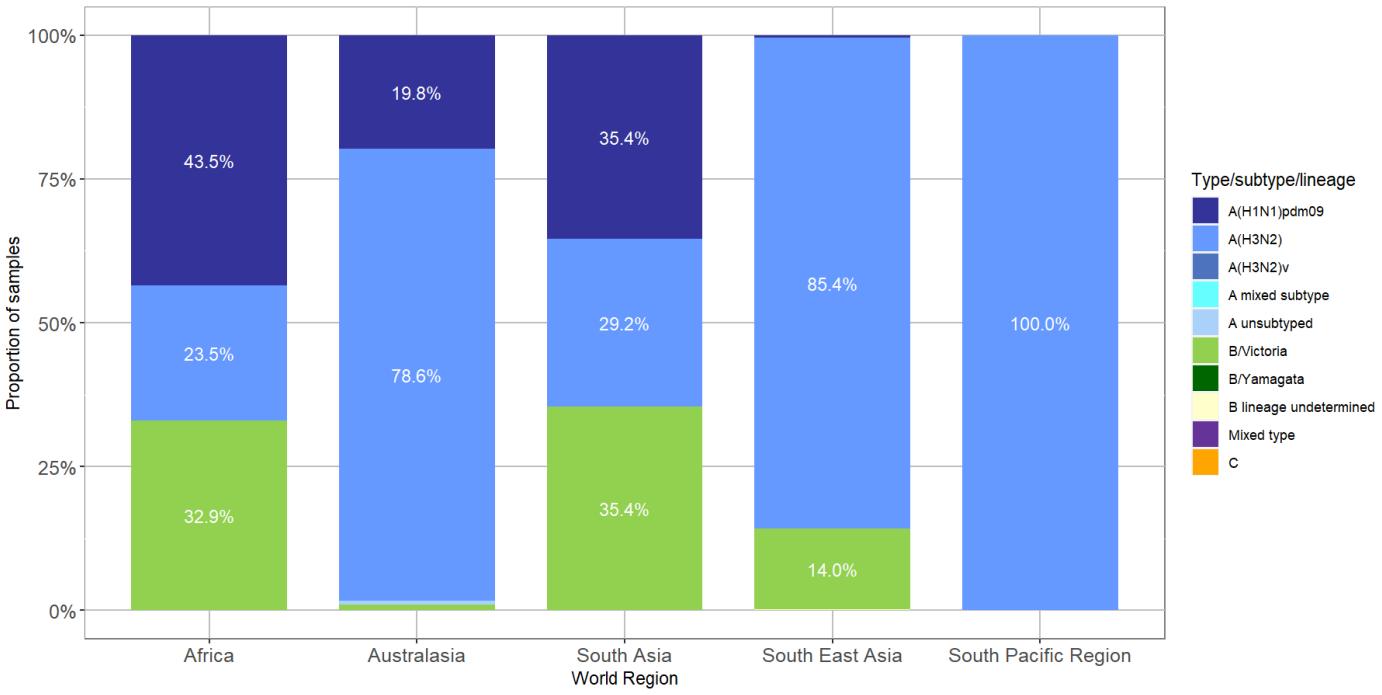
Antigenic analyses 2022

A total of 11947 isolates that were received at the Centre in 2022 were cultured and isolated in MDCK cells, of which 4534 (38.0%) produced a positive result. The largest proportion of viruses were A(H3N2) (78.1%), followed by A(H1N1) pdm09 viruses (18.2%) (Figure 4). The predominance of A(H3N2) viruses for samples received and successfully isolated at the Centre by cell culture was observed in some world regions (Australasia, South East Asia, and South Pacific Region) (Figure 5). In the African and South Asia region, of viruses that were successfully cultured and isolated in cells, there were almost equal proportions of A(H1N1)pdm09, A(H3N2), and B/Victoria viruses.



**A unsubtyped, A mixed, B lineage undetermined*

Figure 5. Influenza sub/types and lineages of isolates received from different world regions during 2022 as determined by antigenic analysis.



Genetic Analysis of Influenza Viruses

Background

A subset of all influenza viruses analysed at the Centre undergoes genetic analysis by sequencing of viral genes. Determining the amino acid sequence of antigenic regions of the HA and NA proteins provides a sensitive method to examine the extent and direction of change in circulating influenza viruses. Routine genetic sequencing of the matrix protein (MP) and non-structural protein (NS) genes is also performed. The Centre also routinely sequences the full genomes of a smaller subset of viruses.

Viruses selected to undergo sequencing include those that exhibit evidence of antigenic drift by HI assay as well as viruses that are generally representative of samples received by the Centre by geography and date of collection. Sequence data are used to compare viruses from different parts of the world and help to inform the selection of vaccine strains.

Next generation sequencing (NGS) techniques are now routinely employed at the Centre for efficient and cost-effective sequencing of whole genomes of viruses, and/or selected influenza virus genes.

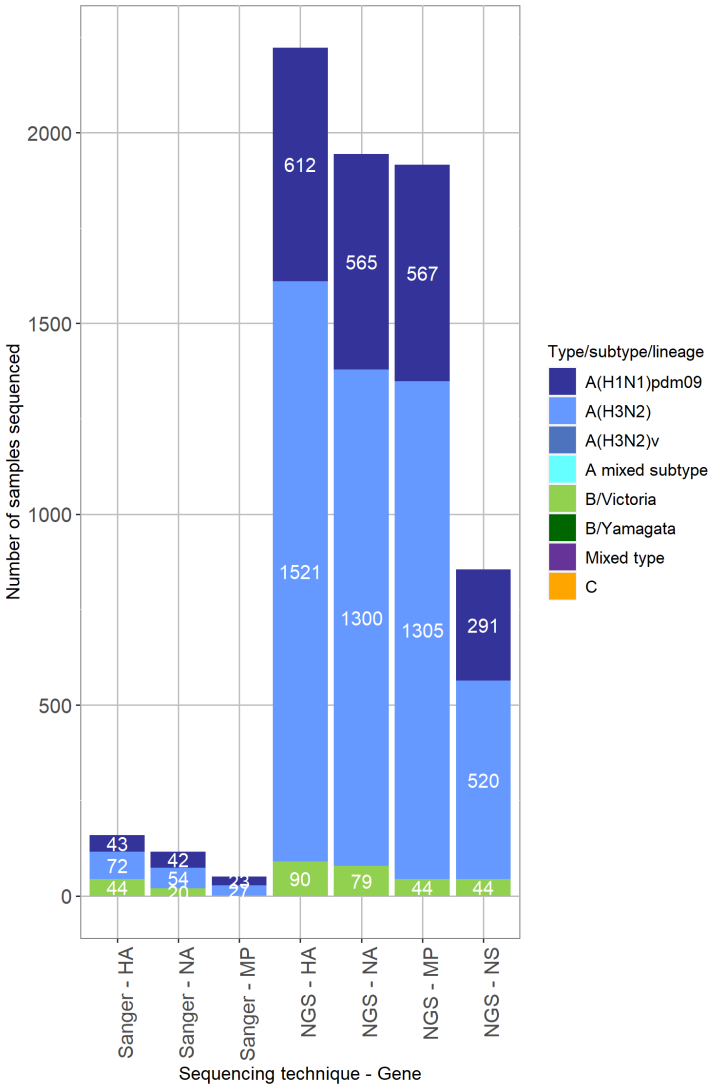


Figure 6. Sequencing of viruses received at the Centre in 2022. Note that some viruses were analysed by both Sanger sequencing and NGS, and are therefore represented twice in this figure.

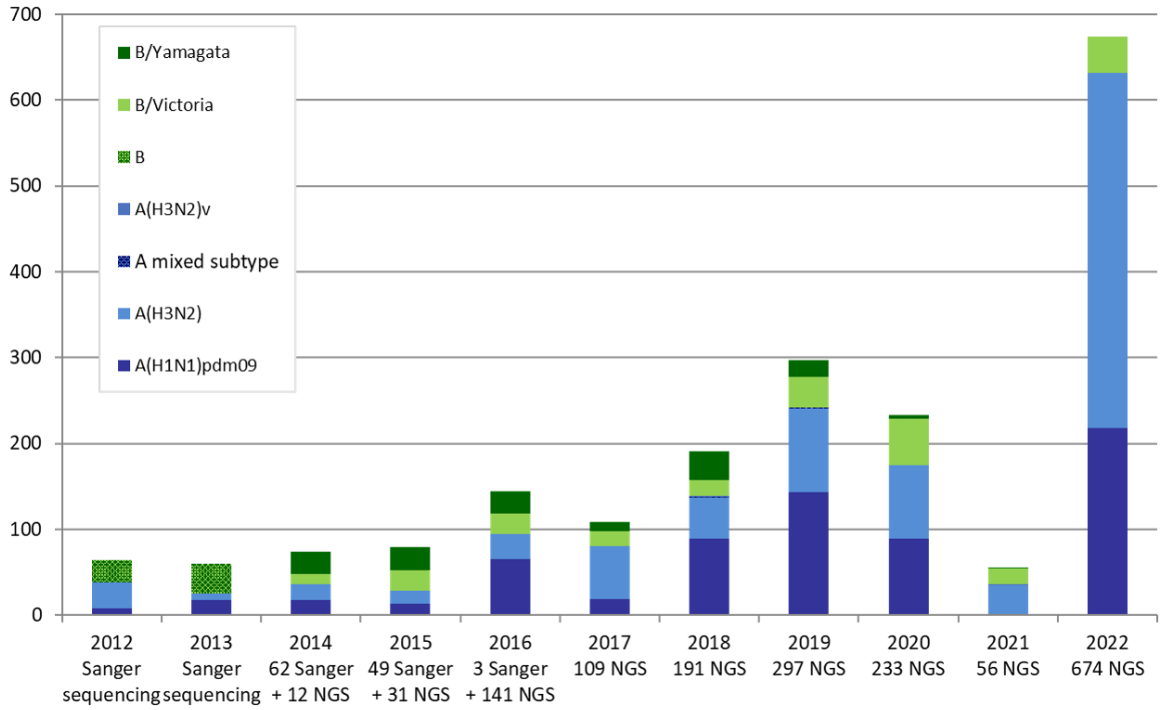
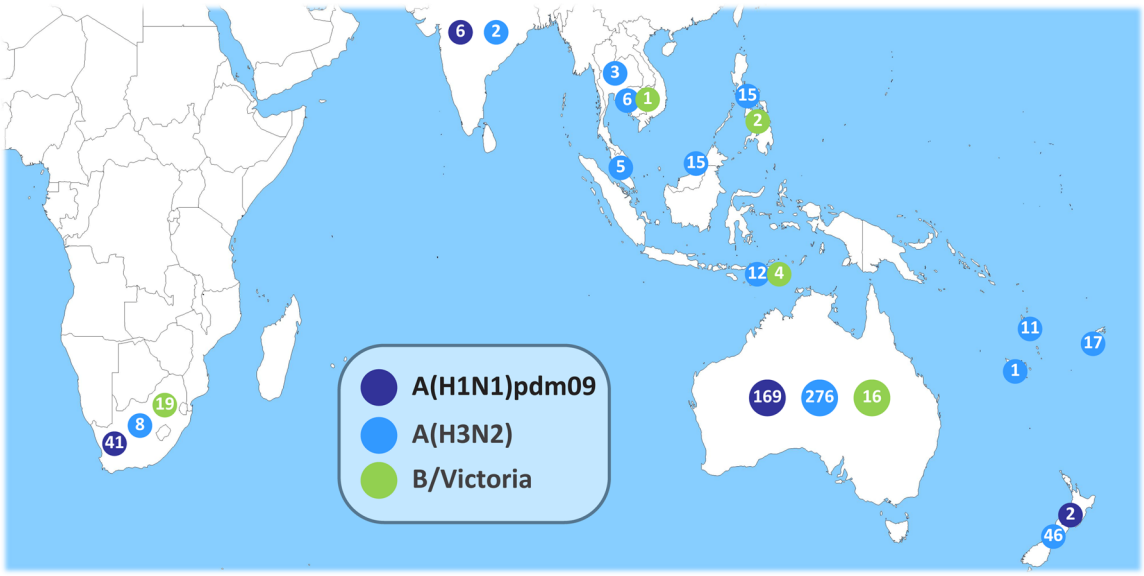


Figure 7. Number of viruses analysed by full genome sequencing 2012 -2022 using Sanger sequencing and

Sequencing 2022

In 2022, 2337 HA, 2044 NA, 1963 MP and 855 NS genes from 2375 human viruses received at the Centre were analysed by Sanger sequencing or NGS (Figure 6). Of these viruses, full genome sequencing was performed on 674 viruses using NGS techniques (Figures 7 and 8). Viruses were selected for these analyses because they were representative of the viruses received and/or because they displayed unusual properties during antigenic analysis.

Figure 8. Geographic spread of submitting laboratories and numbers of viruses analysed by full genome sequencing using NGS techniques at the Centre in 2022.



Submission of Influenza Sequences to GISAID

Background

Virus sequences generated at the Centre are shared with the global influenza community through the EpiFlu™ database, a publicly accessible international repository of influenza virus sequences developed by the Global Initiative on Sharing All Influenza Data (GISAID) (http://www.gisaid.org).

Sequences submitted in 2022

A total of 10316 gene sequences from 3715 human influenza viruses were deposited with GISAID in 2022 (Table 4). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 760 influenza viruses (273 A(H1N1)pdm09 viruses, 463 A(H3N2) viruses and 24 B/Victoria viruses) were also represented in the Centre's submissions (data not shown).

Table 4. Genetic sequences submitted to GISAID by the Centre in 2022.*

Gene / Type/ Subtype/ Lineage	HA	NA	MP	NS	PB1	PB2	PA	NP	Total
A(H1N1)pdm09	611	637	594	322	296	302	291	310	**3396**
A(H3N2)	1380	1345	1278	545	497	490	490	536	**6561**
B/Victoria	102	80	31	31	25	27	29	31	**356**
B/Yamagata^	2	1							**3**
Total	**2128**	**2063**	**1903**	**898**	**818**	**819**	**810**	**877**	**10316**

**Counts include all sequences submitted to GISAID during 2022, which includes viruses received in previous years and viruses sequenced for reference and research purposes.*

^These viruses were collected in 2017 and 2019, but sequences were submitted to GISAID in 2022.

Surveillance Results by Influenza Subtype or Lineage

Viruses were analysed by comparison with reference viruses recommended by WHO for the 2022 Southern Hemisphere vaccines. Using the HI assay, viruses were identified as low-reactors if their titre with the reference antiserum was at least 8-fold lower than the titre of the reference virus. Results of sequencing analysis of the HA region of the haemagglutinin gene are also described in the following sections.

Influenza A(H1N1)pdm09

Antigenic analysis

A total of 768 A(H1N1)pdm09 isolates were analysed by HI assay in 2022. Around 38% of viruses received from Africa were antigenically dissimilar to the cell-grown vaccine reference strain A/Victoria/2570/2019 (Figure 9, Table 5). A small portion (12.45%) of viruses received from Australasia were antigenically dissimilar to A/Victoria/2570/2019. All viruses from South East Asia and South Asia displayed similar antigenic properties to the reference strain.

Haemagglutinin gene sequencing

Sequencing was performed on a total of 650 HA genes. Phylogenetic analysis showed that the majority of circulating A(H1N1)pdm09 viruses sent to the Centre during 2022 were in subclade 6B.1A.5a.2a (Figure 10). With this in mind, the A(H1N1)pdm09 strain for the 2023 Southern Hemisphere recommended vaccine was updated to A/Sydney/5/2021.

Table 5. Antigenic characterisation of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/Victoria/2570/2019 reference virus.

	A(H1N1)pdm09 reference strain: A/Victoria/2570/2019	
Region	**Like**	**Low reactor (%)**
Australasia	626	89 (12.45%)
South East Asia	2	0 (0%)
South Asia	17	0 (0%)
Africa	21	13 (38.24%)
TOTAL	**666**	**102 (13.28%)**

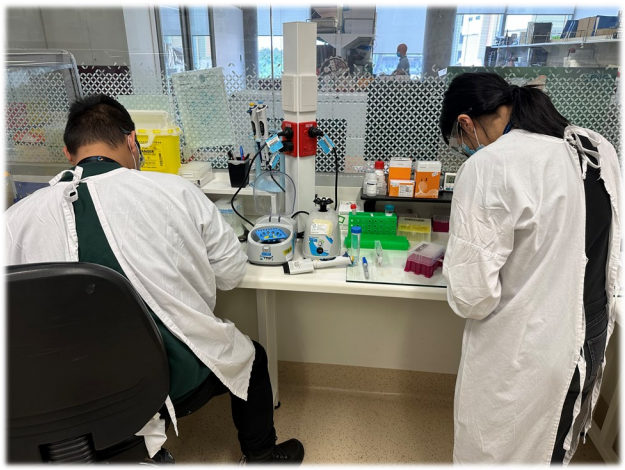
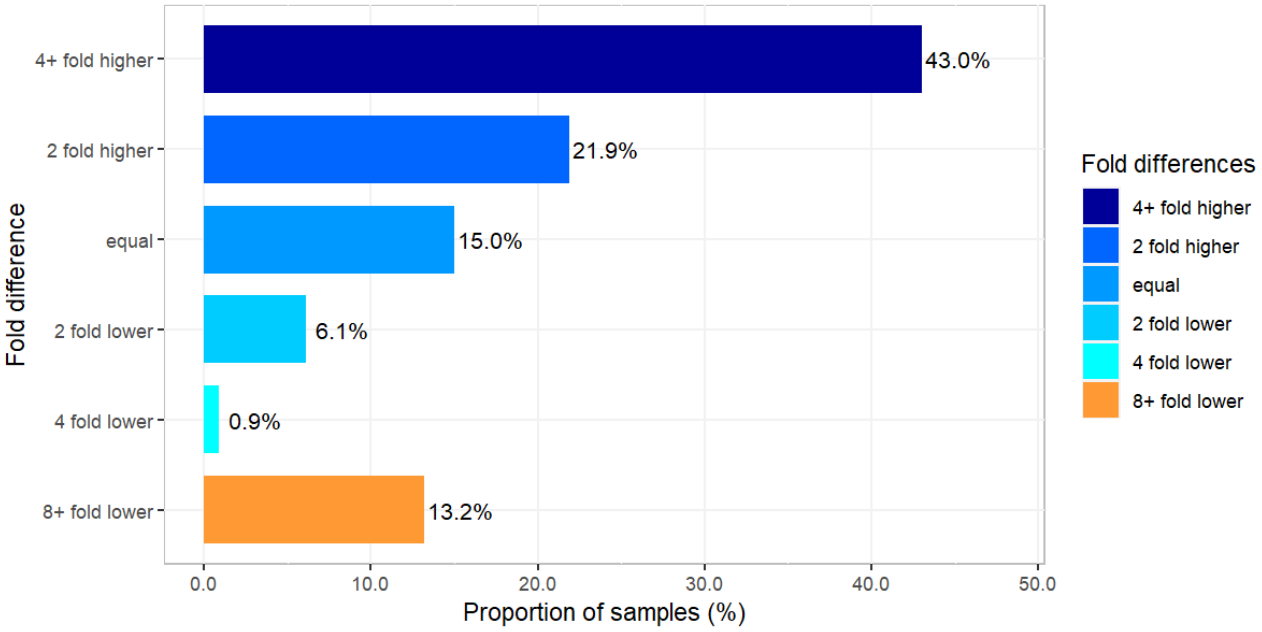


Figure 9. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/ Victoria/2570/2019 reference virus.



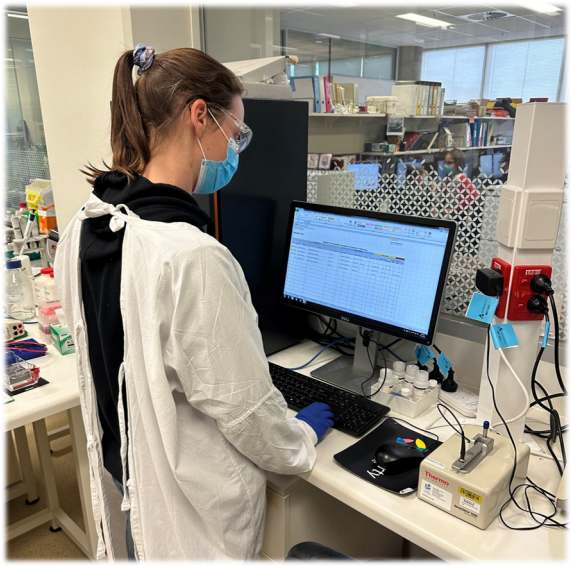
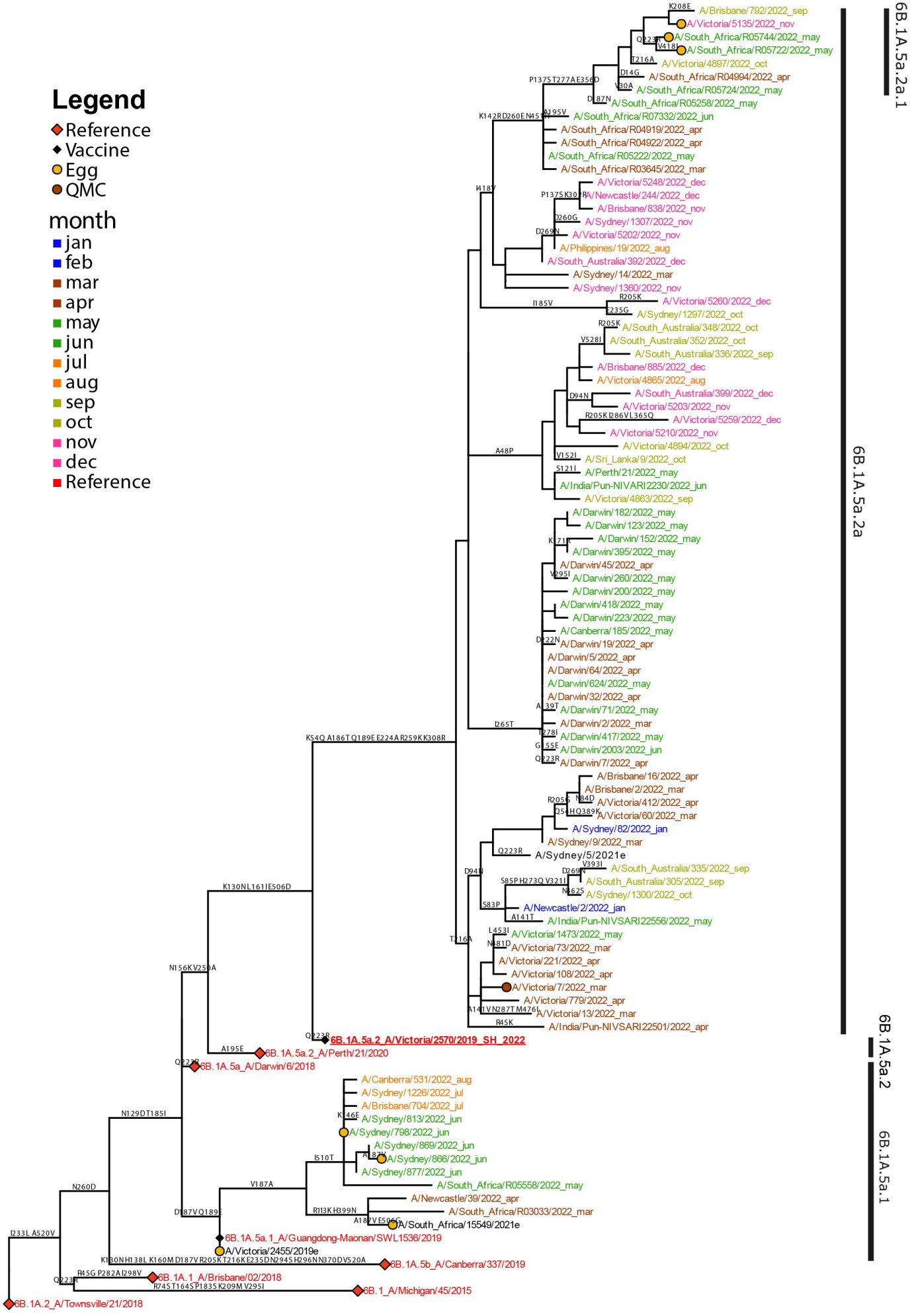


Figure 10. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2022.



