Annual Report 2023

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 2023

Surveillance

The Centre received and processed an unprecedented number of samples during 2023. A total of **15,368 samples** was received, of which **83% were tested**. Of viruses tested, approximately **40%** were **A(H1N1) viruses.**

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.

Research, publications and grants

The Centre further developed its research program during 2023, with Centre staff involved as authors on **70 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)**.

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 2023.

Director’s report

I present the 2023 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.

In 2023 the influenza season in Australia began earlier than the average season in the pre-COVID-19 pandemic period, with the peak of the season occurring in late June, some 3 weeks later than 2022. The Centre received and processed more than 15,000 influenza samples from laboratories in Australia and 23 other countries. The largest proportion of the samples analysed were influenza A(H1N1)pdm09 viruses. The Centre continued to conduct antigenic and genetic characterisation of viruses and noted an increase in genetic diversification of the H1 and H3 HA genes. Notably, no confirmed detections of B/Yamagata lineage viruses continued in 2023 and none have been detected since March 2020. Hence in September 2023, the WHO influenza vaccine composition advisory committee recommended that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines was no longer warranted, and every effort should be made to exclude this component as soon as possible. The Centre also continued routine testing of viruses for reduced susceptibility to neuraminidase inhibitors and the polymerase inhibitor baloxavir marboxil.

During 2023 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 2024 (A/Victoria/4897/2022, A(H1N1)pdm09. Three of the four vaccine strains recommended for the 2024 Southern Hemisphere quadirivalent 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 continued to monitor potential pandemic influenza viruses and sought 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, Maldives, and Timor-Leste. The Centre hosted visitors from Timor-Leste and Mongolia and other countries for training in serologic and molecular techniques.

Centre staff contributed to a total of 70 original research papers, reviews and reports in 2023. 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 Dr Chuan Lim, the Acting Director of VIDRL, and to many other members of VIDRL staff, especially Deborah Williamson and Dallas Wilson for their support of the Centre’s work at every level during 2023. 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 2023. It is a privilege to work with the Centre staff and I look forward to working with our partners