Influenza A(H3N2)

Antigenic analysis

In the past, evolutionary changes made A(H3N2) viruses more difficult to analyse using the conventional HI assay. To avoid binding of the neuraminidase protein to red blood cells, it was necessary to add oseltamivir carboxylate. This resulted in some A(H3N2) samples having insufficient haemagglutination titres to conduct the HI assay, leading to the use of additional methods (such as focus reduction microneutralisation assays (FRA-MNs)) to test the antigenic characteristics of these viruses. However, while 104 FRA-MNs were performed during 2022, no FRA-MNs were performed for A(H3N2) viruses that were unable to be analysed by HI assay.

A total of 2801 A(H3N2) subtype isolates were analysed by HI assay in 2022. Of these, 14 isolates were tested against the cell-grown 2021 Southern Hemisphere recommended vaccine strain A/Darwin/726/2019. All isolates were antigenically dissimilar to the reference strain (Figure 11, Table 6). In addition, 2787 isolates were tested against the cell-grown 2022 Southern Hemisphere recommended vaccine strain A/Darwin/6/2021. The majority of viruses received from Africa were antigenically dissimilar to the reference strain (76.92%). Meanwhile, the majority of viruses received from Australasia and South East Asia were antigenically similar to the reference strain. All viruses received from South Asia and the South Pacific were antigenically similar to the reference strain.

Haemagglutinin gene sequencing

A total of 1559 HA genes from A(H3N2) viruses were sequenced. Phylogenetic analysis indicate that most circulating viruses fell into clade 2a.2a, which contains the 2022 Southern Hemisphere recommended vaccine strain A/Darwin/9/2021 (Figure 13).

Table 6. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the cell-grown A/Darwin/726/2019 reference virus.*

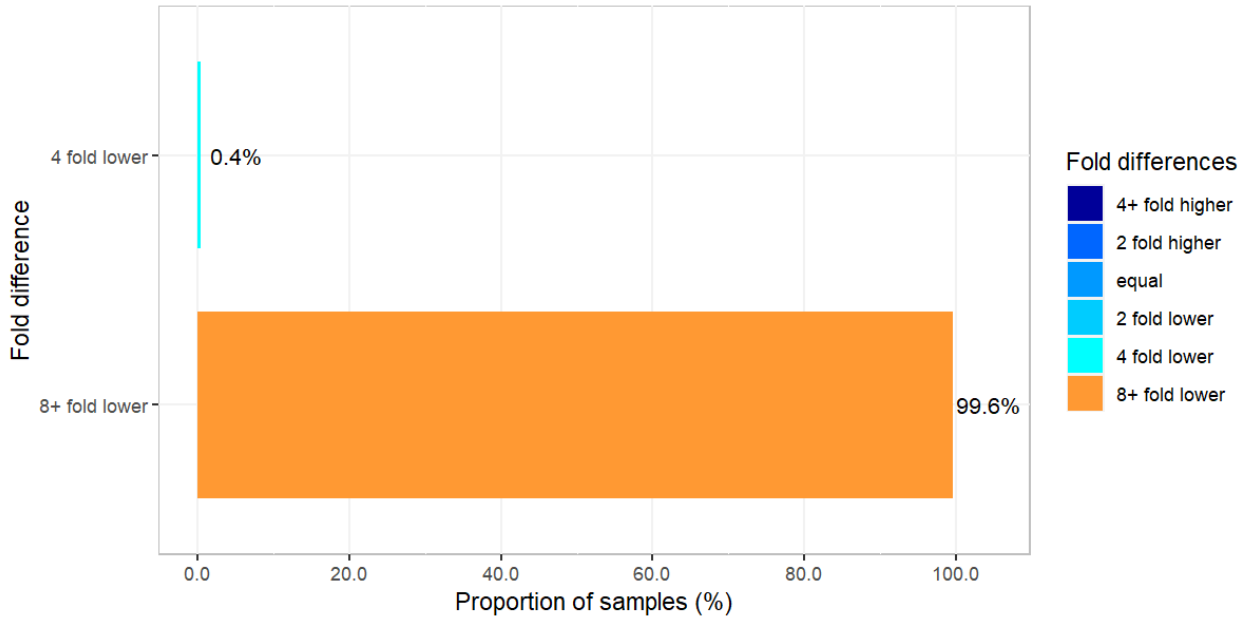
	A(H3N2) reference strain: A/Darwin/726/2019*	
Region	**Like**	**Low reactor (%)**
Australasia	0	1 (100%)
South East Asia	0	3 (100%)
South Asia	0	10 (100%)
TOTAL	**0**	**14 (100%)**

* *Cell equivalent of A/Hong Kong/2671/2019*

Table 7. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the cell-grown A/Darwin/6/2021 reference virus.

	A(H3N2) reference strain: A/Darwin/6/2021	
Region	**Like**	**Low reactor (%)**
Australasia	2450	13 (0.53%)
South East Asia	224	22 (8.94%)
South Asia	4	0 (0%)
South Pacific	61	0 (0%)
Africa	3	10 (76.92%)
TOTAL	**2742**	**45 (1.61%)**

Figure 11. Summary of fold differences in titres of A(H3N2) viruses analysed at the Centre by HI assay compared to the A/ Darwin/726/2019 reference virus.*



* *Cell equivalent of A/Hong Kong/2671/2019.*

Figure 12. Summary of fold differences in titres of A(H3N2) viruses analysed at the Centre by HI assay compared to the A/ Darwin/6/2021 reference virus.

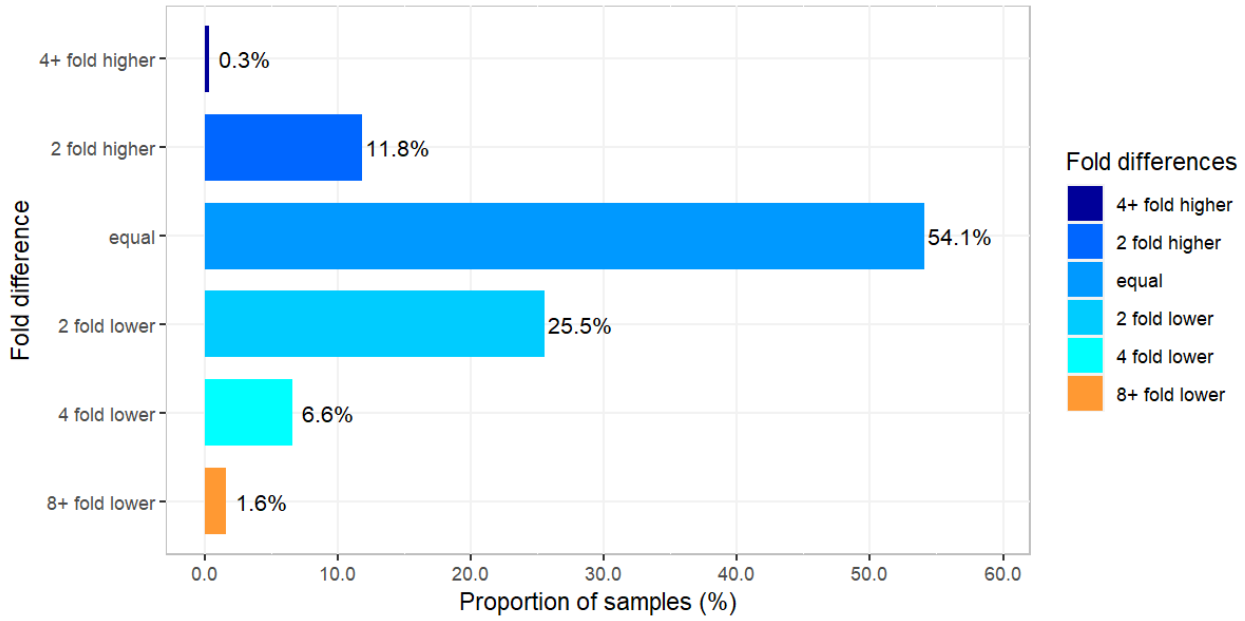
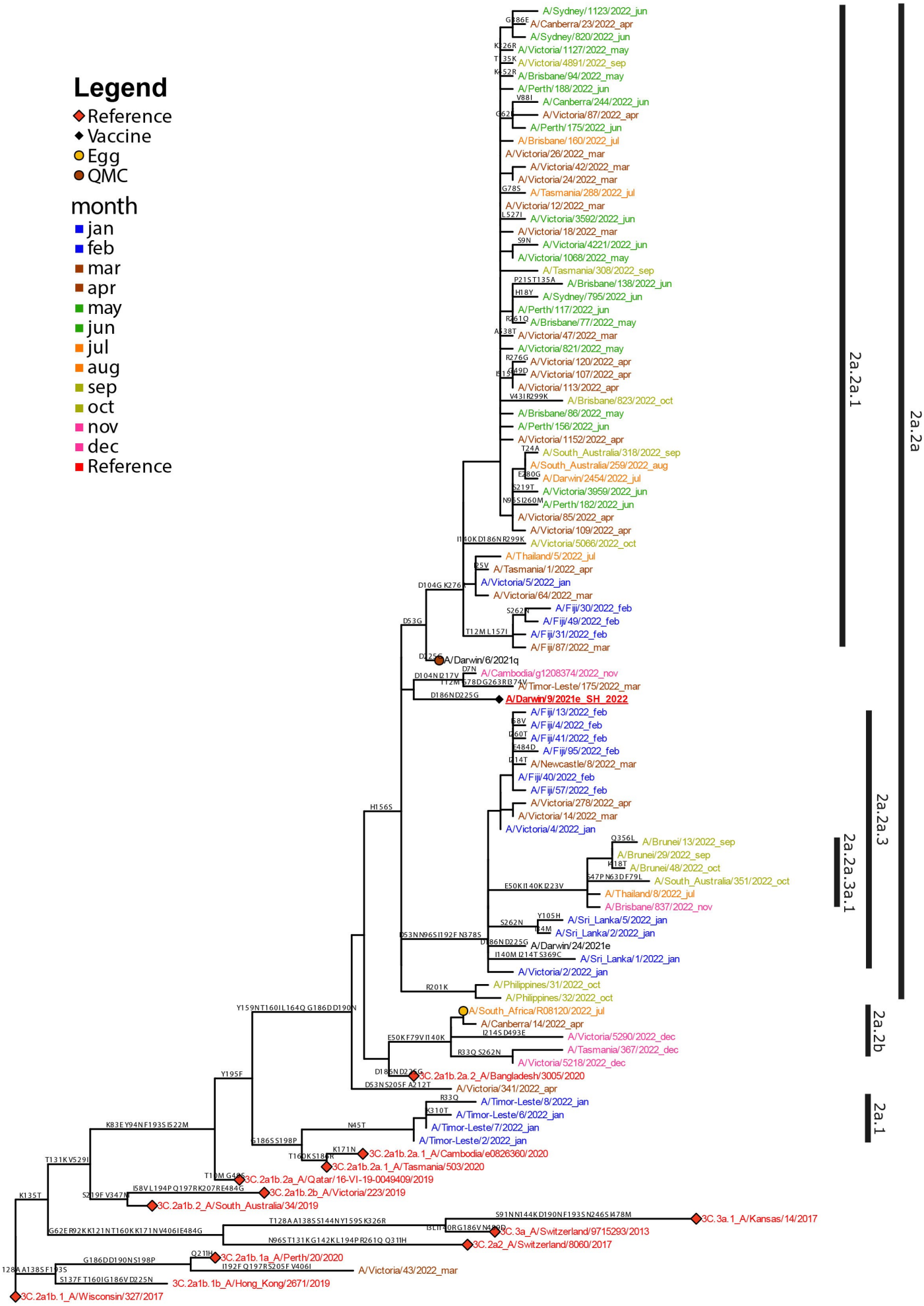


Figure 13. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2022.



Influenza B/Victoria

Introduction

In recent years, there were two antigenically and genetically distinct lineages of influenza B virus in circulation — the B/Victoria/2/87 lineage (represented by the 2022 vaccine strain, B/Austria/1359417/2021), and the B/Yamagata/16/88 lineage (represented by the 2022 vaccine strain B/Phuket/3073/2013). Until 2001, B/Victoria lineage viruses had been restricted to Asia where they tended to alternate in predominance with the B/Yamagata lineage. In 2002 the B/Victoria lineage became the predominant influenza B lineage in most parts of the world. This trend was reversed in 2003 and 2004 when the B/Yamagata lineage predominated. Since then both lineages have co-circulated, with alternating cycles of predominance every few years. During 2022 there were no B/Yamagata lineage viruses detected globally, and the Centre did not receive any samples of these viruses.

Antigenic Analysis

A total of 113 B/Victoria lineage isolates were analysed by HI assay in 2022. Of these, 37 samples were tested against the cell-grown 2021 Southern Hemisphere recommended vaccine strain B/Washington/02/2019. All viruses from South East Asia were antigenically dissimilar to the reference strain, and around 10% of viruses from South Asia were antigenically dissimilar to the reference strain (Figure 14, Table 8). In addition, 76 samples were tested against the cell-grown 2022 Southern Hemisphere recommended vaccine strain B/Austria/1359417/2021. All samples were antigenically similar to the cell-grown reference virus (Figure 15, Table 9).

Haemagglutinin gene sequencing

A total of 110 HA genes were sequenced in B/Victoria lineage viruses. Phylogenetic analysis indicate that the majority of circulating viruses fell into clade V1A.3a.2, which contains the Southern Hemisphere 2022 recommended vaccine strain B/Austria/1359417/2021 (Figure 16).

Table 8. Antigenic characterisation of B/Victoria viruses received at the Centre during 2022 compared to the B/Washington/02/2019 reference virus.

	B/Victoria lineage reference strain: B/Washington/02/2019	
Region	**Like**	**Low reactor (%)**
South East Asia	0	25 (100%)
South Asia	10	1 (9.09%)
TOTAL	**11**	**26 (70.27%)**

Table 9. Antigenic characterisation of B/Victoria viruses received at the Centre during 2022 compared to the B/Austria/1359417/2021 reference virus.

	B/Victoria lineage reference strain: B/Austria/1359417/2021	
Region	**Like**	**Low reactor (%)**
Australasia	33	0 (0%)
South East Asia	39	0 (0%)
Africa	4	0 (0%)
TOTAL	**76**	**0 (0%)**

Figure 14. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to B/ Washington/02/2019 reference virus.

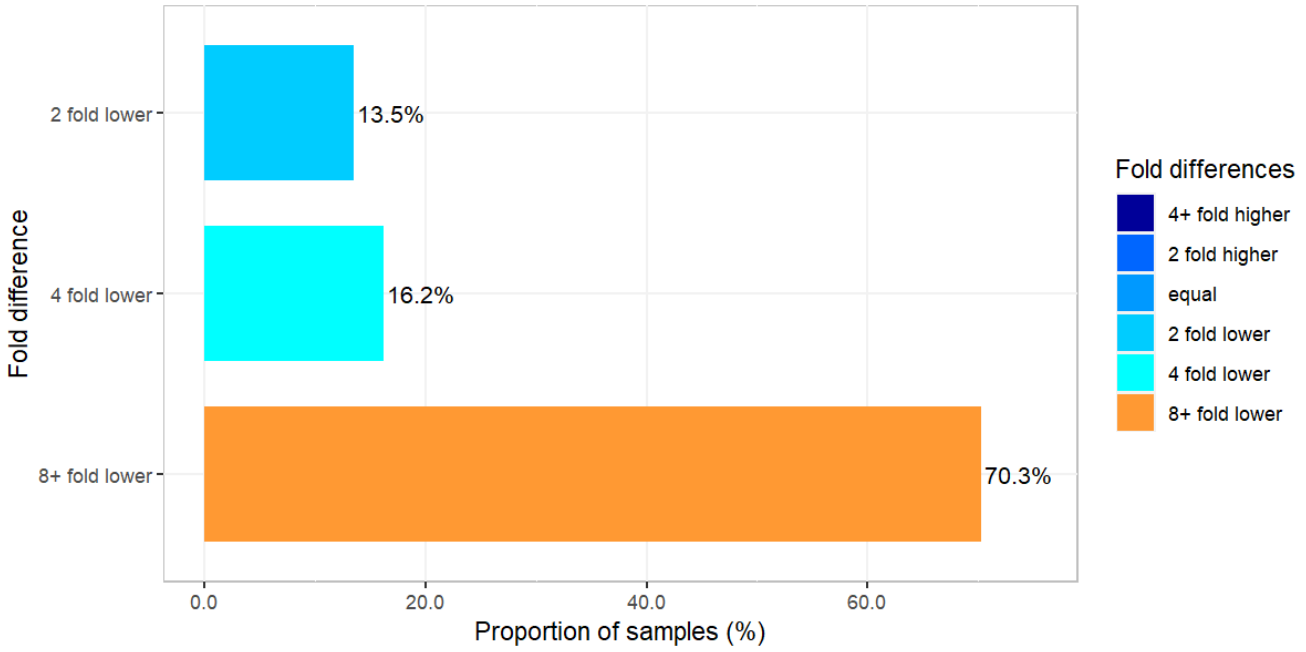


Figure 15. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to B/ Austria/1359417/2021 reference virus.

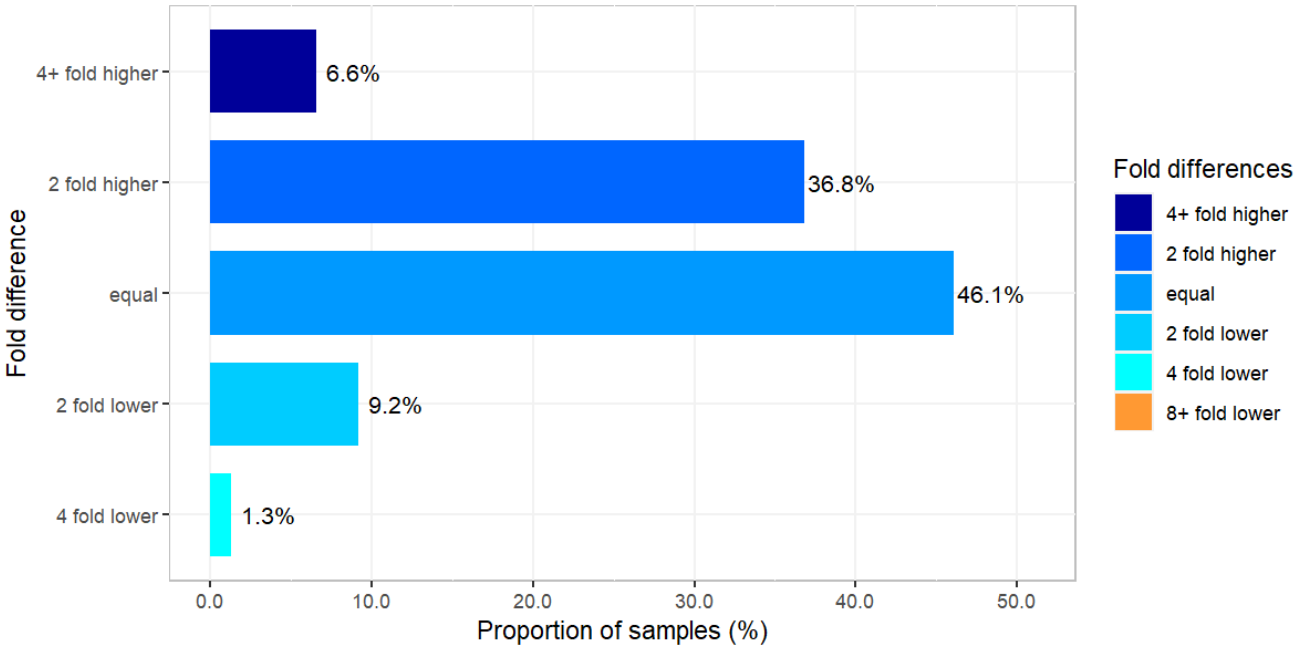
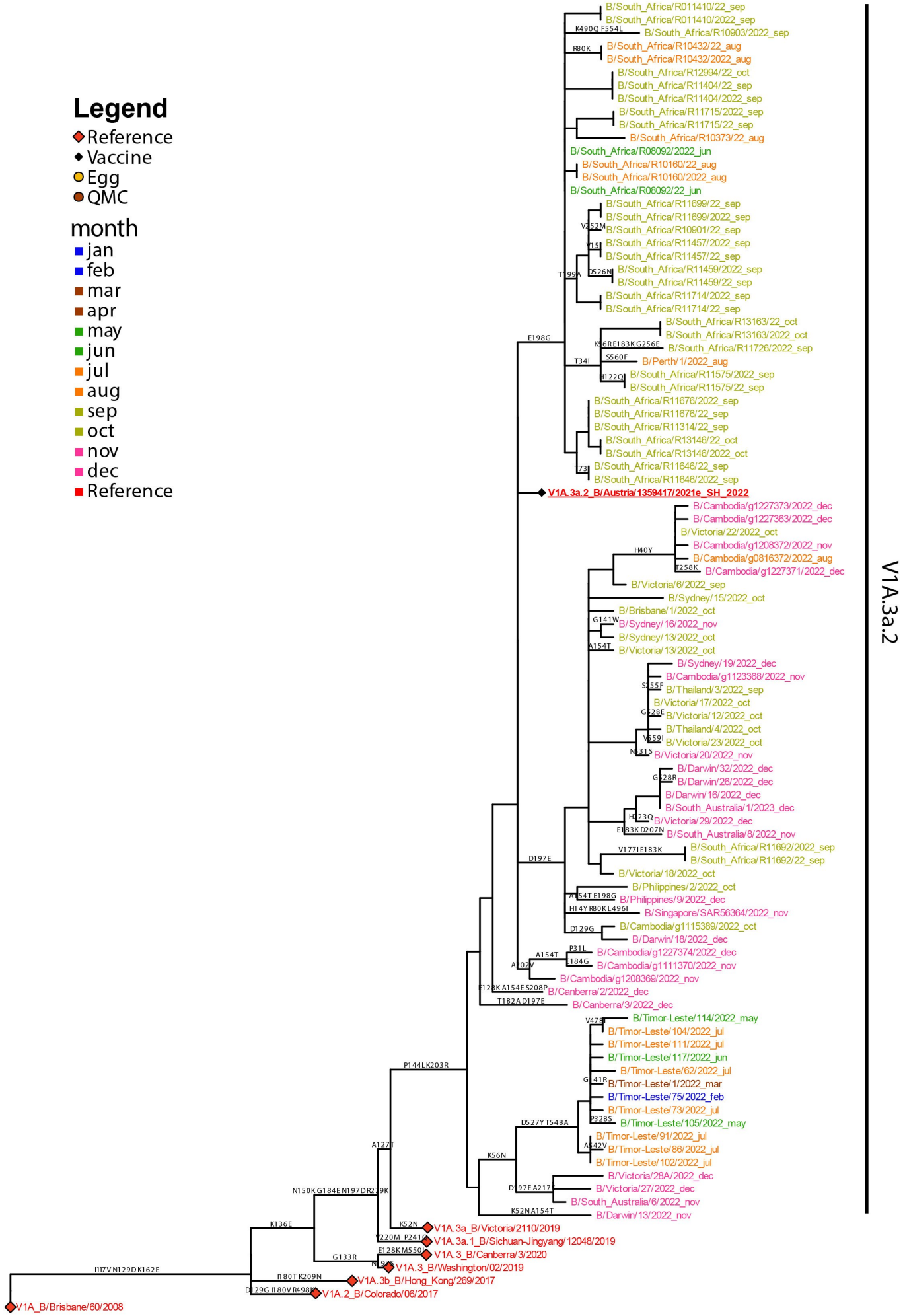


Figure 16. Phylogenetic tree of representative HA genes of B/Victoria viruses received by the Centre during 2022.



Antiviral Drug Resistance Testing

Sensitivity to Neuraminidase Inhibitors (NAIs)

Background

As influenza viruses continually undergo genetic change, their potential to develop resistance to antiviral drugs is an ongoing concern. To detect the emergence of drug-resistant influenza strains that could present future treatment challenges, viruses are tested for their sensitivity to the currently used neuraminidase inhibitors oseltamivir (Tamiflu), zanamivir (Relenza), laninamivir and peramivir. The latter two inhibitors are not currently approved in Australia but used in Korea (peramivir), USA (peramivir) and Japan (laninamivir and peramivir) and under clinical trial in many countries around the world. The Centre has routinely tested and reported the sensitivity of viruses to all four NAIs using the neuraminidase inhibition assay (NAI assay) since 2012. Viruses are routinely screened by an automated NAI assay using a Tecan EVO 200 liquid handling robot.

The sensitivity of viruses to NAIs is measured according to the concentration of drug required to inhibit 50% of NA activity (IC_{50}). The relationship between the IC_{50} value and the clinical effectiveness of a neuraminidase inhibitor against a given virus is not well understood. Further studies would be required to determine whether a virus with an elevated IC_{50} is clinically resistant.

Table 10. Viruses received by the Centre in 2022 and tested by NAI assay, by country.

Type/ subtype/ lineage / Country	A(H1N1)pdm09	A(H3N2)	B/Victoria	B lineage undetermined	TOTAL
Australasia					
Australia	742	1806	34		**2582**
New Zealand	4	144			**148**
South East Asia					
Brunei		30			**30**
Cambodia		11	1		**12**
Malaysia		135			**135**
Philippines	2	17	3		**22**
Singapore		44	28	1	**73**
Thailand		9			**9**
Timor-Leste		65	32		**97**
South Asia					
India	17	14	17		**48**
South Pacific					
Fiji		21			**21**
New Caledonia		43			**43**
Africa					
South Africa	37	14	28		**79**
TOTAL	**802**	**2353**	**143**	**1**	**3299**

Antiviral resistance analyses 2022

NAI assays were used to analyse 3299 viruses for reduced inhibition by the NAIs (Tables 10 and 11). Viruses showing highly reduced inhibition to one or more NAIs underwent further analysis to determine the presence of amino acid substitutions in the NA protein associated with the reduction of inhibition by NAIs.

A total of 2 viruses (2 A(H1N1)pdm09) had highly reduced inhibition by one or more of the NAIs. These viruses underwent further analysis to determine the presence of amino acid substitutions in the NA protein that associated with the reduction of inhibition by NAIs (Table 12), for example histidine to tyrosine at position 275 (H275Y) of the neuraminidase protein of A(H1N1)pdm09 viruses, which reduces inhibition by oseltamivir, or the equivalent H273Y mutation in B viruses.

Table 11. Neuraminidase inhibitor sensitivity of viruses received by the Centre in 2022.*

Type/Subtype/ Lineage	No. tested	Oseltamivir		Peramivir		Laninamivir		Zanamivir	
		RI	HRI	RI	HRI	RI	HRI	RI	HRI
A(H1N1)pdm09	802		2 (0.25%)		2 (0.25%)				
A(H3N2)	2353								
B/Victoria	143								
B lineage	1								
TOTAL	**3299**	**0**	**2 (0.06%)**	**0**	**2 (0.06%)**	**0**	**0**	**0**	**0**

Based on IC_{50}, the NAI sensitivity of each strain is classified as the following: **Normal inhibition = IC_{50} values are within or close to the median IC_{50} of type/subtype-matched viruses tested at the Centre during 2019-2020. **Reduced inhibition (RI)** = IC_{50} values are 10 to 100 fold above the median value of viruses with normal inhibition (5 to 50 fold for influenza B viruses). **Highly reduced inhibition (HRI)** = IC_{50} values are greater than 100 fold above the median value of viruses with normal inhibition (above 50 fold for influenza B viruses).*

Table 12. Characteristics of viruses received by the Centre during 2022 with highly reduced inhibition by NAIs.

Type/ Subtype/ Lineage	Country/city of submitting laboratory	NAI(s) with highly reduced inhibition (marked with *)				Mutation(s) detected
		Oseltamivir	Peramivir	Laninamivir	Zanamivir	
A(H1N1) pdm09	Australia (Sydney)	*	*			H275Y
	Australia (Sydney)	*	*			H275Y

Resistance to Baloxavir Marboxil

Background

Baloxavir marboxil (XofluzaTM) is an antiviral drug that has had regulatory approval for use in the treatment of influenza in Japan and the USA since 2018, and in Australia since 2020. Baloxavir acts by inhibiting the PA endonuclease of influenza A and B viruses, thereby preventing viral replication in host cells. As part of its antiviral drug resistance surveillance program, the Centre has developed a biological assay to detect and monitor circulating influenza viruses with reduced baloxavir sensitivity.

A subset of viruses received at the Centre are selected as temporally and geographically representative viruses and analysed using a phenotypic focus reduction assay (FRA-BX) to detect reduced sensitivity to baloxavir. Viral isolates showing a significant change in antiviral drug susceptibility in the FRA-BX assay are further analysed by sequencing or pyrosequencing of the PA endonuclease gene for known or novel mutations associated with reduced sensitivity to baloxavir, for example for a change in amino acid position 38 of the PA endonuclease from isoleucine to other residues such as threonine or methionine which is known to confer resistance to baloxavir. Selected viruses are also screened for mutations in the I38 position of the PA endonuclease, either by whole genome sequencing conducted as part of the Centre's routine genetic analysis, or pyrosequencing.

Screening for baloxavir resistance in 2022

Until June 2020, a subset of viruses received at the Centre that had been selected as representative viruses from different time periods and geographic locations were analysed using a focus reduction assay (FRA) to detect a reduction in sensitivity to baloxavir. However, due to a solubility issue associated with the active form (baloxavir acid) in the FRA assay, genotypic assays by sequencing and pyrosequencing of the PA endonuclease gene were primarily used during subsequent years to detect any known or novel mutations associated with reduced sensitivity to baloxavir. Analysis of 162 viruses by FRA assay and 801 viruses by pyrosequencing or sequencing did not identify any viruses with mutations in the I38 position of the PA endonuclease (Table 13).

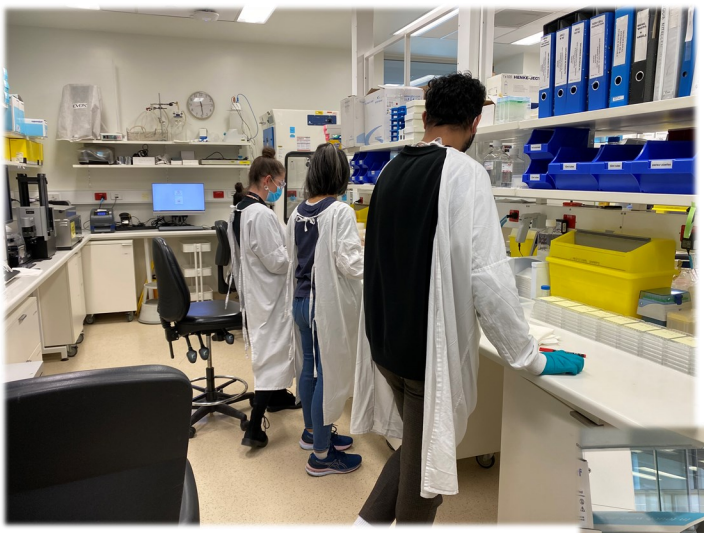


Table 13. Viruses screened for reduced susceptibility to baloxavir during 2022, by FRA-BX assay and pyrosequencing/ sequencing.

	FRA-BX assay				Pyrosequencing/ sequencing			
Type/ subtype/ lineage / Country	A(H1N1)pdm09	A(H3N2)	B/Victoria	TOTAL	A(H1N1)pdm09	A(H3N2)	B/Victoria	TOTAL
Australasia								
Australia	1	79	2	**82**	225	330	17	**572**
New Zealand		5	1	**6**	2	49		**51**
South East Asia								
Brunei						15		**15**
Cambodia		8		**8**		6	1	**7**
Malaysia						5		**5**
Philippines		1	3	**4**		15	2	**17**
Singapore		5	19	**24**				
Thailand		5		**5**				
Timor-Leste						13	7	**20**
South Asia								
India	6			**6**	6	2		**8**
South Pacific								
Vanuatu		4		**4**		11		**11**
Africa								
South Africa		8	10	**18**	42	9	24	**75**
TOTAL	**7**	**120**	**35**	**162**	**275**	**475**	**51**	**801**

Resistance to Adamantanes

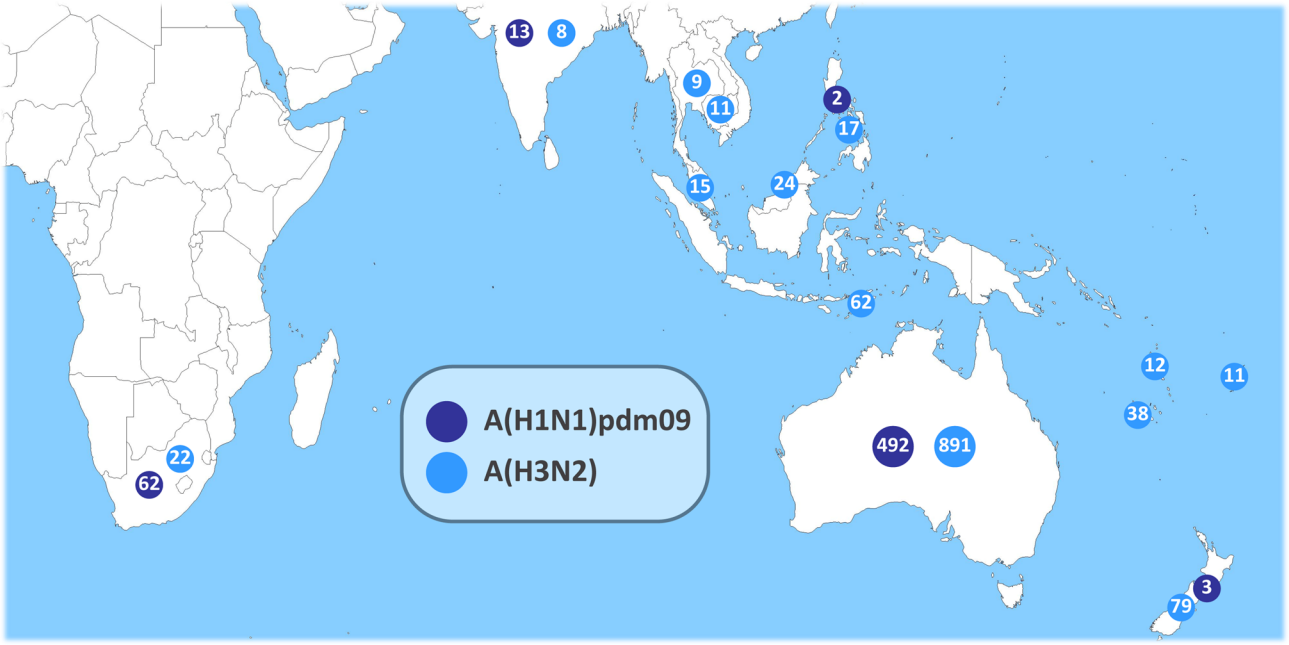
Background

The adamantane class of antiviral drugs (amantadine and rimantadine) were previously used to treat cases of influenza A, but are no longer recommended due to the almost universal adamantane resistance amongst circulating influenza A strains in recent years. All five WHO Collaborating Centres continue to screen submitted viruses for the most common resistance-conferring mutation, serine to alanine at position 31 (S31N), in the influenza A M2 protein.

Screening for adamantane resistance in 2022

Real-time PCR or sequencing was used to analyse 1771 influenza A viruses, which were representative of those submitted to the Centre during 2022 (Figure 17). All of the tested influenza A viruses carried the S31N mutation, indicating that they would be resistant to adamantanes.

Figure 17. Geographic spread of viruses received at the Centre during 2022 and screened for adamantane resistance.



Candidate Vaccine Strains

Background

The Centre collaborates closely with the other WHO Collaborating Centres and vaccine manufacturers to ensure the suitability of candidate strains for inclusion in seasonal vaccines. Selected original clinical specimens containing potential vaccine strains are used to isolate viruses in eggs and qualified Madin-Darby canine kidney (MDCK) cells (QMCs) in laboratories designed for this purpose under conditions consistent with current internationally accepted regulatory requirements for influenza vaccine viruses. These isolates are then analysed by HI assay and genetic sequencing.

Isolation of viruses in eggs in 2022

In 2022, a total of 29 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 76.3% (Tables 14 and 16).

Table 14. Virus isolation in eggs at the Centre in 2022.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	20	17	85.0%
A(H3N2)	18	12	66.7%
Total	**38**	**29**	**76.3%**

Isolation of viruses in cells in 2022

In 2022, a total of 42 viruses were successfully isolated in qualified cells at the Centre, representing an overall isolation rate of 77.8% (Tables 15 and 17).

Table 15. Virus isolation in cells at the Centre in 2022.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	23	18	78.3%
A(H3N2)	31	24	77.4%
Total	**54**	**42**	**77.8%**

Table 16. Potential candidate vaccine strains isolated in eggs at the Centre in 2022.

A(H1N1)pdm09	A(H3N2)
A/South Africa/15549/2021	A/Darwin/36/2021
A/South Africa/15060/2021	A/Iowa/08/2021
A/South Africa/15053/2021	A/Alaska/01/2021
A/Sydney/173/2022	A/Georgia/02/2021
A/Sydney/175/2022	A/Victoria/6/2022
A/Darwin/7/2022	A/Victoria/39/2022
A/Newcastle/39/2022	A/Canberra/1/2022
A/Sydney/866/2022	A/Tasmania/5/2022
A/Sydney/798/2022	A/Sydney/732/2022
A/Sydney/729/2022	A/Thailand/8/2022
A/South Africa/R05744/2022	A/South Africa/R08120/2022
A/South Africa/R05722/2022	A/South Africa/R08953/2022
A/Brisbane/792/2022	
A/Victoria/4880/2022	
A/Victoria/4897/2022	
A/Victoria/5172/2022	
A/Victoria/5135/2022	

Table 17. Potential candidate vaccine strains isolated in cells at the Centre in 2022.

A(H1N1)pdm09	A(H3N2)
A/South Africa/13996/2021	A/South Africa/13327/2021
A/South Africa/14072/2021	A/South Africa/16017/2021
A/South Africa/16316/2021	A/Singapore/SAR8232/2021
A/Newcastle/2/2022	A/Singapore/INFKK0017/2021
A/Victoria/7/2022	A/Fiji/13/2022
A/Sydney/9/2022	A/Fiji/42/2022
A/Darwin/5/2022	A/Victoria/10/2022
A/Darwin/7/2022	A/Victoria/12/2022
A/Sydney/173/2022	A/Victoria/4/2022
A/Sydney/174/2022	A/Victoria/6/2022
A/Brisbane/50/2022	A/Sydney/59/2022
A/Sydney/798/2022	A/Timor-Leste/155/2022
A/Sydney/869/2022	A/New Caledonia/21/2022
A/Sydney/877/2022	A/New Caledonia/55/2022
A/Brisbane/792/2022	A/Victoria/758/2022
A/Victoria/4897/2022	A/Victoria/811/2022
A/Victoria/5172/2022	A/Victoria/878/2022
A/Victoria/5135/2022	A/Sydney/405/2022
	A/Canberra/14/2022
	A/Sydney/732/2022
	A/Sydney/751/2022
	A/South Australia/130/2022
	A/Sydney/1304/2022
	A/Brisbane/837/2022

Preparation and Analysis of Vaccine Seed Viruses

The Centre exchanges candidate vaccine viruses that have been isolated in eggs, as well as post-infection ferret antisera raised against these and other reference viruses, with the other WHO Collaborating Centres to enable direct comparison of strains isolated in the five Centres. During 2022, 13 candidate vaccine viruses that had been received from other WHO Collaborating Centres and laboratories were passaged in eggs at the Centre (Table 18).

Selected egg-isolated candidate vaccine strains are made available to the three laboratories that undertake virus reassortment for WHO — Seqirus, the National Institute for Biological Standards and Control (NIBSC, UK) and New York Medical College (NYMC, USA) — where they are reassorted with established egg-adapted strains to produce potential vaccine seed strains. The reassortant vaccine seed viruses are returned to the Centre, where they are analysed by HI assay and genetic sequencing to ensure that key antigenic and genetic properties of the vaccine virus have been retained. The vaccine seed viruses are distributed to other WHO Collaborating Centres and vaccine manufacturers worldwide through Essential Regulatory Laboratories at the Therapeutic Goods Administration (Australia), NIBSC and the Centre for Biologics Evaluation and Research, Food and Drug Administration (USA).

Table 18. Potential candidate vaccine viruses from other WHO Collaborating Centres isolated at the Centre during 2022.

A(H1N1)pdm09
A/Togo/44/2021
A/Qatar/16-VI-21-3837777/2021
A/North Carolina/01/2021
CBER-48A (A/Sydney/5/2021)
A(H3N2)
A/Netherlands/00007/2021
NIB-130 (A/Darwin/22/2021)
A/Guizhou-liuzhite/326/2022
B/Victoria
B/Austria/1359417/2021
B/Maryland/01/2021
B/Zhejiang-Xiacheng/11085/2021
B/Shanghai-Chongming/38/2021
H5N8
CBER-RG8A (A/Astrakhan/3212/2020)
IDCDC-RG71A

Serological Analyses

Background

Antigenic changes in circulating influenza viruses are also monitored by the extent to which they are inhibited by antibodies produced by subjects who have been immunised with current inactivated seasonal influenza vaccines. Twice a year the WHO Collaborating Centres and Essential Regulatory Laboratories in the WHO surveillance network exchange panels of sera collected from subjects pre- and post-influenza vaccination. These panels are analysed using the HI assay against the current vaccine and representative influenza strains in preparation for the biannual WHO Consultations on the Composition of Influenza Vaccines (Table 19).

Serum panel analyses in February 2022

In February the Centre analysed serum panels from the following age groups: paediatric (0-36 months), paediatric (3-8 years), paediatric (9-17 years), adults (18-64 years), older adults (51-64 years), and elderly adults (>65 years) who had received the 2021-2022 Northern Hemisphere seasonal quadrivalent inactivated egg, cell-based, or recombinant influenza vaccine, in the USA.

A(H1N1)pdm09: The combined data from all WHO Collaborating Centres and ERLs showed that post vaccination geometric mean HI titres (GMT) induced against A/Wisconsin/588/2019-like vaccine viruses reacted well with subclade 5a.2 viruses. Post-vaccination GMTs against some cell-propagated subclade 5a.1 viruses were reduced in some sera panels.

Serological Analyses (continued)

Serum panel analyses in February 2022 (continued)

A(H3N2): Using HI and virus neutralisation (VN) assays, and compared to GMTs against cell culture-propagated A/Cambodia/e0826360/2020-like 2a.1 vaccine viruses, post-vaccination GMTs against many cell-culture propagated 2a.2 viruses were significantly reduced in most serum panels. GMTs against 2a.1 viruses were not reduced.

B/Victoria: When compared to GMTs against cell-culture propagated B/Washington/02/2019-like vaccine viruses, post-vaccination HI GMTs against some 3a.1 viruses were reduced, and for most serum panels reductions were more pronounced for 3a.2 viruses. When compared to the GMTs against the egg-propagated B/Washington/02/2019 vaccine virus, GMTs against most 3a.1 and 3a.2 viruses were significantly reduced.

B/Yamagata: No serology studies were performed for B/Yamagata viruses

Serum panel analyses in September 2022

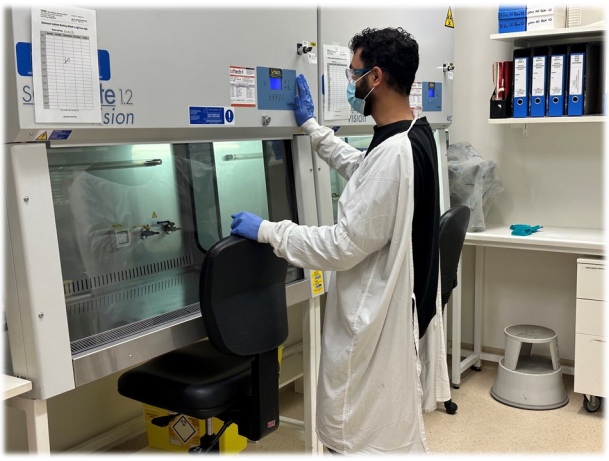
In September, the Centre analysed serum panels from adults (18-64 years) and the elderly (>65 years) who had received either the 2022 Southern Hemisphere seasonal quadrivalent inactivated egg or cell-based vaccine in Australia.

A(H1N1)pdm09: Human serology studies using these serum panels showed minor reductions in post-vaccination HI geometric mean titres (GMTs) for the majority of recently circulating, representative A (H1N1)pdm09 5a.1 viruses when compared to cell culture-propagated A/Wisconsin/588/2019-virus. Significant reductions in HI GMTs were observed for some 5a.2 viruses with additional HA1 amino acid substitutions A186T, Q189E, T216A and E224A, notably so for those with additional amino acid substitutions P137S and K142R. When measured against egg-propagated A/Victoria/2570/2019, most recent A(H1N1)pdm09 viruses showed significantly reduced GMTs.

A(H3N2): Using HI and VN assays, GMTs against most recent representative viruses from genetic groups 2a.2 and 2a.1 were not significantly reduced compared to titres against the cell culture-propagated A/Darwin/6/2021 vaccine virus. Reductions of VN GMTs were more pronounced when compared to egg-propagated A/Darwin/9/2021-like reference viruses.

B/Victoria: There were no significant reductions in post-vaccination HI GMTs against the majority of recent representative B/Victoria lineage viruses from the 3a.2 subgroup when compared to the egg or cell culture-propagated B/Austria/1359417/2021 vaccine viruses. Significant reductions were detected with most serum panels for viruses from clade 1A.3 with additional amino acid substitutions K75E, E128K, T155A and G230N.

B/Yamagata: No serology studies were performed for B/Yamagata viruses.



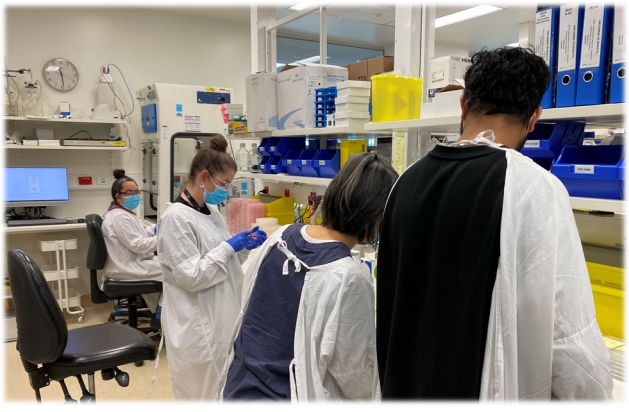


Table 19. Representative and vaccine candidate strains used for serological analyses during 2022.

FEBRUARY	SEPTEMBER
A(H1N1)pdm09	**A(H1N1)pdm09**
A/India/PUN-NIV-323546/2021 (C)	A/Brisbane/50/2022 (C,E)
A/Qatar/16-VI-21-3837777/2021 (C,E)	A/Connecticut/01/2021 (C)
A/Sydney/5/2021 (C,E)	A/Darwin/7/2022 (C)
A/Victoria/2570/2019*^ (C,E)	A/Guangdong-Maonan/SWL1536/2019 (C)
	A/South Africa/R04202/2022 (C)
	A/Sydney/173/2022 (C,E)
	A/Victoria/2570/2019*^ (C,E)
	A/Wisconsin/588/2019 (C)
A(H3N2) (microneutralisation assays)	**A(H3N2) (microneutralisation assays)**
A/Cambodia/e0826360/2020 (C,E)	A/Darwin/6/2021*^ (C,E)
A/Darwin/11/2021 (C)	A/Guangdong-Zhongshan/1443/2022 (C)
A/Darwin/24/2021 (C)	A/Guizhou-Liuzhite/326/2022 (E)
A/Darwin/36/2021 (C)	A/Maryland/02/2021 (C)
A/Darwin/6/2021*^ (E)	A/Newcastle/58/2022 (C)
A/Maryland/02/2021 (C)	A/Singapore/GP1048/2022 (C)
	A/Tasmania/1/2022 (C)
	A/Timor-Leste/117/2022 (C)
	A/Victoria/39/2022 (C,E)
	A/Victoria/6/2022 (C,E)
B/Victoria	**B/Victoria**
B/Austria/1359417/2021*^ (C,E)	B/Austria/1359417/2021*^ (C,E)
B/Darwin/11/2021 (C)	B/Netherlands/11263/2022 (C)
B/Maryland/01/2021 (E)	B/Sydney/1/2022 (C)
B/Shanghai-Chongming/38/2021 (C,E)	B/Sydney/4/2022 (C)
B/Washington/02/2019 (C,E)	
B/Yamagata	
B/Phuket/3073/2013* (C,E)	

**Trivalent vaccine strain ^Quadrivalent vaccine strain*

[E]: Egg-grown virus [C]: Cell-grown virus

Recommendations on Influenza Vaccines

WHO Consultations on the Composition of Seasonal Influenza Vaccines

The antigenic, genetic, antiviral resistance and serological data generated from the Centre's surveillance activities are incorporated into detailed dossiers for use at the WHO Consultations on the Composition of Influenza Vaccines in February (for the Northern Hemisphere) and September (for the Southern Hemisphere).

The Centre Director and Deputy Director participate in preparatory teleconferences and then meet at the face-to-face Consultation with WHO, representatives from the other WHO Collaborating Centres and the four Essential Regulatory Laboratories (Center for Biologics Evaluation and Research, US Food and Drug Administration, USA; National Institute for Biological Standards and Control, UK; National Institute of Infectious Diseases, Japan; Therapeutic Goods Administration, Australia). Vaccine effectiveness estimates were also presented by the Centre's senior epidemiologist in person at the Consultation in September. Consultations are also attended by observers from the World Organisation for Animal Health (WOAH), the University of Cambridge, several WHO National Influenza Centres and other relevant organisations. In 2022 WHO made the recommendations reported below.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2022-2023, Geneva, Switzerland, 25 February 2022

It is recommended that quadrivalent vaccines for use in the 2022-2023 influenza season (Northern Hemisphere winter) contain the following:

Egg-based vaccines

- 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 vaccines

- 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^.

It is recommended that trivalent vaccines for use in the 2022-2023 influenza season (Northern Hemisphere winter) contain the following:

Egg-based Vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Darwin/9/2021 (H3N2)-like virus^; and
- a B/Washington/02/2019 (B/Victoria lineage)-like virus.

Cell– or recombinant-based vaccines

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

^ *Viruses originally isolated as egg-derived candidate vaccine viruses at the WHO Collaborating Centre in Melbourne.*

WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2023, Geneva, Switzerland, 23 September 2022

It is recommended that quadrivalent vaccines for use in the 2023 influenza season (Southern Hemisphere winter) contain the following:

Egg-based vaccines

- an A/Sydney/5/2021 (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 vaccines

- an A/Sydney/5/2021 (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^.

It is recommended that trivalent vaccines for use in the 2023 influenza season (Southern Hemisphere winter) contain the following:

Egg-based Vaccines

- an A/Sydney/5/2021 (H1N1)pdm09-like virus^;
- an A/Darwin/9/2021 (H3N2)-like virus^; and
- a B/Washington/02/2019 (B/Victoria lineage)-like virus.

Cell– or recombinant-based vaccines

- an A/Sydney/5/2021 (H1N1)pdm09-like virus^;
- an A/Darwin/6/2021 (H3N2)-like virus^; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

^ Viruses originally isolated as egg-derived candidate vaccine viruses at the WHO Collaborating Centre in Melbourne.

In addition to the overall recommendations as described above, WHO lists candidate vaccine viruses (CVVs) that may be suitable for inclusion in vaccines. These CVVs, which are listed on the WHO website, are antigenically similar to the recommended vaccine strains. In 2022 the following candidate vaccine viruses, which were originally isolated at the Centre in either eggs or cells, were listed by WHO as being suitable for vaccine use following the indicated meeting.

Type/Subtype/ Lineage	Egg-derived CVVs	Cell-derived CVVs
A(H1N1)pdm09	A/Victoria/2570/2019 (Feb) A/Victoria/3/2020 (Feb) A/Victoria/1/2020 (Feb) A/Sydney/5/2021 (Sep)	A/Sydney/5/2021 (Sep)
A(H3N2)	A/Darwin/9/2021 (Feb, Sep) A/Darwin/6/2021 (Feb, Sep)	A/Darwin/11/2021 (Feb, Sep)
B/Victoria	B/Singapore/WUH4618/2021 (Feb, Sep)	B/Singapore/WUH4618/2021 (Feb, Sep)
B/Yamagata	B/Phuket/3073/2013 (Feb, Sep) B/Brisbane/9/2014 (Feb, Sep)	B/Brisbane/9/2014 (Feb, Sep) B/Singapore/INFKK-16-0569/2016 (Feb, Sep) B/Singapore/INFKK-16-0610/2016 (Feb, Sep)

 # Indicates CVVs newly included in the WHO list of viruses suitable for vaccine use

Australian Seasonal Influenza Vaccine Recommendation

Whereas the WHO makes recommendations on suitable viruses for inclusion in seasonal influenza vaccines, in individual countries the decision on the composition of vaccines is made by national or regional authorities. In Australia, the Therapeutic Goods Administration makes the decision on the advice of the Australian Influenza Vaccine Committee (AIVC). The Centre Director and Deputy Director both serve on the AIVC.

The AIVC met on 6 October 2022 and recommended that the following viruses be used for influenza vaccines in the 2023 Southern Hemisphere influenza season:

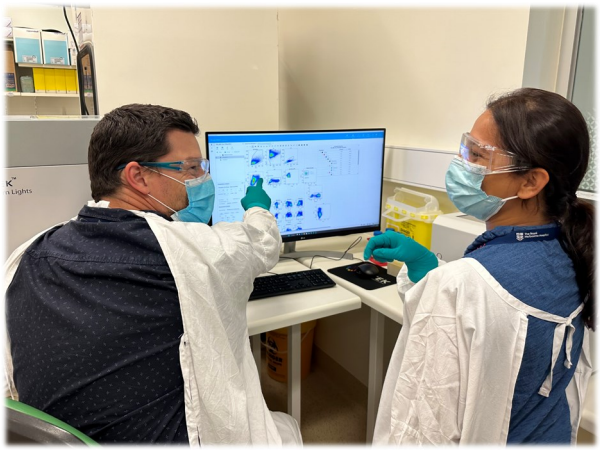
Egg-based quadrivalent vaccines:

- an A/Sydney/5/2021 (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-based trivalent vaccines:

- an A/Sydney/5/2021 (H1N1)pdm09-like virus
- an A/Darwin/6/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

The A(H1N1)pdm09, A(H3N2), and B/Victoria lineage viruses are recommended for the trivalent vaccines.



Training

Training and Support of National Influenza Centres

The Centre provides support in the form of training and advice to WHO National Influenza Centres (NICs) and other diagnostic laboratories, especially in the Asia-Pacific region. Strengthening technical capabilities and infrastructure for surveillance work in regional laboratories increases their capacity to detect and characterise circulating influenza viruses and to identify viruses with pandemic potential, thus further supporting the GISRS surveillance network. Centre staff are involved in training visiting scientists at the Centre, participate in regional workshops and visit laboratories to provide direct assistance in strengthening surveillance capabilities.

Training Programs and Visits to Regional Laboratories

Patrick Reading and **Jean Moselen** worked collaboratively during an emergency deployment to the National Referral Hospital (NRH) molecular laboratory in Honiara, Solomon Islands (22 February 2022 – 22 March 2022). They provided technical assistance and training in PCR techniques to build and strengthen NRH diagnostic capacity for detection of SARS-CoV-2 in clinical samples. This was funded by the Department of Foreign Affairs and Trade (DFAT) Indo-Pacific Centre for Health Security through the COMBAT-AMR project.

Patrick Reading, **Jean Moselen**, and **Miku Kuba** worked with the Secretariat of the Pacific Community (SPC) and DFAT Australia to advise on the implementation of PCR testing in Pacific Islands for molecular diagnosis of respiratory virus infections. This work has involved (i) guidance and advice on building new facilities or renovation of existing facilities, (ii) advice of all equipment and consumables to purchase for a functional PCR laboratory, (iii) regular online meetings for advice and planning to Pacific Island Countries, (iv) development of training materials for PCR, including training videos, lectures, SOPs and other guidance documents, (v) and advice and evaluation regarding the usefulness of automated platforms in the Pacific and (vi) delivery of remote training to Pacific Island Countries that are setting up PCR for the first time. Countries receiving support, advice and training include Vanuatu, Cook Islands, Solomon Islands, Tonga, Tuvalu, Samoa and Kiribati. Since July 2021, our team have supported and completed training with Vanuatu and Kiribati and these countries have now commenced PCR testing for the first time. DFAT subsequently organised for an Australian scientist to be seconded to Tuvalu for 6 months (Feb – July 2022) with the aim of working with our team to enhance laboratory capacity in this island nation. This position has been extended to continue into 2023.

Patrick Reading continued to work with the WHO Western Pacific Regional Office (WPRO) and WHO Country Offices to provide advice for the expansion of PCR testing networks in particular countries, including Cambodia and Mongolia. This work has involved advising on building and renovation of PCR laboratories, purchase of suitable equipment and consumables and provision of training materials to assist laboratories setting up PCR for the first time. He has also been working with WPRO to advise on molecular testing kits and technologies for respiratory viruses.

Training Programs and Visits to Regional Laboratories (continued)

Patrick Reading continued as a Consultant and Advisor to the Australia Indonesia Health Security Partnership. This role involves working with different partner agencies to provide advice and support to diagnostic laboratories within Indonesia.

Yi-Mo Deng taught the International Influenza and SARS-CoV-2 Genetic Sequencing Course at the Thai National Influenza Center in Nonthaburi, Thailand, between 22-25 August 2022

Sheena Sullivan was engaged by the WHO Country Office in Cambodia on a joint programme review of acute respiratory diseases, Cambodia. The review was held from 27 October – 4 November 2022 in Phnom Penh, with site visits to various sentinel sites around the country.

Patrick Reading was involved a training workshop to strengthen influenza-like illness (ILI) and severe acute respiratory infections (SARI) surveillance in the Pacific, in Nadi, Fiji, between 9-11 November 2022.

Patrick Reading was involved in the joint national and international review of influenza preparedness in Dili, Timor-Leste (surveillance review and laboratory assessment), between 21-25 November 2022. Patrick Reading led the Laboratory Team to assess the Laboratório Nacional de Saúde to determine the strengthening required for designation as a National Influenza Centre in the future. At the same time, an international Surveillance Team also assessed influenza surveillance capacity in Timor Leste. The Laboratory Team of international experts also included:

Dr ASM Alamgir (retired Principal Scientific Officer (PSO), IEDCR, Bangladesh)

Ms Lilee Shrestha (Chief Medical Technologist, NPHL, Nepal)

Mr Francis Yesurajan Inbanathan (Technical Officer, Laboratory, IHM-WHE-SEARO)

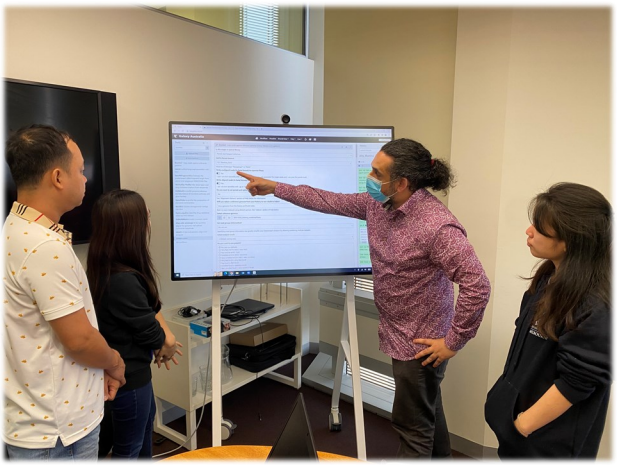
Training Programs and Visits to Regional Laboratories (continued)

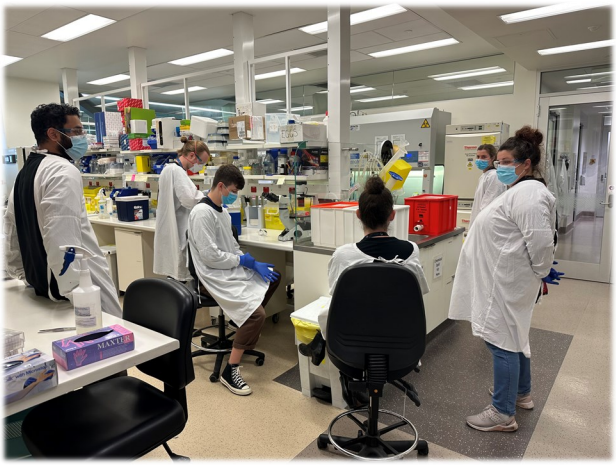
Patrick Reading visited the National Institute of Public Health and Institut Pasteur du Cambodge in Phnom Penh, Cambodia on 1 and 2 December 2022, respectively. This visit included a dinner with past trainees who have undertaken training at the Centre (post-2017).

Yi-Mo Deng went to the Ethiopia Public Health Institute in Addis Ababa, Ethiopia, as a WHO consultant to carry out SARS-CoV-2 whole genome sequencing training using the Oxford Nanopore platform, between 5-16 December 2022. She was responsible for designing the training program, delivering lectures, reviewing protocols, supervision of experimental procedures, training in bioinformatic analysis and GISAID tools for analysis and submission, making recommendations to both the laboratory and the WHO, as well as further online follow up troubleshooting.

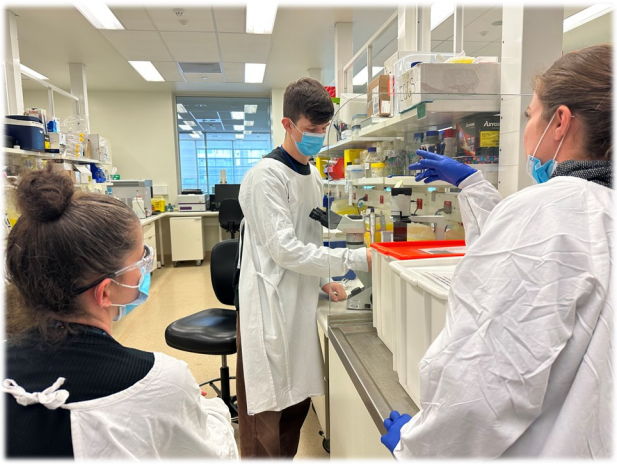
Centre-based Training

Ammar Aziz, **James Barnes**, **Ian Barr**, **Presa Chanthalavanh**, **Yi-Mo Deng**, **Xiaomin Dong**, **Steven Edwards**, **Olivia Lay**, **Heidi Peck**, **Patrick Reading**, **Cleve Rynehart**, **Natalie Spirason**, **Paul Whitney**, and **Tasoula Zakis** were all involved in delivering a training workshop on influenza virus to laboratory scientists from Institut Pasteur du Cambodge, Phnom Penh, Cambodia (two scientists), and the National Institute of Public Health, Phnom Penh, Cambodia (three scientists), between 3-14 December 2022. The workshop involved training in detecting and characterising influenza virus in clinical samples and viral isolates, as well as techniques in genetic analysis. Another workshop was run concurrently on whole genome sequencing and bioinformatic analysis of influenza viruses.





The **Serology team** led by **Heidi Peck**, alongside **Paul Whitney**, were involved in training Bryden Bird from the Institute of Environmental Science and Research, Wellington, New Zealand, between 7-21 November 2022. The main objective of his training was to learn new serological techniques for the antigenic analysis of influenza and RSV, using a cell-based Focus Reduction Assay (FRA). He also spent time observing the serology group carry out routine surveillance tasks such as cell culture and virus isolation.



Research

The Centre continues to develop and expand its research interests across a range of projects, both within the Centre and with external collaborators.

Antivirals and Viral Fitness

Centre staff and students

Mariana Baz (until August), Sook Kwan Leah Brown, Paulina Koszalka, Harry Stannard, Nikita Deshpande, Ian Barr, Kanta Subbarao

Research overview

This research stream mainly focuses on the evaluation of the effectiveness of approved and investigational influenza antivirals, as well as determining the risk of the emergence of drug resistant viruses, which may spread more widely amongst the community. We also study the viral fitness of different drug resistant variants which have emerged during in vitro passaging, or during clinical trials. Selected viruses are evaluated for their transmissibility in ferrets. This information provides insights into the likelihood that such viruses could spread more easily or not in the community.

Collaborators

Smitha Georgy (Faculty of Veterinary and Agricultural Sciences, University of Melbourne); Rubaiyea Farrukee and Sarah Londrigan (University of Melbourne), Daniel Steinfort (Royal Melbourne Hospital), Cecilia Cassaravilla, Fernando Silveira, and Manuel Baz (University of the Republic, Uruguay).

James McCaw, Pengxing Cao, and Alex Zarebski (University of Melbourne); Jesse Bloom (Fred Hutchinson Cancer Research Centre, Seattle WA, USA); Jean-Francois Rossignol (Romark Laboratories, Tampa FL, USA); Takao Shishido and Keiko Baba (Shionogi TechnoAdvance Research, Osaka, Japan); Wendy Barclay (Imperial College London, London, United Kingdom); Aeron hurt (Roche laboratories) David Williams (CSIRO ACDP) and Jeff Butler (CSIRO, ACDP).

Highlights and developments 2022

A number of publications were achieved the group in 2022, highlighting the broad and impactful research conducted.

1. Panzera Y, et. al. 2023. *Memórias do Instituto Oswaldo Cruz* (accepted 2022)
2. Baz M, et. al. 2022. *Emerg Infect Dis*
3. Stannard HL, et. al. 2022. *Commun Biol*
4. O'Neill G, et. al. 2022. *Commun Dis Intell (2018)*
5. Koszalka P, et. al. 2022. *mBio*
6. Koszalka P, et. al. 2022. *PLoS Pathog*
7. Brown SK, et. al. 2022. *Antiviral Res*

The group worked to establish contemporary influenza virus models in ferrets to explore the antiviral efficacy of molnupiravir, a licensed drug for the treatment of COVID-19, although initially approved in 2019 for clinical trials against influenza. The group pursued this study in ferrets and sought to observe the effects of Molnupiravir alone or in combination with oseltamivir, exploring the reduction of viral titres in upper and lower respiratory tract tissue, viral shedding, and aerosol transmission post antiviral treatment. This work is being written up and will soon be submitted for publication.

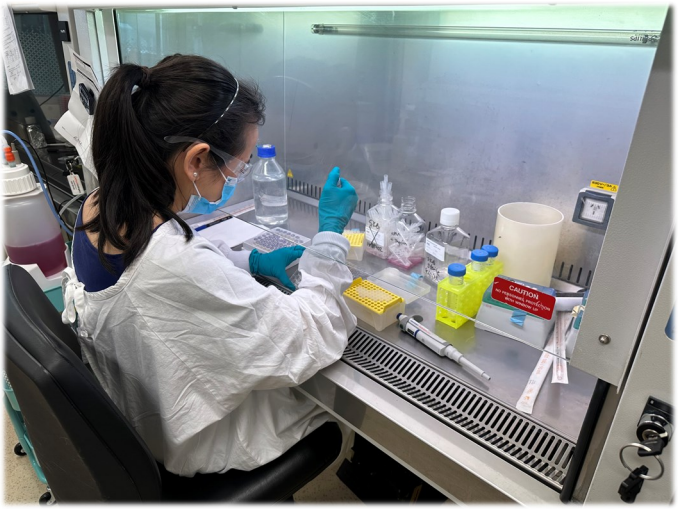
The group also used the established ferret models to explore the antiviral efficacy of a green tea extract component, EGCG, previously explored in vitro to have broad spectrum antiviral affects. This project has been completed and is in the final stages of writing for publication.

Antivirals and Viral Fitness (continued)

The group worked on a project that assessed the cross-reactivity to Omicron BA.1, BA.2, and BA.5 neutralising antibodies elicited by ancestral, Delta, and Omicron BA.1 SARS-CoV-2 infection in mice. This study has been published in Emerging Infectious Disease. The group was also involved in a project initiated by F. Hoffman-La Roche Ltd where in vitro antiviral activity of AT-511, a potential antiviral against SARS-CoV-2, was assessed. This report was submitted to F. Hoffman-La Roche Ltd in June 2022. The group also completed 3 collaborative projects:

1. Detection and genome characterisation of SARS-CoV-2 P. 6 lineage in dogs and cats living with Uruguayan COVID-19 patients (published)
2. Testing the efficacy of *Quillaja brasiliensis* nanoparticle vaccine as an adjuvant for inactivated trivalent influenza vaccine in mice (publication under review in Frontiers in Immunology)
3. Immune response, endothelial biomarkers and severity of respiratory failure in COVID-19 patients (research article in preparation)

The group also standardised the protocol to generate air-liquid interface (ALI) cultures of primary bronchial epithelial cells (pBECs) from patient bronchial brushings and created a biobank of pBECs. Bronchial brushings were obtained from collaborators Sarah Londrigan (University of Melbourne) and Daniel Steinfort (Royal Melbourne Hospital). The group has characterised the ALI pBECs using fluorescence microscopy and flow cytometry, confirming their use in infections with several respiratory viruses including Influenza (H1N1pdm09, H3N2), RSV (A&B), SARS-CoV-2 (ancestral, delta, Omicron BA.1 and BA.5 strains), Rhinovirus, HMPV, and PIV.



Avian influenza

Centre staff

Michelle Wille

Research overview

Avian influenza viruses can pose a threat to humans via direct infection from an avian source. If the virus has the ability to replicate well in humans and transmit, there is potential that such viruses may cause an influenza pandemic. We routinely sample migratory shorebirds and resident ducks in Australia to determine what types of avian influenza viruses are circulating amongst avian populations. The Centre is involved with the characterisation of viruses sampled from birds in Australia, including culture, sequencing and phylogenetic analysis. Furthermore, to understand overall exposure of Australian wild birds to influenza A virus, we are also screening blood samples for antibodies against influenza A viruses. In the case of shorebirds, this will allow us to assess not only the burden of influenza locally, but also provide insight into influenza exposure of these birds while at their northern breeding grounds, and during their annual migration.

Collaborators

Marcel Klaassen (Deakin University, Victoria); Edward Holmes (University of Sydney, Sydney NSW); Frank Wong (Australian Centre for Disease Preparedness [ACDP], Geelong VIC); Andrew Breed (Australian Government Department of Agriculture), National Avian Influenza Wild Bird Program (Wildlife Health Australia).

Highlights and developments 2022

In 2022, we collected and screened 1519 paired swab and serum samples from wild Anseriformes (ducks) and Charadriiformes (shorebirds and terns) in Victoria, Tasmania and Western Australia, with 39 influenza A virus detections. Through sequencing, the viruses comprise H1, H2, H3, H5 (low pathogenic), H6 and H10, and the vast majority were collected from duck species during the winter months.

In addition to routine sample collection, we performed heightened surveillance from September – November, coinciding with the return of migration birds to rule out HPAI incursion. All swab samples were negative for influenza and none of the serum samples which were positive by ELISA were positive by HI when using a 2.3.4.4b antigen. Results of heightened surveillance were published in *Influenza and other Respiratory Viruses* (2023).

With the increased in intensity of HPAI outbreaks in Europe, we are performing a risk assessment including mapping putative incursion pathways, an evaluation of the national passive surveillance network to understand the likelihood of HPAI detection through this system, and finally, capacity and speed of identification and response of HPAI in Australia. The report was commission by Wildlife Health Australia for the Department of Agriculture, Fisheries and Forestry.

Chestnut Teal (left) play an important role in the maintenance of AIV in Australia. Short-tailed Shearwaters (right) were sampled as part of heightened surveillance following their arrival from Beringia. Photos by Michelle Wille.

Early Recognition and Response to Influenza Infection

Centre staff

Patrick Reading, James Barnes

Research overview

Our research, which is undertaken at the Centre and at the University of Melbourne, investigates how the body first recognises and responds to infections with influenza and other respiratory viruses. We employ in vitro studies using human proteins and cells, as wells as in vivo studies using mouse and ferret models of infection. We are also interested in assessing novel treatment and vaccine platforms for influenza and other respiratory viruses in vitro and in animal models of infection.

Our current studies are focused on:

I. How different cell types in the respiratory tract sense and respond to influenza virus infection,
II. Identifying specific host proteins that are expressed in virus-infected cells and can interfere with the entry, replication and/or release of influenza and other respiratory viruses,
III. Utilising approaches to simulate host innate immunity to limit the impact of subsequent infection with influenza or other respiratory viruses and
IV. Working collaboratively with researchers at the University of Queensland to develop and assess novel vaccines against influenza and other respiratory viruses.

Collaborators

Keith Chappell, Daniel Watterson, Paul Young (University of Queensland); Nathan Bartlett (University of Newcastle); Daniel Steinfort (Royal Melbourne Hospital); Andrew Brooks, Justine Mintern, Stephen Kent, Linda Wakim, Georgia Deliyannis, Carol Hartley and Joanne Devlin (The University of Melbourne), Gunther Hartmann and Eva Bartok (University Hospital, Bonn, Germany)

Highlights and developments 2022

One aspect of our research has focused on understanding and characterising particular intracellular proteins (termed restriction factors) that are expressed or induced in host cells, which can block the replication of influenza and/or other respiratory viruses. We utilise approaches to overexpress or delete putative restriction factors to determine their role in blocking virus replication and to characterise their mechanism/s of antiviral activity against influenza virus and respiratory syncytial virus (RSV).

Working with collaborators at University Hospital, Bonn in Germany we have also been using synthetic RNA molecules that target specific intracellular pattern recognition receptors to stimulate host innate immunity and to provide protection against subsequent influenza and respiratory syncytial virus (RSV) infections in mouse and ferret models of infection.

In addition, we have been working on collaborative projects to investigate and assess the use of novel recombinant vaccines to provide protection against SARS-CoV-2, as well as against a range of additional viruses. An important aspect of this has been to work towards establishing laboratory assays to measure antibody-dependent cell mediated cytotoxicity (ADCC) responses following vaccination and/or virus infection.

In 2022 our research group was funded by the NHMRC and the Coalition of Epidemic Preparedness Innovations (CEPI). Overall, our research contributed to seven peer-reviewed publications during 2022, in The Journal of Virology (x3), Viruses, The Journal of Clinical Investigation and The Journal of Immunology. Dr Reading is co-lead of a research group at the University of Melbourne consisting of two post-doctoral scientists, four Ph.D. students and one Master of Biomedical Science student. Dr Reading also supervises James Barnes, a research assistant based at the Centre, who has been investigating ADCC responses to vaccination and infection, as well as assessing novel influenza vaccines in ferret models of infection.

Epidemiology

Centre staff

Sheena Sullivan, Tanya Diefenbach-Elstob, Genevieve O'Neill (until March), Arseniy Khvorov (University of Melbourne, UoM), Leslie Dowson (UoM), Ellie Robinson (UoM) Hasanthi Abeykoon (UoM), Catherine Pendrey (ANU)

Research overview

We are interested in using surveillance data to examine fluctuations in influenza activity and vaccine effectiveness across populations and seasons. We have been working with influenza sentinel surveillance systems operating in Australia to estimate influenza vaccine effectiveness in the community, and conduct various simulation studies to understand the validity of vaccine effectiveness estimates for influenza vaccine strain selection. This work has extended to COVID-19 vaccines, with studies on vaccine effectiveness in the Victorian population in collaboration with the Department of Health.

The group is also interested in quantifying outcomes of influenza and COVID-19 infection and vaccination among pregnant women, including vaccine effectiveness for both mother and baby, severe maternal morbidity, and perinatal outcomes. This work uses large administrative datasets including US health insurance claims data, supported with funding from the US National Institutes of Health.

We are also interested in exploring the immunological responses to vaccination that explain waning vaccine effectiveness and lower vaccine effectiveness in people who are repeatedly vaccinated. To that end we work closely with the immunology research team on several sero-epidemiology studies to understand the immunological mechanisms underlying these observations. We are also exploring the immune responses to vaccination among cancer patients who among those at greatest risk of severe disease following infection.

Leslie Dowson is studying the impact of COVID-19 outbreaks in aged care, methods for increasing outbreak response in aged care and the effect of COVID-19 restrictions on aged care staff.

Collaborators

VE studies: Monique Chilver (University of Adelaide); James Fielding (VIDRL); Benjamin Cowling (University of Hong Kong), Kylie Ainslie (National Institute for Public Health and the Environment, The Netherlands); Jose Canevari (Victorian Department of Health), Allen Cheng (Monash).

Perinatal outcomes: Annette Regan (University of San Francisco), Onyebuchi Arah (University of California, Los Angeles)

Serological studies: Benjamin Teh (Peter Macallum Cancer Centre); Kylie Carville (VIDRL); David Smith (PathWest, Perth); Adam Kucharski (London School of Hygiene and Tropical Medicine); Christopher Blyth (Telethon Kids Institute); Helen Marshall (Women and Children's Hospital); Allen Cheng (Alfred Hospital); Kristine Macartney (Sydney Children's Hospital Network); Peter Wark (John Hunter Hospital); Julia Clark (Brisbane Children's Hospital); Benjamin Cowling (University of Hong Kong); Min Levine (US CDC); Scott Hensley (University of Pennsylvania).

Aged care: Noleen Bennett, Lyn-Li Lim (VICNISS), Claire Kaufman (Victorian Department of Health), Michael Muleme, Bridgette McNamara (Barwon PHU), Frances Ampt (Western PHU), Mohana Baptista, Solomon Silverstein (South Eastern PHU), Jennifer Dittmer (Loddon Mallee PHU), Aaron Osborne , Annaliese van Diemen, Vivek Ravindran (North East PHU), Sophie Legge (Uniting AgeWell).

Epidemiology (continued)

Highlights and developments 2022

We continued to work with the Australian Sentinel Practices Research Network (ASPREN), the Victorian General Practice Sentinel Surveillance (VicSPIN) network, and the Influenza Complications Alert Network (FluCAN), to evaluate the effectiveness of Australian quadrivalent inactivated seasonal influenza vaccines in 2022. HI assay and sequencing data generated by the Centre were used to inform VE estimates, and patient information obtained from the surveillance programmes was used to inform selection of viruses for sequencing (e.g. vaccination status). As always, all ASPREN samples were received at the centre. In addition, in 2022, 67% of FluCAN samples were received, reflecting enhanced efforts to ensure these samples are included in the Centre's virological surveillance, and to improve the quality of vaccine effectiveness estimates possible through that network. The epidemiology group compiled the Global Influenza Vaccine Effectiveness Report, which was presented by Sheena Sullivan at the WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2023.

We continued to explore potential biases in test-negative studies, with a special interest in unexplored biases relevant to COVID-19 vaccines. Dr Sullivan secured funding from veski to support a post-doctoral researcher (Hasanthi Abeykoon) to continue work initiated by Arseniy Khvorov. Preliminary results were shared at the Conference on Retroviruses and Opportunistic Infections (CROI) in February 2022.

Dr Sullivan continued working with colleagues in the US (Annette Regan and Onyebuchi Arah) to understand vaccine effectiveness and the burden of influenza and COVID-19 during pregnancy, with several manuscripts published as a result of this work (1,2). The team, led by Dr Regan, secured additional funding through the National Institutes of Health to support this research.

Drs Sheena Sullivan and Annette Fox (Immunology unit) and Adam Kucharski (London School of Hygiene and Tropical Medicine) continued leading a large longitudinal cohort study to understand the long-term effects of repeated influenza and COVID-19 vaccination in hospital workers. This study commenced in 2020, with recruitment in six Australian cities, with all laboratory analysis conducted at the Centre. Work from this cohort was presented at the Options XI for the Control of Influenza meeting held in Belfast in September 2022. A systematic review of repeat vaccine effectiveness studies was conducted for this study (Ellie Robinson) and was published in Lancet Respiratory Medicine (3).

We continued working on other serological studies (see Human Immunity to Influenza). In these studies, the epidemiology group is working to develop tools to better analyse antibody titre data (Arseniy Khvorov).

The team published papers describing transmission routes and the impact of outbreaks in aged care (4,5). Abstracts reporting on the experiences of aged care staff were accepted as oral presentations at conferences (to be held in 2023).

1. Regan AK, et. al. 2022. *J Infect Dis.*
2. Regan AK, et. al. 2022. *Paediatric and Perinatal Epidemiology*.
3. Jones-Gray E, et. al. 2023. *Lancet Resp Med.* (accepted in 2022)
4. Muleme M, et. al. 2023. *J Am Med Dir Assoc.* (prepared in 2022)
5. Sullivan SG, et. al. 2023. *Infect Control Hosp Epidemiol.* (accepted in 2022)

Evolution, Modelling and Serological Responses to Influenza Viruses

Centre staff

Ian Barr, Malet Aban, Annette Fox

Research overview

We are undertaking several collaborative projects, both with local and international groups, to investigate various aspects of influenza virus evolution and the immune responses to influenza viruses and vaccines.

Collaboration with the University of Cambridge has continued on their project titled, 'Advanced vaccination and immunity management strategies to protect from influenza virus infection'. This project is funded by the US Department of Health and Human Services via the Biomedical Advanced Research and Development Authority (BARDA) and CEIRS (Centers of Excellence for Influenza Research and Surveillance) group based at the Mount Sinai Hospital (New York City NY, USA). Work has continued using reverse engineered HA mutant influenza viruses (changes introduced by site directed mutagenesis) and antibody escape mutants, in order to better understand the major steps that contribute to immune escape and evolution of influenza viruses. Extensive antigenic testing (using both HI and virus microneutralisation assays) of mutated viruses using a combination of ferret and human antisera has continued.

Further work has continued with Marios Koutsakos on his NHRMC Investigator grant project 'Antigenic evolution of influenza B viruses (IBV) and antibody landscapes'. This project aims to better understand the antigenic evolution of the influenza B HA protein across influenza B lineages (ancestral, B/Yamagata, B/Victoria) using antigenic cartography and virus sequencing. Antibody landscapes against IBV strains from 1940-2019 will be constructed from individuals aged 1-70 years and cross-sectionally sampled between 1992-2020. We recently received ancestral influenza B isolates to add on to the panel of viruses we have available for testing.

Collaborators

Derek Smith and Sam Wilks (University of Cambridge, UK); Yoshihiro Kawaoka (The University of Wisconsin, Madison WI, USA and The University of Tokyo, Japan); Ron Fouchier (Erasmus University, Rotterdam, The Netherlands); Marios Koutsakos (The University of Melbourne).

Highlights and developments 2022

Currently preparing manuscript for publication.

Immunity to Respiratory Viruses

Centre staff and student

Annette Fox, Louise Carolan, Sheena Sullivan, Stephany Sanchez, Yi Liu, Anastasia Jessica Hadiprodjo, Ziheng Zhu

Research overview

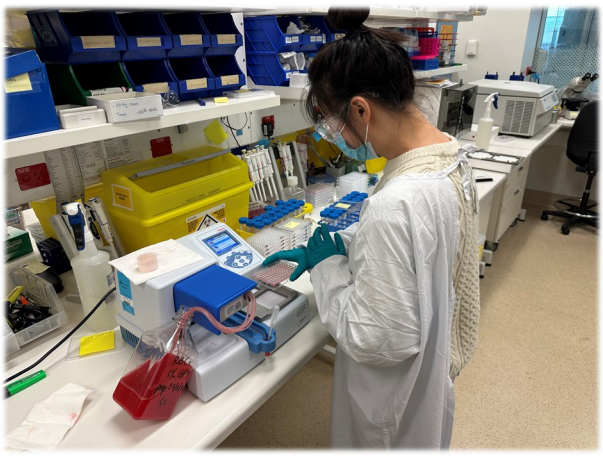
A key goal of our work is to identify strategies to improve the immunogenicity and, in turn, effectiveness of seasonal influenza vaccines. It is challenging to induce long-term immunity against highly mutable viruses such as influenza, not only due to immune escape, but also to a propensity for antibody levels to decline with successive exposures to variant influenza virus strains. This phenomenon was first described in the 1950's and referred to as original antigenic sin. It is thought that immune responses (antibodies or B cells) induced by prior influenza exposures interfere with the development of immunity to new strains. We have established several human influenza cohorts to document and investigate the effects of prior influenza exposures on influenza vaccine responses, and have developed techniques to explore the specificity of antibody and B cell responses to influenza vaccination. Techniques such as reverse genetics to generate viruses with mutations of selected antigenic sites have also been used to investigate parameters that may affect antigenic characterisation of influenza viruses using primary infection ferret sera (antisera). Finally, with the emergence of COVID-19, we have also adapted our techniques to characterise B cell and antibody responses to SARS-CoV-2 infection and vaccination in our cohorts.

Collaborators

Rogier van Doorn (Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam); Le Quynh Mai (National Institute of Hygiene and Epidemiology, Hanoi, Vietnam); Scott Boyd (Stanford University, Stanford CA, USA); Mark Thompson (Centre for Disease Control, Atlanta, USA); Derek Smith (Centre for Pathogen Evolution, Infectious Diseases Research Centre, Cambridge University, Cambridge, UK); Alain Townsend (Weatherall Institute of Molecular Medicine, Oxford University, Oxford UK); Maryna Eichelberger (US Food and Drug Administration, Silver Spring MD, USA; Kim Jacobson (Monash University); Katherine Kedzierska (The University of Melbourne); David Price (The University of Melbourne, VIDRL); Adam Wheatley (The University of Melbourne); Ben Cowling (Hong Kong University)

Highlights and developments 2022

During 2022 we continued to follow immune responses to influenza vaccination among hospital workers participating in a longitudinal cohort study established in 2020 by Drs Sheena Sullivan (Epidemiology unit) and Annette Fox (Immunology unit) at the Centre, and Adam Kucharski (London School of Hygiene and Tropical Medicine). 3159 sera from 1073 participants recruited from 5 hospitals across Australia were tested in HI against viruses representing egg and cell-grown equivalents of the A(H1N1), A(H3N2), and B/Victoria components of the vaccine administered in 2022. The A(H3N2) component of the vaccine was changed from 2021 (A/Hong Kong/2671/2019) to 2022 (A/Darwin/9/2021) whereas the A(H1N1) component was unchanged (A/Victoria/2570/2019). Notably, the proportion seroconverting was higher against A (H3N2) than in previous years, but lower against A (H1N1) than in previous years. Combined data gathered by the end of participant investigations in 2023 will help to understand the combined effects of vaccination history and antigenic change on vaccine immunogenicity.



Immunity to Respiratory Viruses (continued)

We conducted extensive investigations of immune responses to COVID-19 vaccination among 457 of the hospital workers (Figure R1). 183 received Astra Zeneca AZD1222 and 274 received Pfizer BNT162b2 vaccine, which are Adenovirus vectored (AdV) and mRNA vaccines, respectively. Pre and post COVID-19 vaccination sera were assessed using an in-house surrogate virus neutralisation test (sVNT), which measures antibody titres against SARS-CoV-2. Median post-vaccination sVNT antibody titres were 4.2 times lower for AdV compared to mRNA vaccinees (Figure R1c, $p < .001$). Median percentages of memory B cells that were RBD+ were 8.3 times lower for AdV compared to mRNA vaccinees on day 7 (Figure R1e). Geometric mean IgG titres against Ad5 hexon rose 2.7-fold after AdV vaccination, but were not correlated with anti-spike antibodies. The results suggest that mRNA induced substantially more sVNT antibody than AdV vaccine due to greater B cell expansion and targeting of the RBD. The relatively poor immunogenicity of the AdV vaccine does not appear to be due to anti-vector immunity.

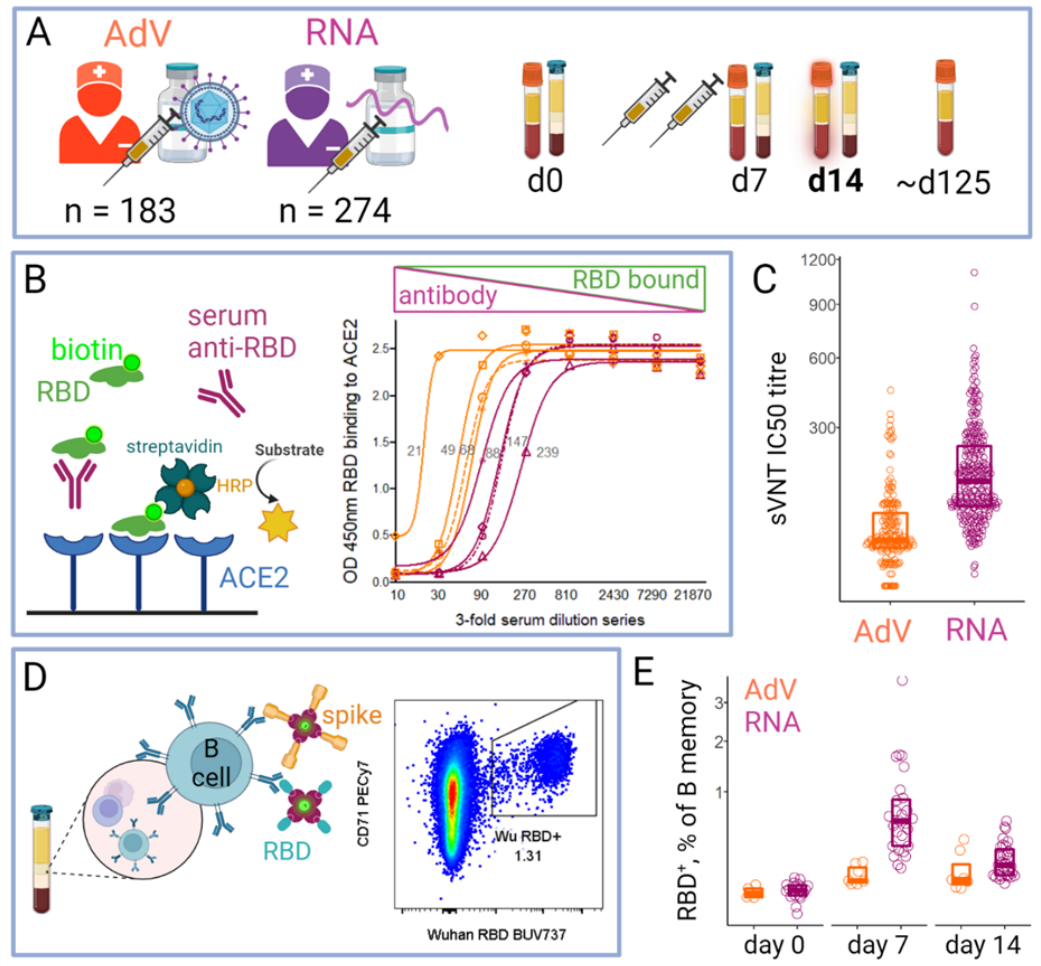


Figure R1. *COVID-19 vaccine study. (A) Participants and sampling. (B) Schematic of the surrogate virus neutralisation test (sVNT) and an example of raw data for sera from AdV and RNA vaccine recipients (n = 4 each). (C) sVNT antibody titres of all sera tested by vaccine type. (D) Schematic of peripheral blood mononuclear cell (PBMC) analysis by flow cytometry to detect Sars-CoV-2 spike and RBD reactive B cells. A representative FACS plot shows gating of B cells that have high expression of CD71 activation marker and that bind RBD. (E) Percentage of memory B cells that are RBD+, showing all samples tested by time-point and vaccine type. Created with Biorender*

Participants of the hospital worker cohort were followed for breakthrough SARS-CoV-2 infections. Very few infections were detected until Omicron variants emerged in December 2021, at least 100 days after participants received their second dose of COVID-19 vaccine. 310 reported being infected of whom 74 provided blood approximately 7, 14 and/or 30 days post infection. Sera were titrated against RBD of ancestral vaccine strain (~Wuhan) and Omicron strain in sVNT assay, and PBMCs were assessed by flow cytometry to detect B cells reactive with spike and RBD of ancestral and Omicron strains, as shown in Figure R1.

Immunity to Respiratory Viruses (continued)

The results show that vaccination with the ancestral Wuhan strain induces sVNT antibodies against Wuhan but not Omicron RBD. Omicron break-through infection induces sVNT antibodies against both Wuhan and Omicron RBD, but titres remain substantially higher against Wuhan. Accordingly, the RBD+ B cell population retains a bias towards ancestral Wuhan strain RBD, particularly among antibody producing plasmablasts. However, B cells may show some evolution towards Omicron RBD. In summary, the results show that infection with Omicron variants induces antibodies against itself as well as substantial memory B cell recall and back-boosting of antibodies against the past vaccine strain. This provides evidence to support the use of vaccines containing updated variant strains.

During 2022 we completed serology for an early life influenza imprinting study in collaboration with Centre Director Prof Kanta Subbarao. The study scheme is depicted in Figure R2a. 19 children aged 6 - 60 months were recruited between 2019 and 2021 and were classified according to their prior exposure to influenza A through infection only (n = 9), vaccination only (n = 8) or no exposure (n = 2). Blood was collected pre and post vaccination and plasma tested to determine HI antibody titres against 7 A(H1N1) and 13 A(H3N2) viruses including viruses representative of vaccine strains administered and of strains circulating during the children's lifetimes. Vaccination induced higher titres and titre -rises against A(H3N2) viruses among children with prior infection than with prior vaccination (Figure R2b,c).

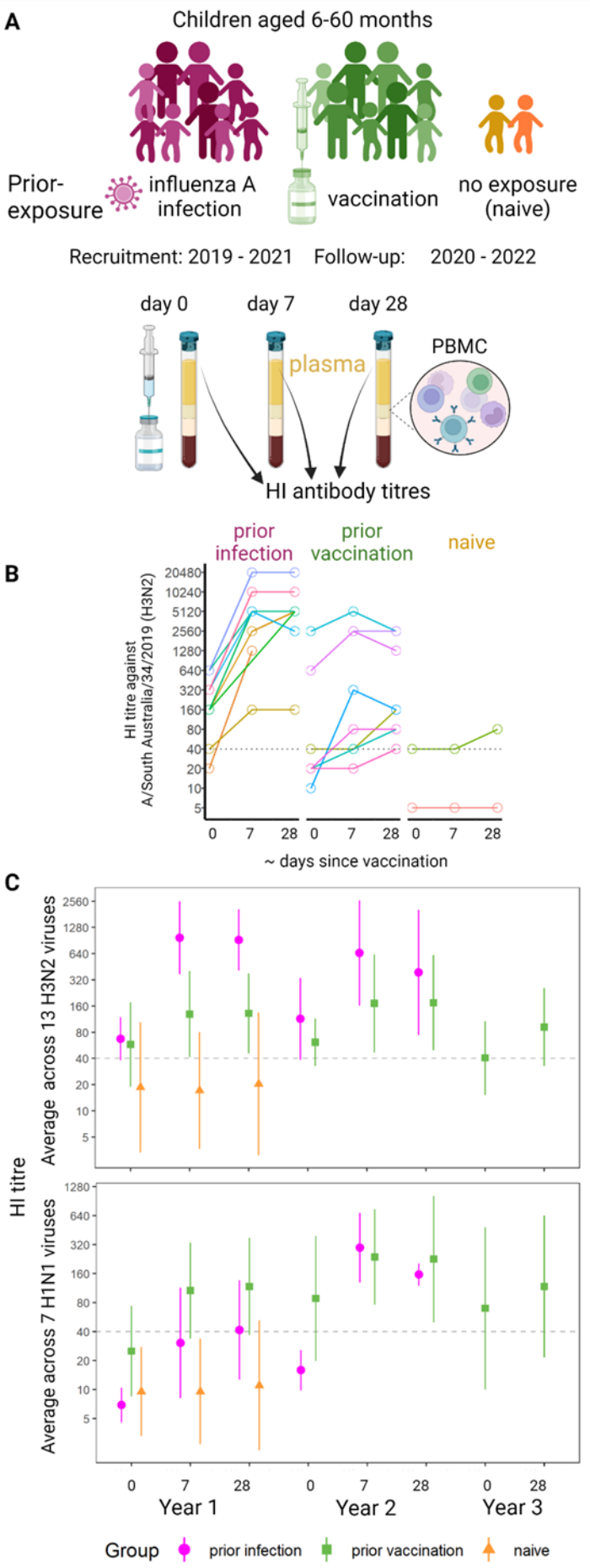


Figure R2. *Influenza imprinting study overview. (A) Schematic of the study including recruitment, sample collection and sample testing. (B) HI titres against A/South Australia/34/2019 (H3N2) are shown for all samples collected in study year 1 with lines connecting time-points for each individual grouped by influenza exposure history. (C) All HI antibody titres are summarized as geometric mean titres averaged across 13 A(H3N2) viruses (top panel) and 7 A(H1N1) viruses (bottom panel). Data is separated by prior exposure type, study year, and time-point.*

Immunity to Respiratory Viruses (continued)

In contrast, children with prior infection had low titres against A(H1N1) viruses compared to children with prior vaccination at all time-points in the first study year (Figure R2c). Influenza naïve children had negligible titre rise against any virus despite receiving a two dose vaccination regimen. This small pilot study indicates that infection may be better than vaccination for priming antibody responses to influenza vaccination, particularly against the A(H3N2) component. While priming infection did not induce detectable antibodies against A(H1N1) viruses, it appeared to prime vaccine responses against H1N1 since titre rise was similar among previously infected and previously vaccinated and greater than among naïve children (Figure R2c). In subsequent years H1N1 antibody titre rise was at least as high among the infection primed group. This paradoxical effect of infection resembles the effects of live attenuated influenza vaccines (LAIV). Future B cell analyses will help to determine whether infection induces H1N1 reactive memory B cells but not high affinity B cells and long-lived antibody secreting cells.

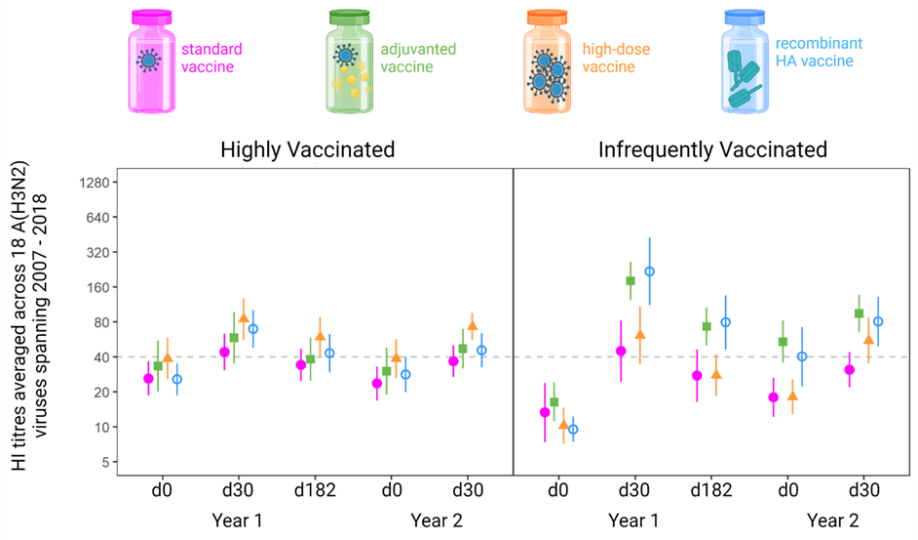


Figure R3. *Antibody responses induced by four different influenza vaccine formulations among older adults from Hong Kong classified according to their history of influenza vaccination. Highly vaccinated have been vaccinated in all five preceding years. Infrequently vaccinated have not been vaccinated in any of the preceding five years. 33-35 participants were tested per vaccine type, ~ half of whom were highly and infrequently vaccinated.*

In 2022 we completed serology for several other collaborative studies. 707 sera were obtained from a study comparing the immunogenicity of different vaccine formulations in older Adults in Hong Kong (PIVOT, Clinical Trials Registration. NCT03330132). The serology study included 137 participants of whom 35 received standard vaccine, 34 received adjuvanted vaccine; 35 received high-dose, and 33 received recombinant influenza vaccine. Half of each vaccine group had been vaccinated each of the preceding 5 years (highly vaccinated) and half had been vaccinated in none of the preceding 5 years (infrequently vaccinated). Sera collected before and after vaccination in two successive years were tested by HI to determine antibody titres against 30 A(H3N2) viruses to understand the impact of vaccine type and vaccination history on the breadth of antibody responses (Figure R3). Preliminary analysis indicates that antibody responses induced by influenza vaccination are poor among highly vaccinated compared to infrequently vaccinated. Moreover, while adjuvanted and recombinant vaccines induced higher antibody titres and titre rises among infrequently vaccinated older adults they induced similar titres to standard vaccine among highly vaccinated adults. The results suggest that alternate vaccine formulations perform better in infrequently vaccinated people but do not overcome the attenuation of vaccine antibody responses associated with repeated vaccination.

Finally, sera from a study of influenza vaccination among 71 immunocompromised children undergoing treatment for cancer were assessed to determine the effect of giving up to three doses of vaccine. Sera collected before vaccination and ~ 1 month after each dose of vaccine were tested by HI assay to determine antibody titres against vaccine strains and equivalent egg-grown strains. The results suggest that antibody titres increase with each additional dose given, however a subset of children respond poorly regardless of the number of doses received. T cell responses will be analysed in these children to determine whether there may be any benefit of additional doses.

Collaborative Agreements

The Centre is party to two collaborative research and development agreements with industry bodies. As with all potential collaborations with the commercial sector, these agreements have undergone review to ensure that they support the Centre's objective of advancing global public health, have scientific merit and adhere to the principles of neutrality, transparency, independence and accountability.

Agreement with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) (2012-2022)

Centre staff: Several staff are involved in this CRADA

Overview: This project aims to enhance the number and geographic range of influenza vaccine viruses isolated in eggs as candidates for commercial influenza vaccine manufacture.

Highlights and developments 2022:

An egg isolate of A(H1N1)pdm09 was derived at the Centre (A/Victoria/2570/2019) and was used as the A(H1N1)pdm09 egg-derived vaccine component for the Southern Hemisphere (SH) influenza vaccine in 2022. This strain was also recommended for the Northern Hemisphere (NH) influenza vaccine for 2022-2023. A new egg isolate of A(H1N1)pdm09 was derived at the Centre (A/Sydney/5/2021) and was recommended for the SH 2023 vaccine component.

An egg isolate of A(H3N2) was derived at the Centre (A/Darwin/9/2021). This was used as the A (H3N2) egg-derived vaccine component for the SH influenza vaccine in 2022 and 2023, and was also recommended for the NH influenza vaccine for 2022-2023.

For the full recommendation for the SH 2022 vaccine, click here.

For the full recommendation for the NH 2022-2023 vaccine, click here.

Collaborative Research and Development Agreement with Seqirus (formerly BioCSL) (2021-2025)

Centre staff: Several staff are involved in this CRADA

Overview: The Centre continues to isolate and evaluate various seasonal influenza virus cell isolates derived from the use a proprietary qualified Seqirus cell line (MDCK 33016PF). Virus cell isolates were evaluated as potential cell culture candidate vaccine viruses (cc-CVV) based on their antigenic properties, genetic sequence and growth properties.

Highlights and developments 2022:

A qualified cell isolate of A(H3N2) was derived at the Centre (A/Darwin/11/2021) that formed the basis of the A(H3N2) cell-derived vaccine component recommended for the SH influenza vaccine in 2022. In addition, B/Singapore/WUH4618/2021 derived at the Centre was also a recommended B/Austria/1359417/2021 (B/Victoria lineage)-like virus for the 2022 SH vaccine.

For the full list of candidate vaccine viruses, click here.

Research Funding and Awards

Centre staff members are Chief, Co-, or Associate Investigators in grants administered across 2022 (includes those awarded outside of 2022):

US National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Health (NIH) Grant: ***Does repeated influenza vaccination constrain influenza immune responses and protection?***

USD $4,200,000 was awarded to **Annette Fox** and **Sheena Sullivan** for the period 2019-2024. The grant is administered by the University of Melbourne and the work will be undertaken at the Centre, the University of Melbourne, University of Western Australia, Alfred Hospital, University of Queensland, Sydney Children's Hospital Network, University of Adelaide and University of Newcastle. **Kanta Subbarao** is a Co-Investigator on the project. In addition, a USD $700,000 supplement to this project was given to investigate COVID-19 outcomes.

NIAID/NIH CEIRS subaward: ***Natural history of SARS-CoV-2 in comparison to influenza A virus: a multi-site study focused in the Southern Hemisphere and equatorial regions***

USD $629,251 was awarded to **Kanta Subbarao** (Chief Investigator for Australian sites) and **Annette Fox** (Co-Investigator) for the period 2020 -2022. The grant is administered by the University of Melbourne.

NIH subcontract to establish the Antiviral Drug Discovery (AviDD) Center for Antiviral Medicines and Pandemic Preparedness (CAMPP)

USD $324,000 was awarded to **Kanta Subbarao** (Co-Investigator) for the period 2022-2023. The grant is administered by the University of Melbourne.

NHMRC MRFF: ***Aerosol Infection Research: Better mOdels to Reduce iNdoor Exposure (AIRBORNE)*** **within the MRFF 2021 program** ***COVID-19 Treatment Access and Public Health Activities***

$998,339 was awarded to **Kanta Subbarao** (Lead Investigator) and **Sheena Sullivan** (Co-Investigator) for the period 2022-2025. The grant is administered by the University of Melbourne.

NIAID/NIH CEIRS subaward: ***The effect of prior natural infection or vaccination ('imprint') on subsequent response to influenza vaccine in children'***

USD $561,009 was awarded to **Kanta Subbarao** (Chief Investigator), **Annette Fox** (Key Personnel), and **Sheena Sullivan** (Key Personnel) for the period 2018-2022. The grant is administered by the University of Melbourne.

NIAID/NIH CEIRS subaward: ***Assessing transmission of COVID-19 in occupationally exposed health care workers***

USD $602,746 was awarded to **Kanta Subbarao** (Chief Investigator) for the period 2020-2022. The grant is administered by the University of Melbourne.

NHMRC Investigator Grant: ***Translating virus biology and host immunity for influenza control***

$1,800,000 was awarded to **Kanta Subbarao** (Chief Investigator) for the period 2020-2025. The grant is administered by the University of Melbourne.

Victorian Department of Health and Human Services grant: ***Evaluating direct and indirect effects of SARS-CoV-2 on multiple organ systems using stem cell-derived tissues***

$500,000 was awarded to **Kanta Subbarao** (Co-Investigator) for the period 2020-2023. The grant is administered by the University of Melbourne.

NHMRC Medical Research Future Fund (MRFF: ***The Platform trial In COVID-19 vaccine BOOsting (PICOBOO)***

$4,157,377.94 was awarded to **Kanta Subbarao** (Associate Investigator) for the period 2022-2024. The grant is administered by the University of Melbourne.

NHMRC MRFF: ***Bringing Optimised COVID-19 vaccine Schedules To ImmunoCompromised populations (BOOST-IC)***

$2,911,774.24 was awarded to James McMahon (Chief Investigator) for the period 2022-2024, with a subaward to **Kanta Subbarao** (Co-Investigator). The grant is administered by the University of Melbourne.

Research Funding and Awards (continued)

Doherty Agility Grants Scheme: ***Experiences of Australian aged care workers related to Infection Prevention and Control measures during COVID-19 pandemic***

$40,000 was awarded to **Sheena Sullivan** (Co-Investigator) for the period 2021-2022. The grant was administered by the Peter Doherty Institute for Infection and Immunity.

Victorian Near-miss Award Pilot program fellowship (part of the Victorian Health and Medical Research Workforce project)

$74,000 was awarded to **Sheena Sullivan** for the period 2022-2023. The grant is administered by the University of Melbourne.

NIH project grant (R01): ***Uptake, Safety and Effectiveness of COVID-19 Vaccines during Pregnancy***

USD $1,277,429 was awarded to **Sheena Sullivan** (Co-Investigator) for the period 2022-2025. The grant is administered by the University of Melbourne.

Australian Research Council (ARC) Discovery Early Career Researcher Award (DECRA): ***How ecology shapes the viromes of wild birds***

$419,016 was awarded to **Michelle Wille** for the period 2020-2023. The grant is administered by the University of Sydney.

Research Students

PhD Candidates

Dr Paulina Koszalka was conferred her Ph. D from Monash University in December 2022. Her project was titled 'Efficacy, resistance and drug interactions for influenza antivirals in clinical development', under the supervision of **Kanta Subbarao**, Vijaykrishna Dhanasekaran (Monash University), Stephen Turner (Monash University), and Aeron Hurt (Roche).

Ms Jessie Goldsmith commenced her Ph. D candidature at the University of Melbourne. Her project is titled, 'What can we learn about influenza as Australia's COVID-19 suppression strategy ends?', under the supervision of **Sheena Sullivan**, Katherine Gibney, and Trish Campbell.

Masters students

Ms Arada Hirankitti commenced her Masters of Science (Bioinformatics) project with the University of Melbourne. The project is titled, 'Understanding COVID-19: BCR analysis workflow for studying asymptomatic patients', under supervision of **Annette Fox**, **Ammar Aziz**, and **Stephany Sanchez**. April 2022—October 2023

Dr Catherine Pendrey commenced her Masters of Philosophy in Applied Epidemiology (MAE) with the Australian National University (ANU). Her projects cover epidemiology of influenza and other respiratory viruses, including the re-emergence of influenza in Victoria following the COVID-19 pandemic, and measuring the burden of influenza cases and hospitalisations averted by vaccination. She is under supervision of **Sheena Sullivan** and Rezanur Rahaman (ANU).

Honours students

There were no Honours students at the Centre during 2022

Work experience students

Ms Abby Nguyen from Haileybury completed a work experience placement on 11 November 2022.

Communications and Advisory Activities

The Centre actively contributes to the knowledge and understanding of influenza in scientific and public health domains through many different forums. Centre staff members participate in WHO meetings and workshops to support the ongoing work and growth of WHO GISRS, as well as providing advice on influenza to the Australian Government. Centre staff members publish peer-reviewed journal papers and present numerous talks and posters.

Publications and Reports

The Centre continued to build its research and surveillance profile with the publication of 71 original research papers, reviews and reports in 2022.

Centre Publications 2022

1. Abrehart T, Suryadinata R, McCafferty C, Jacobson J, Ignjatovic V, Robinson P, Crawford NW, Monagle P, **Subbarao K**, Satzke C, Wurzel D. 2022. Age-related differences in SARS-CoV-2 binding factors: An explanation for reduced susceptibility to severe COVID-19 among children? Paediatr Respir Rev 44:61-69.
2. Arah OA, **Sullivan SG**, Fell DB, Regan AK. 2022. Analyzing Uncontrolled Confounding of the Perinatal Health Effects of Severe Acute Respiratory Syndrome Coronavirus 2 Infection During Pregnancy. J Infect Dis 226:1678-1680.
3. Audsley JM, Holmes NE, Mordant FL, Douros C, Zufan SE, Nguyen THO, Kedzierski L, Rowntree LC, Hensen L, **Subbarao K**, Kedzierska K, Nicholson S, Sherry N, Thevarajan I, Tran T, Druce J. 2022. Temporal differences in culturable severe acute respiratory coronavirus virus 2 (SARS-CoV -2) from the respiratory and gastrointestinal tracts in a patient with moderate coronavirus disease 2019 (COVID-19). Infect Control Hosp Epidemiol 43:1286-1288.
4. 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**. 2022. Influenza virus infection history shapes antibody responses to influenza vaccination. Nat Med 28:363-372.
5. **Bailie CR**, **Leung VK**, Orr E, Singleton E, Kelly C, Buising KL, Cowie BC, Kirk MD, **Sullivan SG**, Marshall C. 2022. Performance of hospital-based contact tracing for COVID-19 during Australia's second wave. Infect Dis Health 27:15-22.
6. **Bailie CR**, **Tseng YY**, **Carolan L**, Kirk MD, Nicholson S, **Fox A**, **Sullivan SG**. 2022. Trend in Sensitivity of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Serology One Year After Mild and Asymptomatic Coronavirus Disease 2019 (COVID-19): Unpacking Potential Bias in Seroprevalence Studies. Clin Infect Dis 75:e357-e360.
7. Ballou WR, Baylor N, Cueni T, Dzau V, Fukuda K, Garcia PJ, Gupta A, Kadillli E, Kerr L, Larson HJ, Simpson J, **Subbarao K**, Yadav P. 2022. The Influenza Imperative: An Urgent Need to Leverage Lessons from COVID-19 to Prepare for a Global Response to Seasonal and Pandemic Influenza. NAM Perspect 2022.
8. **Barr IG**, Williams TC, Salimi V, Buchholz UJ. 2022. Addendum to Proposal for Human Respiratory Syncytial Virus Nomenclature below the Species Level. Emerg Infect Dis 28:764.
9. **Baz M**, **Deshpande N**, Mackenzie-Kludas C, Mordant F, Anderson D, **Subbarao K**. 2022. SARS-CoV-2 Omicron BA.1 Challenge after Ancestral or Delta Infection in Mice. Emerg Infect Dis 28:2352-2355.
10. Belser JA, Lau EHY, Barclay W, **Barr IG**, Chen H, Fouchier RAM, Hatta M, Herfst S, Kawaoka Y, Lakdawala SS, **Lee LYY**, Neumann G, Peiris M, Perez DR, Russell C, **Subbarao K**, Sutton TC, Webby RJ, Yang H, Yen HL. 2022. Robustness of the Ferret Model for Influenza Risk Assessment Studies: a Cross-Laboratory Exercise. mBio 13:e0117422.
11. **Brown SK**, **Tseng YY**, **Aziz A**, **Baz M**, **Barr IG**. 2022. Characterization of influenza B viruses with reduced susceptibility to influenza neuraminidase inhibitors. Antiviral Res 200:105280.
12. Brusco NK, Alafaci A, Tuckerman J, Frawley H, Pratt J, Daley AJ, **Todd AK**, **Deng YM**, **Subbarao K**, **Barr I**, Crawford NW. 2022. The 2018 annual cost burden for children under five years of age hospitalised with respiratory syncytial virus in Australia. Commun Dis Intell (2018) 46.

Centre Publications 2022 (continued)

13. Chang JJ, Gleeson J, Rawlinson D, De Paoli-Iseppi R, Zhou C, Mordant FL, Londrigan SL, Clark MB, **Subbarao K**, Stinear TP, Coin LJM, Pitt ME. 2022. Long-Read RNA Sequencing Identifies Polyadenylation Elongation and Differential Transcript Usage of Host Transcripts During SARS-CoV-2 In Vitro Infection. Front Immunol 13:832223.

14. Chen Q, Langenbach S, Li M, Xia YC, Gao X, Gartner MJ, Pharo EA, Williams SM, Todd S, Clarke N, Ranganathan S, Baker ML, **Subbarao K**, Stewart AG. 2022. ACE2 Expression in Organotypic Human Airway Epithelial Cultures and Airway Biopsies. Front Pharmacol 13:813087.

15. Chung YT, Kuan CY, Liao GR, Albrecht RA, **Tseng YY**, Hsu YC, Ou SC, Hsu WL. 2022. A variant NS1 protein from H5N2 avian influenza virus suppresses PKR activation and promotes replication and virulence in mammals. Emerg Microbes Infect 11:2291-2303.

16. Clarke M, Mathew SM, Giles LC, Pena AS, **Barr IG**, Richmond PC, Marshall HS. 2022. A Prospective Study Investigating the Impact of Obesity on the Immune Response to the Quadrivalent Influenza Vaccine in Children and Adolescents. Vaccines (Basel) 10.

17. Dhanasekaran V, **Sullivan S**, Edwards KM, Xie R, **Khvorov A**, Valkenburg SA, Cowling BJ, **Barr IG**. 2022. Human seasonal influenza under COVID-19 and the potential consequences of influenza lineage elimination. Nat Commun 13:1721.

18. Eden JS, Sikazwe C, Xie R, **Deng YM**, **Sullivan SG**, Michie A, Levy A, Cutmore E, Blyth CC, Britton PN, Crawford N, **Dong X**, Dwyer DE, Edwards KM, Horsburgh BA, Foley D, Kennedy K, Minney-Smith C, Speers D, Tulloch RL, Holmes EC, Dhanasekaran V, Smith DW, Kok J, **Barr IG**. 2022. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. Nat Commun 13:2884.

19. **Farrukee R**, Gunalan V, Maurer-Stroh S, **Reading PC**, **Hurt AC**. 2022. Predicting Permissive Mutations That Improve the Fitness of A(H1N1)pdm09 Viruses Bearing the H275Y Neuraminidase Substitution. J Virol 96:e0091822.

20. Feng S, Enosi Tuipulotu D, Pandey A, Jing W, Shen C, Ngo C, Tessema MB, Li FJ, Fox D, Mathur A, Zhao A, Wang R, Pfeffer K, Degrandi D, Yamamoto M, **Reading PC**, Burgio G, Man SM. 2022. Pathogen-selective killing by guanylate-binding proteins as a molecular mechanism leading to inflammasome signaling. Nat Commun 13:4395.

21. **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**. 2022. Opposing Effects of Prior Infection versus Prior Vaccination on Vaccine Immunogenicity against Influenza A(H3N2) Viruses. Viruses 14.

22. **George AM**, **Wille M**, Wang J, Anderson K, Cohen S, **Moselen J**, Lee LYY, Suen WW, Bingham J, Dalziel AE, **Whitney P**, **Stannard H**, **Hurt AC**, Williams DT, **Deng YM**, **Barr IG**. 2022. A novel and highly divergent Canine Distemper Virus lineage causing distemper in ferrets in Australia. Virology 576:117-126.

23. Gilbertson B, **Subbarao K**. 2022. A new route to vaccines using PROTACs. Nat Biotechnol 40:1328-1329.

24. Gillies MB, Burgner DP, Ivancic L, Nassar N, Miller JE, **Sullivan SG**, Todd IMF, Pearson SA, Schaffer AL, Zoega H. 2022. Changes in antibiotic prescribing following COVID-19 restrictions: Lessons for post-pandemic antibiotic stewardship. Br J Clin Pharmacol 88:1143-1151.

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Presentations

Centre staff members presented talks and posters at numerous events during 2022, including national and international conferences, WHO meetings, educational lectures and research seminars.

ORAL PRESENTATIONS

Event/Institute; Location, date	SPEAKER, Title(s)
11th Australian Ornithological Conference; Auckland, 8-10 February 2022	MICHELLE WILLE: The ecology of avian influenza virus in Australian wild birds
Turkish Infectious Diseases Congress; Virtual Forum, March 2022	KANTA SUBBARAO: Global Circulation of Influenza in the time of COVID-19
Viruses-Sponsored International COVID-19 Workshop; Virtual Forum, 1-3 March 2022	KANTA SUBBARAO: SARS-CoV-2 Variants and Vaccines: The TAG-CO-VAC WHO advisory committee
Lessons Learned from COVID: Guiding pandemic preparedness and response; Melbourne, 1 March 2022	SHEENA SULLIVAN: How did influenza prepare us for the COVID-19 pandemic and how will COVID-19 reshape our influenza pandemic plan
2022 Thoracic Society of Australia and New Zealand Virtual Conference; Virtual Forum, 2 March 2022	KANTA SUBBARAO: Understanding novel viruses – models of SARS-CoV-2 in the lab

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
2022 Thoracic Society of Australia and New Zealand Virtual Conference; Virtual Forum, 2 March 2022	KANTA SUBBARAO: Influenza vaccine development
Chief Veterinary Officer's Forum, Australian Government; Virtual Forum, 3 March 2022	MICHELLE WILLE: The ecology and evolution of avian influenza A viruses in Australia
The Royal College of Pathologists of Australasia (RCPA) Pathology Update 2022; Virtual Forum, 5 March 2022	KANTA SUBBARAO: Neutralising antibodies in COVID-19
Pre-European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Day on COVID-19; Virtual Forum, 23 March 2022	KANTA SUBBARAO: Molecular surveillance of influenza virus subtype for designing seasonal vaccine composition
Influenza Masterclass 2022: CV outcomes, COVID-19 and influenza vaccination; Virtual Forum, 23 March 2022	SHEENA SULLIVAN: 2022 flu season and potential for co-infection with COVID-19
National Centre for Immunisation Research and Surveillance (NCIRS) webinar - Managing seasonal respiratory viruses: Flu and SARS-CoV-2 Winter 2022; Virtual Forum, 5 April 2022	KANTA SUBBARAO: Update on influenza disease worldwide and the impact of COVID-19
Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) 171st Meeting of the Vaccines and Related Biological Products Advisory Committee; Virtual Forum, 6 April 2022	KANTA SUBBARAO: Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC)
Department of Microbiology and Immunology, the University of Melbourne; Melbourne, 28 April 2022	MICHELLE WILLE: Towards an understanding of the ecology of viruses in wild birds
Clinical Vaccinology Update (CVU) webinar; Virtual Forum, 28 April 2022	SHEENA SULLIVAN: Influenza: a post COVID-19 landscape
Doherty and NCIRS course in vaccinology and immunisation science; Virtual Forum, May 2022	KANTA SUBBARAO: Viral Evolution: Implications for Vaccine Strain Selection
Harvard School of Public Health Vaccine course; Virtual Forum, May 2022	KANTA SUBBARAO: Equitable distribution of vaccines: COVAX
RCPA National Microbiology Webinar; Virtual Forum, May 2022	KANTA SUBBARAO: What's new with influenza in 2022?
CSIRO Australian Centre for Disease Preparedness Seminar Series; Virtual Forum, 5 May 2022	MICHELLE WILLE: Towards an understanding of the ecology of viruses in wild birds
2022 NRL Asian Summit; Virtual Forum, 24 May 2022	JEAN MOSELEN: Supporting and strengthening molecular diagnostics for SARS-CoV-2 in the Pacific
2020 Julius Youngner Lecture; Pittsburgh, USA, 25 May 2022	KANTA SUBBARAO: SARS-CoV-2 and Influenza: Lessons from Pandemic Respiratory Viruses

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
Institut Pasteur Korea x Doherty Institute Joint Symposium for Collaboration; Seongnam, Korea, 2 June 2022	IAN BARR: Surveillance and Research activities at the Melbourne WHO Collaborating Centre for Reference & Research on Influenza
Communicable Diseases & Immunisation Conference 2022; Sydney, 20-22 June 2022	SHEENA SULLIVAN: Surveillance implications of the maturing antibody response one year after SARS-CoV -2 infection
Communicable Diseases & Immunisation Conference 2022; Sydney, 20-22 June 2022	SHEENA SULLIVAN: Detection of influenza infection through supervised hotel quarantine in Australia
Communicable Diseases & Immunisation Conference 2022; Sydney, 20-22 June 2022	SHEENA SULLIVAN: Using network analysis to understand disease spread and inform public health interventions
I-MOVE (Influenza Monitoring Vaccine Effectiveness) meeting; Virtual Forum, 22 June 2022	SHEENA SULLIVAN: Reseeding events in the 2022 Australian influenza season
Keystone Symposia - Respiratory Viruses: New Frontiers; Keystone, USA, 29 June - 2 July 2022	PAULINA KOSZALKA: Combination treatment with Baloxavir and Oseltamivir in ferrets infected with Baloxavir resistant viruses
Keystone Symposia - Respiratory Viruses: New Frontiers; Keystone, USA, 29 June - 2 July 2022	KANTA SUBBARAO: Strategies to improve seasonal and pandemic influenza vaccines
Introductory Trainee Education Program in Infectious Diseases (INTREPID) 2022 webinar; Virtual Forum, 7 July 2022	KANTA SUBBARAO: Non-COVID Respiratory Viruses
Australian Society for Microbiology Meeting; Virtual Forum, 13 July 2022	HARRY STANNARD: Assessing the fitness of a dual-antiviral drug resistant human influenza virus in the ferret model
Australian Society for Microbiology Meeting; Sydney, 11-14 July 2022	KANTA SUBBARAO: SARS-CoV-2 and Influenza: Lessons from pandemic respiratory viruses
2nd Australasian COVID-19 Conference; Sydney, 21-22 July 2022	KANTA SUBBARAO: The impact of virus evolution on treatment options for COVID-19
NIAID Workshop on Generation and Measurement of Vaccine Durability; Virtual Forum, 27-28 July 2022	KANTA SUBBARAO: What is the contribution of mucosal vs. systemic Abs to protection against respiratory virus infections?
1st Annual CEIRR (formerly CEIRS) Network Meeting; Memphis, USA, 14-17 August 2022	ANNETTE FOX: Influenza vaccine responses among young children first exposed to influenza antigens via infection versus vaccination
1st Annual CEIRR (formerly CEIRS) Network Meeting; Memphis, USA, 14-17 August 2022	KANTA SUBBARAO: SARS-CoV-2 Vaccine Strain Selection
15th Bi-Regional Meeting of National Influenza Centres and Influenza Surveillance in the WHO's Western Pacific and South-East Asia Regions; Virtual Forum, 29-31 August 2022	IAN BARR: Influenza Activity in the Southern Hemisphere
OPTIONS XI for the Control of Influenza; Belfast, UK and Northern Ireland, 26-29 September 2022	ANNETTE FOX: Influenza vaccine responses among young children first exposed to influenza antigens via infection versus vaccination

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
OPTIONS XI for the Control of Influenza; Belfast, UK and Northern Ireland, 26-29 September 2022	KANTA SUBBARAO: Airborne Transmission of Respiratory Viruses
OPTIONS XI for the Control of Influenza: Mini -school of influenza - a preparatory session; Belfast, UK and Northern Ireland, 26 September 2022	KANTA SUBBARAO: Influenza and SARS Cov-2 lesson learned for future preparedness
Keystone Symposia: Novel approaches to global infectious diseases; Brussels, Belgium, 26-29 October 2022	KANTA SUBBARAO: Universal Influenza Vaccines
Australasian Shorebird Conference 2022; Virtual Forum, 29-30 October 2022	MICHELLE WILLE: Diversity of avian influenza virus in Australian waders and their role in long distance virus introductions
Australasian Shorebird Conference 2022; Virtual Forum, 29-30 October 2022	MICHELLE WILLE: Bird flu and the future risk to Australian wild birds
WOAH Regional Expert Group Meeting for diseases of poultry in Asia and the Pacific Region; Geelong, 31 October - 2 November 2022	MICHELLE WILLE: Wildlife surveillance and surveillance at the human-animal-wild bird interface
World Influenza Day; Virtual forum, 1 November 2022	KANTA SUBBARAO: WHO Technical Advisory Group on COVID-19 Vaccine Composition (WHO TAG-CO-VAC)
Pacific Public Health Surveillance Network (PPHSN) LabNet meeting; Nadi, Fiji, 7-9 November 2022	PATRICK READING: The Doherty Institute: Supporting Pacific Island Countries and Territories
Pacific Public Health Surveillance Network (PPHSN) LabNet meeting; Nadi, Fiji, 7-9 November 2022	PATRICK READING: One Health and its Relevance in the Pacific
Training Workshop to Strengthen Influenza-like Illness (ILI) and Severe Acute Respiratory Infections (SARI) Surveillance in the Pacific; Nadi, Fiji, 9-11 November 2022	PATRICK READING: Influenza virus - Current Global Overview
Training Workshop to Strengthen Influenza-like Illness (ILI) and Severe Acute Respiratory Infections (SARI) Surveillance in the Pacific; Nadi, Fiji, 9-11 November 2022	PATRICK READING: Global Influenza Surveillance and Importance of Influenza Vaccines
WHO Meeting to Review Progress in Phase-2 of the RSV Surveillance based on the GISRS; Amman, Jordan, 29 November - 1 December 2022	XIAOMIN DONG: A simplified, amplicon□based method for whole genome sequencing of human respiratory syncytial viruses
Informal Consultation on the Development of a new Asia Pacific Health Security Action Framework; Siem Reap, Cambodia, 30 November 2022	PATRICK READING: Speaker in Session 1: Health Security and Public Health Emergencies – Partnerships in the COVID-19 response
Australian Virology Society (AVS) 11 Meeting; Gold Coast, 5-8 December 2022	KANTA SUBBARAO: Rational treatment strategies for SARS-CoV-2 derived from studies in human pluripotent stem cell models

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
Australian Virology Society (AVS) 11 Meeting; Gold Coast, 5-8 December 2022	MICHELLE WILLE: Towards an understanding of virus ecology in wildlife: from 'one hostone virus' models to viromes
Australian Virology Society (AVS) 11 Meeting; Gold Coast, 5-8 December 2022	PAULINA KOSZALKA: A combination of molnupiravir and oseltamivir is superior to either drug alone for the treatment of influenza in ferrets
Australian Virology Society (AVS) 11 Meeting; Gold Coast, 5-8 December 2022	PATRICK READING: Modulation of CD81 by the E3 ubiquitin ligase MARCH8 inhibits replication of HSV-1 – a novel mechanism of MARCH8-mediated virus restriction

POSTER PRESENTATIONS	
Event/Institute; Location, date	**SPEAKER, Title(s)**
35th International Conference on Antiviral Research (ICAR); Virtual Forum, 21-24 March 2022	SOOK KWAN BROWN: Characterization of influenza B viruses with reduced susceptibility to influenza neuraminidase inhibitors
9th Australasian Vaccines & Immunotherapeutics Development Meeting; Kingscliff, NSW, 1-4 May 2022	HEIDI PECK: Enhanced isolation rates of influenza viruses in a qualified cell line compared to embryonated hens eggs improves the probability of well-matched influenza vaccines
18th Negative Strand RNA Virus meeting; Braga, Portugal, 12-17 June 2022	PATRICK READING: RIG-I activation inhibits replication of influenza A virus and respiratory syncytial virus in mammalian cells and in mouse and ferret models of infection
OPTIONS XI for the Control of Influenza; Belfast, UK and Northern Ireland, 27 September 2022	ANNETTE FOX: Egg adaptations and vaccine immunogencity: beneficial effect of maintaining glycosylation while allowing other egg-adaptive changes
OPTIONS XI for the Control of Influenza; Belfast, UK and Northern Ireland, 27 September 2022	ANNETTE FOX: Influenza vaccine responses to A (H1N1)pdm09 antigens in 2020 and 2021 among repeatedly vaccinated healthcare workers
OPTIONS XI for the Control of Influenza; Belfast, UK and Northern Ireland, 27 September 2022	ANNETTE FOX: Impact of prior vaccination on breadth of antibody response among healthcare workers after influenza vaccination
12th International RSV Symposium; Belfast, UK and Northern Ireland, 29 September - 2 October 2022	YI-MO DENG: A simplified, amplicon-based method for whole genome sequencing of human respiratory syncytial viruses
Australian Virology Society (AVS) 11 Meeting; Gold Coast, 5-8 December 2022	NIKITA DESHPANDE: Characterisation of viral interactions between Influenza, SARS-CoV-2 and other circulating respiratory viruses
Australian Virology Society (AVS) 11 Meeting; Gold Coast, 5-8 December 2022	MELANIE DUNCAN: Replicative fitness of seasonal Influenza A virus H3N2 in human cell lines: Does fitness correlate with the persistence of clades in the human population?

Centre Staff Retreat

The Centre retreat was held in-house on 12 December 2022 at the Doherty Institute.

Staff from each section were able to reflect and discuss the intense influenza season of 2022, in addition to discussing strategies to improve processes for 2023.

Other discussions included topics around new technologies being developed and utilised at the Centre, as well as how the Centre could continue to contribute to the GISRS initiative by WHO alongside new initiatives such as the Centres for Disease Control in Australia, and the Australian Institute for Infectious Disease (AIID).

Team building exercises and other light hearted activities also helped to round out the one day event.

Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2022.

Ammar Aziz
RSV Genotyping Consensus Consortium, *Member*

Ian Barr
Australasian Vaccine & Immunotherapeutics Development Group, *Organising Committee*
Australian Influenza Vaccine Committee (Therapeutic Goods Administration)
Centre of Excellence for Influenza Research and Surveillance) program at St Jude Children's Research Hospital, *Scientific Advisory Committee*
Doherty Institute PC3 Laboratory Users Group, *Member*
Public Health Laboratory Network (Department of Health), *Committee member*
Influenza and other respiratory viruses, *Editorial Board*

Mariana Baz:
WHO Expert Working Group for GISRS Surveillance of Antiviral Susceptibility, *Member*
World Society for Virology, *Conference Organising Committee*
World Society for Virology, *Vice President – Australia/New Zealand*
World Society for Virology Membership Review Committee, *Deputy*
Microorganisms, *Guest Editor*

Yi-Mo Deng
WHO Working Group for GISRS PCR detection for influenza surveillance, *Member*

Annette Fox

International Committee on Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response. US National Academy of Medicine. 2020-2021, *Member*
Victorian Infection and Immunity Network, *Committee member*

Naomi Komadina
Global Initiative on Sharing All Influenza Data (GISAID), *GISAID Technical Group (Chair)*

Katie Milne
Medical Laboratory Quality Network
Victorian Infectious Disease Reference Laboratory NATA Action Group, *Member*

Patrick Reading
Australian Respiratory Virology Meeting, *Organising committee*
Doherty Institute, *Discipline leader, Education and Professional Development*
Influenza and Other Respiratory Viruses, *Editorial board*

Kanta Subbarao
ACT Accelerator COVAX Pillar Independent Product Group, *Member*
Australian Academy of Health and Medical Sciences, *Fellow*
Australian Influenza Vaccine Committee (Therapeutic Goods Administration*), Member*
COVID-19 Vaccines and Treatments for Australia – Science and Industry Technical Advisory Group (SITAG), *Member*
Doherty Institute Leadership Group, *Member*
Doherty Institute Operational Management Committee, *Member*
Doherty Institute, Discipline leader, *Global Health*
External Advisory Board, FLUCOP consortium, *Member*
Human Animal Spillover and Emerging Diseases Scanning (HASEDS) group, *Member*
National Influenza Surveillance Committee (Department of Health) NIH, Bethesda, MD, USA, *Chair*

Committees and Advisory Groups (continued)

Kanta Subbarao (continued)
Scientific Advisory Board for the Universal Influenza Vaccine Project at Mount Sinai School of Medicine, New York City NY, USA, *Member*
Scientific Advisory Board for the University of Pennsylvania Center of Excellence for Influenza Research and Response (CEIRR), *Member*
Scientific Advisory Committee for Maddie Riewoldt's Vision, Australia, *Member*
Taskforce for the development of an R&D roadmap for coronavirus vaccines, *Member*
WHO Advisory Group on Human Challenge Studies for COVID-19 Vaccines, *Member*
WHO Working group on Influenza Preparedness and Response, *Member*
WHO Pandemic Influenza Preparedness (PIP) Framework Partnership Contribution Independent Technical Expert Mechanism (PCITEM), *Member*
WHO Technical Advisory Group on COVID-19 Vaccine Composition 2021-2022, *Chair*
Cell, *Advisory Board*
Cell Host and Microbe, *Editorial board*
Journal of Virology, *Editorial board*
mBio, *Editorial board*
Med, *Editorial board*
PLoS Pathogens, *Section Editor*

Sheena Sullivan
CDNA working group for National COVID-19 Surveillance Plan, *Working Group Member*
International Society for Influenza and Other Respiratory Viruses, *Council Member*
National Influenza Surveillance Committee (Department of Health and Aged Care), *Member*
MMS Early and Mid Career Academic Advisory Group, University of Melbourne, *Mid Career Representative for the Department of Infectious Diseases*
International Journal of Epidemiology, *Associated Editor*
Influenza and Other Respiratory Viruses, *Associated Editor*

Michelle Wille
National Avian Influenza Wild Bird Surveillance, *Steering Committee*
Victorian Wader Study Group, *Member*
Wildlife Health Australia, *Member*

Visitors to the Centre

The Centre was pleased to host the following visitors during 2022.

Date	VISITOR and affiliation
25 July 2022	A/PROF RAYMOND LIN; National Public Health Laboratory/National Centre for Infectious Diseases, Singapore; Visiting scientist, Visit/chat/lunch with Sheena Sullivan and Ian Barr
25 August 2022	MR DARIUS EVERETT; Communicable Diseases Branch, Office of Health Protection & Response (OHPR); Australian government, Tour
25 August 2022	MS ALEXANDRA RODRIGUEZ; Laboratories and Health Security Section, Office of Health Protection & Response (OHPR); Australian government, Tour
1 September 2022	DR TANYA GOLUBCHIK; Sydney Institute of Infectious Diseases, University of Sydney and CIDM-PH, Sydney; Visiting scientist, To discuss probe capture method for NGS sequencing coverage
1 September 2022	DR REBECCA ROCKETT; Sydney Institute of Infectious Diseases, University of Sydney and CIDM-PH Sydney; Visiting scientist, To discuss probe capture method for NGS sequencing coverage
24 October 2022	A/PROF BARNABY YOUNG; National Centre for Infectious Diseases, Singapore; Tour while visiting Doherty for other meetings
18 November - 10 December 2022	DR DAVID HODGSON; London School of Hygiene & Tropical Medicine, London, UK; Visiting scientist, Visiting the Fox Group
23-24 November 2022	PROF MALIK PEIRIS; University of Hong Kong, Hong Kong SAR; Visiting scientist, Visit/chat with Kanta Subbarao and Ian Barr while visiting the Doherty Institute for the Annual Symposium

Engagement in WHO activities

Event; Location, Date	Centre staff involved
WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2022-2023; Geneva, Switzerland, 21-24 February 2022	Kanta Subbarao, Ian Barr, Heidi Peck attended
Monkeypox research: What study designs can be used to address the remaining knowledge gaps for monkeypox vaccines?; Virtual Forum, 2 August 2022	Sheena Sullivan was invited to participate in a panel discussion
15th Bi-Regional Meeting of National Influenza Centres and Influenza Surveillance in the WHO's Western Pacific and South-East Asia Regions; Virtual Forum, 29-31 August 2022	Ammar Aziz, Heidi Peck, Sheena Sullivan, Tasoula Zakis, Yi-Mo Deng attended Ian Barr attended and was Moderator for Plenary Session 3, Day 2
WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2023; Belfast, UK and Northern Ireland, 19-22 September 2022	Ian Barr, Kanta Subbarao, Sheena Sullivan, Yi-Mo Deng attended
WHO Meeting of the Global Influenza Surveillance and Response System: From 70th Anniversary to 100 Years; Belfast, UK and Northern Ireland, 24-25 September 2022	Ian Barr, Kanta Subbarao, Yi-Mo Deng attended
WPRO Regional Forum for WHO CCs and visits to Cambodian laboratories; Phnom Penh, Cambodia, 25 November - 1 December 2022	Patrick Reading attended

Engagement in WHO activities (continued)

Event; Location, Date	Centre staff involved
The Fourth Regional Forum of WHO Collaborating Centres in the Western Pacific; Siem Reap, Cambodia, 28-29 November 2022	Patrick Reading attended
WHO Meeting to Review Progress in Phase-2 of the RSV Surveillance based on the GISRS; Amman, Jordan, 29 November - 1 December 2022	Ian Barr attended
WHO Meeting to Review Progress in Phase-2 of the RSV Surveillance based on the GISRS; Amman, Jordan, 29 November - 1 December 2022	Xiaomin Dong attended
Informal Consultation on the Development of a new Asia Pacific Health Security Action Framework; Siem Reap, Cambodia, 30 November 2022	Patrick Reading attended

Other Conference Participation and Professional Engagement

Centre staff members also participated in the following events as attendees and/or in other roles during 2022.

Event; Location, Date	Centre staff involved
NIH virtual listening series on gain of function research; Virtual Forum, 27 April 2022	Kanta Subbarao was an invited speaker
9th Australasian Vaccines & Immunotherapeutics Development Meeting; Virtual Forum, 1-4 May 2022	Hilda Lau attended
9th Australasian Vaccines & Immunotherapeutics Development Meeting; Kingscliff, NSW, 1-4 May 2022	Ian Barr was a Session Chair and attendee
9th Australasian Vaccines & Immunotherapeutics Development Meeting; Virtual Forum, 1-4 May 2022	Louise Carolan attended
9th Australasian Vaccines & Immunotherapeutics Development Meeting; Virtual Forum, 1-4 May 2022	Paul Whitney attended
Illumina Genomics Summit '22; Melbourne, 21 June 2022	Jean Moselen attended
ADAPT for Flu: reAl-world eviDence surveillAnce Policy summiT; Sydney (Hybrid), 23 June 2022	Sheena Sullivan was Conference Co-organiser, Session Chair
WHO Consultant, Global Influenza Program (GIP); 1 July 2022 onwards (to present)	Yi-Mo Deng was a part-time consultant
1st Annual CEIRR (formerly CEIRS) Network Meeting; Memphis, USA, 14-17 August 2022	Ian Barr and Sheena Sullivan attended
Visit to CDC Atlanta to see collaborators; Atlanta, USA, 18-19 August 2022	Annette Fox and Sheena Sullivan visited
OPTIONS XI for the Control of Influenza; Belfast, UK and Northern Ireland, 26-29 September 2022	Ian Barr and Yi-Mo Deng attended Sheena Sullivan attended, chaired two sessions, was Co-Chair of the Public Health stream and a member of the Scientific Organising Committee

Other Conference Participation and Professional Engagement (continued)

Event; Location, date	Centre staff involvement
12th International RSV Symposium; Belfast, UK and Northern Ireland, 29 September - 2 October 2022	Ian Barr and Paul Whitney attended (Paul Whitney—virtual attendance)
Keystone Symposia: COVID and Beyond: Novel Approaches to Global Infectious Diseases; Brussels, Belgium, 26 - 29 October 2022	Kanta Subbarao participated in a career roundtable discussion
Food and Agriculture Organization of the United Nations meeting - Better detection, better response: A regional consultation on avian influenza surveillance in Asia; Geelong, 2-4 November 2022	Michelle Wille attended and participated in the panel discussion
VIIN Young Investigator Symposium; Melbourne, 16 November 2022	Annette Fox attended and was a Judge

Community Engagement

The Director, Deputy Director and other staff members participated in requests from media representatives for interviews and comments throughout 2022.

Ian Barr

- Participated in an interview with RN Breakfast titled, "'Flurona' poses new health risk of severe double infections", published 1 February 2022; https://www.abc.net.au/radionational/programs/breakfast/flurona-poses-new-health-risk-of-severe-double-infections/13735660
- Featured in an article by the Australian Associated Press titled, 'Australians urged to get their flu jab', published 6 March 2022; https://www.aap.com.au/news/australians-urged-to-get-their-flu-jab/
- Wrote an article for The Conversation titled, 'Flu, COVID and flurona: what we can and can't expect this winter', published 17 March 2022; https://theconversation.com/flu-covid-and-flurona-what-we-can-and-cant-expect-this-winter-177826
- Participated in an interview with ABC Mid North Coast to discuss the recent Conversation article, published 17 March 2022
- Featured in an article by The Age titled, '"It's really dangerous now": Australia's influenza hiatus set to end, published 19 March 2022; https://www.smh.com.au/national/it-s-really-dangerous-now-australia-s-influenza-hiatus-set-to-end-20220318-p5a5w7.html
- Featured in an article by SBS News titled, 'Overshadowed by COVID-19, influenza cases could soon start to climb', published 30 March 2022; https://www.sbs.com.au/news/article/overshadowed-by-covid-influenza-cases-could-soon-start-to-climb/heaepfbdf
- Featured in an interview by 9 News Australia titled, ''Influenza is definitely back': March cases jump up', published 5 April 2022; https://www.9news.com.au/national/why-are-people-getting-sick-now-in-australia-common-cold-influenza-on-the-rise/a3b596b2-f526-4fe0-80a5-eb5600df49de
- Participated in an interview with Brisbane Times titled, 'Double shot: Experts urge jabs for COVID-19 and flu while winter is coming', published 6 April 2022; https://www.brisbanetimes.com.au/national/queensland/double-shot-experts-urge-jabs-for-covid-19-and-flu-while-winter-is-coming-20220406-p5ab7g.html
- Participated in an interview with Brisbane Times titled, 'We've lived through COVID, now beware the flu', published 12 April 2022; https://www.theage.com.au/national/we-ve-lived-through-covid-now-beware-the-flu-20220412-p5acza.html

Community Engagement (continued)

Ian Barr (continued)

- Participated in an interview with ABC News titled, 'Your questions about flu season and vaccines answered as a COVID winter looms', published 20 April 2022; https://www.abc.net.au/news/health/2022-04-20/flu-season-covid-vaccines-winter-influenza-questions-answered/100989936
- Participated in an interview with The Sydney Morning Herald titled, 'NSW headed for 'significant flu epidemic' as cases triple', published 28 April 2022; https://www.smh.com.au/national/nsw/nsw-headed-for-significant-flu-epidemic-as-cases-triple-20220427-p5agfi.html
- Participated in an article by Gavi, The Vaccine Alliance titled, 'Bird flu: How worried should we be?', published 29 April 2022; https://www.gavi.org/vaccineswork/bird-flu-how-worried-should-we-be
- Was on ABC Radio Melbourne to answer questions about influenza with Lisa Leong, published 8 May 2022; https://www.abc.net.au/radio/melbourne/programs/sundays/sundays/13862654
- Participated in an interview with Nine News titled, 'Flu strain circulating now may have very sinister origins, study suggests', published 11 May 2022; https://www.9news.com.au/health/h1n1-influenza-strain-direct-descendant-of-killer-1918-spanish-flu-pandemic-new-study-finds/82ad359f-c639-44ac-9d12-e2788f2a5d88
- Participated in an interview on RN Breakfast with Patricia Karvelas, published 24 May 2022; https://www.abc.net.au/radionational/programs/breakfast/qld-to-make-flu-shot-free-as-cases-surge/13895898
- Participated in an interview with Guardian Australia titled, All Australians should be offered free flu vaccines to prevent "disaster", experts say', published 25 May 2022; https://www.theguardian.com/australia-news/2022/may/25/all-australians-should-be-offered-free-flu-vaccines-to-prevent-disaster-experts-say?CMP=Share_iOSApp_Other
- Participated in an interview with RACGP titled, 'Less than 10% of under-fives vaccinated against flu', published 25 May 2022; https://www1.racgp.org.au/newsgp/clinical/less-than-10-of-under-fives-vaccinated-against-flu
- Participated in an interview with Nature News titled, 'Why unprecedented bird flu outbreaks sweeping the world are concerning scientists', published 26 May 2022; https://www.nature.com/articles/d41586-022-01338-2
- Participated in an interview with the Bendigo Advertiser titled, 'Influenza cases among young people and children in Australia has risen this year, but experts say don't panic', published 27 May 2022; https://www.bendigoadvertiser.com.au/story/7752830/flu-cases-in-children-on-the-rise-but-dont-panic-and-get-the-jab-say-experts/
- Participated in an interview with ABC News titled, 'Flu vaccinations are being urged as cases rise. So, how effective is this winter's jab?', published 27 May 2022; https://www.abc.net.au/news/health/2022-05-27/flu-vaccination-influenza-shot-disease-virus-immune-case-numbers/101100218
- Participated in an interview with The Age titled, 'Free flu shots for Victorians as strain affecting kids drives up cases', published 30 May 2022; https://www.theage.com.au/national/victoria/flu-strain-that-hits-kids-more-helps-drive-up-cases-amid-fears-for-hospitals-20220530-p5apn0.html
- Participated in an interview with ABC National News, urging people to get vaccinated against influenza, published 31 May 2022
- Participated in an interview with The Age/Sydney Morning Herald titled, 'So, more people are "virus naïve". Now what?', published 6 June 2022; https://www.theage.com.au/lifestyle/health-and-wellness/so-more-people-are-virus-naive-now-what-20220602-p5aql0.html
- Participated in an interview with Shepparton News titled, 'Flu hits hard across the nation', published 12 June 2022; https://www.sheppnews.com.au/news/flu-hits/
- Participated in an interview with Bloomberg News titled, 'Australia's Early Flu Season Shows Americans Need Their Shots', published 13 June 2022; https://www.washingtonpost.com/business/australias-early-flu-season-shows-americans-need-their-shots/2022/06/11/0a366808-e9db-11ec-a422-11bbb91db30b_story.html
- Participated in an interview with 3AW Breakfast titled, 'WHO influenza expert's confronting warning to those who haven't had the flu jab', published 14 June 2022; https://www.3aw.com.au/who-influenza-experts-confronting-warning-to-those-who-havent-had-the-flu-jab/

Community Engagement (continued)

Ian Barr (continued)

- Participated in an interview with The Age titled, 'Is the flu worse than before? How quickly can I be reinfected? Influenza expert Ian Barr answers readers' questions', published 28 June 2022; https://www.theage.com.au/national/is-the-flu-worse-than-before-how-quickly-can-i-be-reinfected-influenza-expert-ian-barr-answers-readers-questions-20220628-p5ax49.html
- Participated in an interview with IFPMA on the current influenza season in Australia and predictions for the northern hemisphere, published 12 July 2022; https://twitter.com/IFPMA/status/1546494520358948864?s=20&t=H6iZ5tENhdjQFNU58lZcAg
- Participated in an interview with The Age titled, 'Flu season fizzles out, but chance of a double peak looms', published 2 August 2022; https://www.theage.com.au/national/victoria/flu-season-fizzles-out-but-chance-of-a-double-peak-looms-20220726-p5b4s9.html
- Was quoted in an article by The Baharat News Switzerland titled, 'How Australians defeated their flu epidemic', published 21 December 2022; https://www-thebharatexpressnews-com.cdn.ampproject.org/c/s/www.thebharatexpressnews.com/how-australians-defeated-their-flu-epidemic/?amp

Annette Fox

- Publication was featured on the Doherty Institute website, with the article titled, 'Could repeated flu jabs decrease effectiveness?', published 15 December 2022; https://www.doherty.edu.au/news-events/news/could-repeated-flu-jabs-decrease-effectiveness

Patrick Reading

- Featured in an article by The Island Sun titled, 'Aust-Solomons tackle COVID-19 with boost to testing capability', published 23 March 2022; https://theislandsun.com.sb/aust-solomons-tackle-covid-19-with-boost-to-testing-capability/
- Featured in an article by the Doherty Institute titled, 'Building COVID-19 diagnostic capacity in the Solomon Islands', published 22 April 2022; https://www.doherty.edu.au/news-events/news/building-covid-19-diagnostic-capacity-in-the-solomon-islands

Kanta Subbarao

- Participated in an interview with Cosmos Magazine titled, 'What we know about Omicron', published 17 January 2022; https://cosmosmagazine.com/health/covid/omicron-update-170122/
- Featured in an article by Politico titled, 'Search is on for next-generation COVID-19 vaccines', published 27 January 2022; https://www.politico.eu/article/navigating-uncharted-waters-designing-next-generation-covid-19-vaccines/
- Participated in an interview by Fortune Magazine titled, 'Will we need Omicron-specific COVID vaccines? A leading virologist says the global system for flu shots could be a model to help us decide', published 1 February 2022; https://fortune.com/2022/01/31/covid-omicron-vaccine-variants-flu-shots-who/
- Participated in the Health Security Partnerships Roundtable with the United States Secretary of State, Antony Blinken and others, published 10 February 2022; https://about.unimelb.edu.au/newsroom/news/2022/february/us-secretary-of-state-antony-blinken-visits-university-of-melbourne/_recache?utm_content=story&utm_medium=social&utm_source=twitter
- Featured in an article by the Peter Doherty Institute titled, 'Influenza in 2022: animal and human public health collaboration essential', published 7 March 2022; https://www.doherty.edu.au/news-events/news/influenza-in-2022-animal-and-human-public-health-collaboration-essential
- Featured in an article by Lancet Infectious Diseases titled, 'Kanta Subbarao-confronting influenza and COVID-19', published 1 April 2022; https://linkinghub.elsevier.com/retrieve/pii/S1473-3099(22)00172-4

Community Engagement (continued)

Kanta Subbarao (continued)

- Participated in an interview with The Age titled, '"Influenza is back": Victoria gets first flu season for three years', published 29 April 2022; https://www.theage.com.au/national/victoria/influenza-is-back-victoria-gets-first-flu-season-for-three-years-20220428-p5ah0f.html
- Featured in an article by the Peter Doherty Institute for Infection and Immunity titled, '$8.9m in Medical Research Future Funds grants for Doherty Institute researchers', published 2 September 2022; https://www.doherty.edu.au/news-events/news/8.9m-medical-research-future-funds-grants-doherty-institute-researchers
- Participated in an interview with The Age/Sydney Morning Herald titled, 'Why Australia lags behind the US on Omicron vaccines', published 2 September 2022; https://www.smh.com.au/national/why-australia-s-newest-vaccine-is-four-variants-too-late-20220901-p5begi.html
- Participated in an interview with COSMOS Magazine titled 'Why we need nasal-spray vaccines', published 2 September 2022; https://cosmosmagazine.com/health/nasal-spray-vaccines-covid/
- Participated in an interview with The Atlantic titled, 'The Strongest Signal That Americans Should Worry About Flu This Winter', published 7 September 2022; https://www.theatlantic.com/science/archive/2022/09/flu-season-winter-2022-covid-masking/671356/

Sheena Sullivan

- Featured in an article by The Peter Doherty Institute for Infection and Immunity titled, 'Beyond the COVID-19 pandemic: increasing the uptake of influenza vaccination by health and aged care workers' on the recent Medical Journal of Australia article, published 6 June 2022; https://www.doherty.edu.au/news-events/news/increasing-uptake-of-flu-vaccination-by-health-and-aged-care-workers
- Participated in an interview with ABC News titled, 'Flu seasons, like the COVID-19 pandemic, have become unusual and unpredictable. Here's why', published 12 June 2022; https://www.abc.net.au/news/2022-06-12/flu-seasons-shaken-up-by-covid-restrictions-travel-vaccines/101134986
- Participated in an interview with Guardian Australia titled, 'Don’t want to get sick this winter? The pandemic health habits to keep long term', published 16 June 2022; https://www.theguardian.com/lifeandstyle/2022/jun/16/dont-want-to-get-sick-this-winter-the-pandemic-health-habits-to-keep-long-term?
- Quoted in an article by The Irish Times titled, 'Flu cases likely to be high in Europe this winter, Australian experts say', published 6 November 2022; https://www.irishtimes.com/health/2022/11/06/flu-cases-likely-to-be-high-in-europe-this-winter-australian-experts-say/
- Publication was featured on the Doherty Institute website, with the article titled, 'Could repeated flu jabs decrease effectiveness?', published 15 December 2022; https://www.doherty.edu.au/news-events/news/could-repeated-flu-jabs-decrease-effectiveness

Michelle Wille

- Wrote an article for the Peter Doherty Institute titled, 'High burden of avian influenza in the Northern Hemisphere, and what it means for us here in Australia', published 3 March 2022; https://www.doherty.edu.au/news-events/news/high-burden-of-avian-influenza-in-the-northern-hemisphere-and-what-it-means-for-us-here-in-australia
- Participated in an article by Gavi, The Vaccine Alliance titled, 'Bird flu: How worried should we be?', published 29 April 2022; https://www.gavi.org/vaccineswork/bird-flu-how-worried-should-we-be
- Participated in an interview with El Mundo Salud titled, 'La amenaza de la gripe aviar: "Cada vez son más frecuentes los casos de cepas raras"', published 29 April 2022; https://www.elmundo.es/ciencia-y-salud/salud/2022/04/29/626a6b0b21efa0e11d8b456e.html
- Wrote an article for Pursuit titled, 'Tracking Avian Influenza to Safeguard Australia', published 25 May 2022; https://pursuit.unimelb.edu.au/articles/tracking-avian-influenza-to-safeguard-australia

Community Engagement (continued)

Michelle Wille (continued)

- Participated in an interview with Nature News titled, 'Why unprecedented bird flu outbreaks sweeping the world are concerning scientists', published 26 May 2022; https://www.nature.com/articles/d41586-022-01338-2

Website and social media

The Centre website was maintained and updated throughout the year, with information provided on the progress of the influenza season and vaccine recommendations by WHO and the TGA. During 2022, the website was viewed by 7,957 unique users from 156 different countries. The majority of visits to the website were from Australia, followed by the USA.

The Centre continued to operate its Twitter account in during 2022. The Centre's Twitter profile gained 105 followers during the year, with a total of 921 followers by 31 December 2022.

Scan to access our Centre video, which was updated in May 2022 and is also available from the Centre website

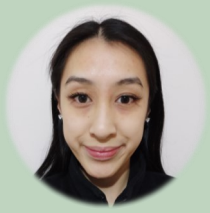
New and departing staff members

New staff

Dr Tanya Diefenbach-Elstob
Epidemiologist
(June)

Dr Melanie Duncan
Medical Scientist
(February)

Mr Steven Edwards
Medical Scientist
(August)



Ms Olivia Lay
Medical Scientist
(August)

Dr Yi Liu
Post-Doctoral Researcher
(May)

Ms Yen Tran
Administrative Officer
(January)

Departing staff

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.

Dr Naomi Komadina was the Bioinformatics Head and had worked at the Centre for almost 28 years. She retired from the Centre at the start of July.

Dr Mariana Baz was the Senior Scientist for the Antiviral group for around 16 months. She has now returned to Canada to pursue a new professional opportunity.

Ms Jean Moselen was a Medical Scientist with the Molecular group for three years. She has now taken on a role as a Medical Scientist with the Translational Diagnostics lab at VIDRL.

Management and staff

Director
Prof Kanta Subbarao

Deputy Director
Prof Ian Barr

Administrative officer
Yen Tran*

Quality & Regulatory Officer
Katie Milne

Educator/Research scientist
Prof Patrick Reading

Laboratory Manager/ Senior Medical Scientist
Dr Paul Whitney

Communications officer
Dr Miku Kuba

Surveillance

ANTIGENIC ANALYSIS
Head: Heidi Peck
Medical scientists:
Monica Bobbitt
Presa Chanthalavanh
Joelle Dharmakumara
Leah Gillespie
Lani Metuisela
Megan Triantafilou
Tasoula Zakis
Laboratory Assistant:
Violeta Stojceva

GENETIC ANALYSIS
Head: Dr Yi-Mo Deng
Medical scientists:
Dr Xiaomin Dong
Steven Edwards*
Pina Iannello
Hilda Lau
Olivia Lay*
Jean Moselen (until Sep)
Natalie Spirason

ANTIVIRAL DRUG SENSITIVITY
Head: Dr Mariana Baz (until Aug)
Medical scientist: Sook Kwan Brown

BIOINFORMATICS
Manager: Dr Naomi Komadina (until Jul)
Bioinformatician: Dr Ammar Aziz

Vaccine development

VACCINE CANDIDATES
Head: Heidi Peck
Medical scientists:
Hilda Lau
Cleve Rynehart

CELL-BASED VACCINES
Head: Heidi Peck
Medical scientists:
Cleve Rynehart
Sally Soppe

Research

IMMUNITY TO RESPIRATORY VIRUSES
Senior research scientist:
Dr Annette Fox
Post-Doctoral researchers
Dr Yi Liu*
Dr Stephany Sanchez
Dr Ryan (Yeu-Yang) Tseng (until Apr)
Research assistant
Louise Carolan
Anastasia Jessica Hadiprojo

ANTIVIRALS AND ANIMAL INFLUENZAS
Senior research scientist:
Dr Mariana Baz (until Aug)
Post-Doctoral researchers
Dr Nikita Deshpande
Dr Melanie Duncan*
Dr Michelle Wille (Honorary)
Research assistants:
Malet Aban
Harry Stannard
Ph. D Candidate:
Paulina Koszalka (Medical Scientist from May)

EARLY IMMUNE RESPONSES TO INFLUENZA
Senior research scientist:
Prof Patrick Reading
Research assistant:
James Barnes

Epidemiology

Head:
A/Prof Sheena Sullivan
Epidemiologists:
Tanya Diefenbach-Elstob*
Genevieve O'Neill (until Mar)
Research assistant:
Arseniy Khvorov
Ph D Candidate:
Jessie Goldsmith
MAE Candidate:
Catherine Pendrey

**New staff members in 2022*