Prof Kanta Subbarao
Centre Director

Surveillance

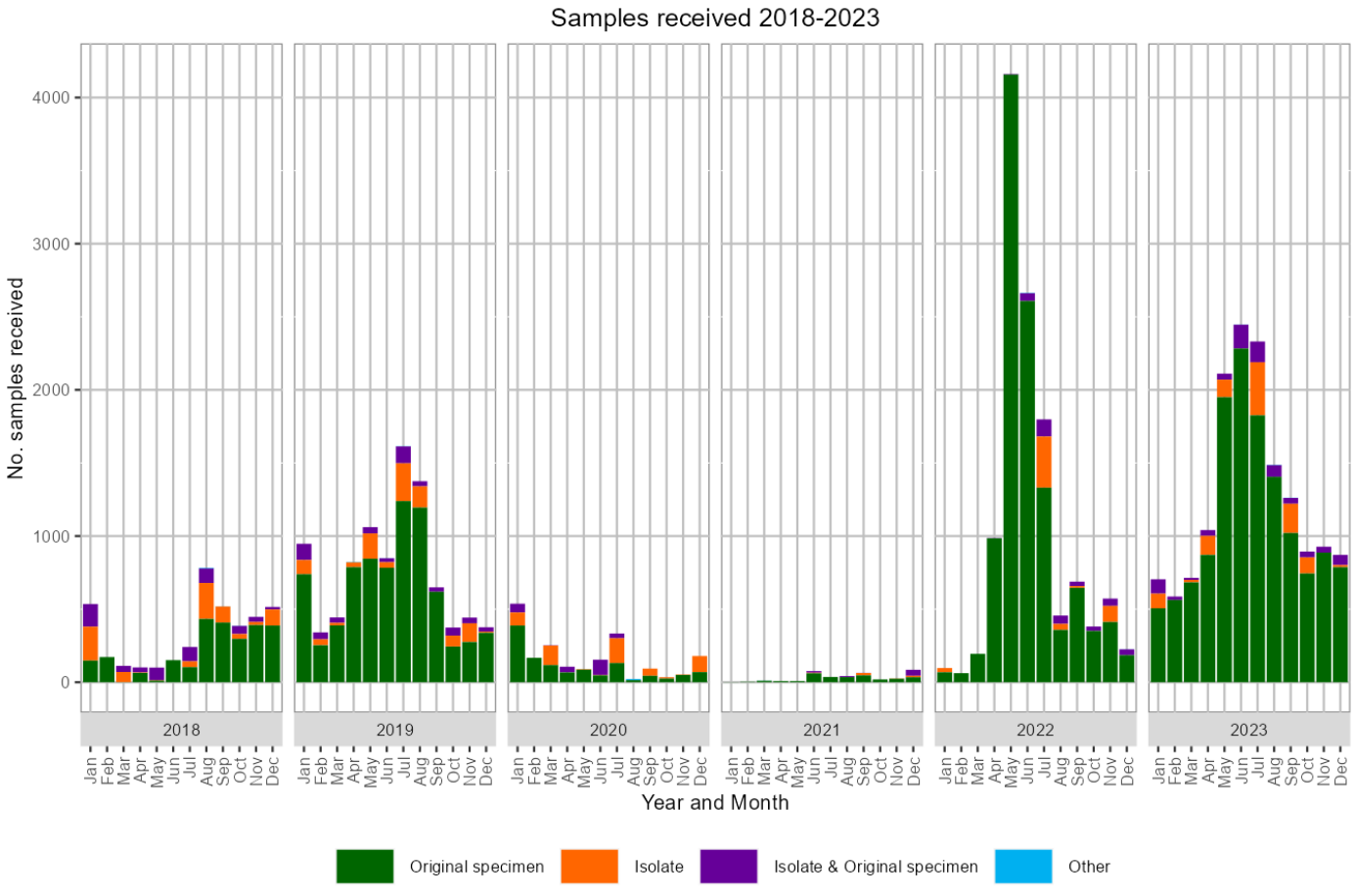
Introduction

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 HA subtypes that are genetically and antigenically distinct, as well as 11 NA subtypes. Influenza B viruses are not classified into subtypes, but rather into the B/Victoria and B/Yamagata lineages. Of note, laboratory confirmed cases of B/Yamagata lineage viruses have not been detected since March 2020. Currently there are three predominant influenza viruses circulating in the human population — influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B (Victoria lineage).

Figure 1. Samples received by the Centre, 2018-2023.



Receipt of Influenza Viruses

During 2023 the Centre received 15,368 clinical specimens and/or virus isolates from 67 laboratories in 23 countries (Figures 1 and 2, Table 1). This is significantly higher than the number of samples received by the Centre during 2022, and is consistent with the high number of influenza infections during the 2023 Australian influenza season. This can be attributed to the easing of various restrictions implemented during 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 5-9 years (Figure 3). 3416 samples 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 reverse-transcription polymerase chain reaction (RT-PCR) and are also required for recovery of egg isolates that may represent 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 15,260 samples tested, a total of 12,693 samples (83.2%) were successfully isolated by cell culture and/or analysed by real-time 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, 40.1% were identified as A(H1N1)pdm09, 32.3% were B/Victoria, 12.6% were A(H3N2) viruses, 4.8% were A (unsubtyped), 10.3% were B (lineage undetermined) (Table 3).

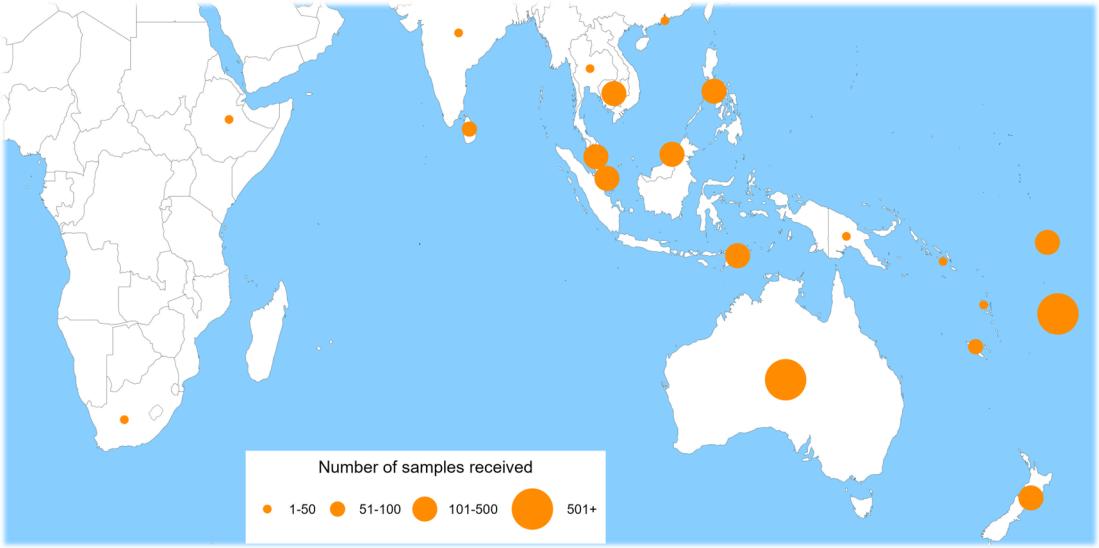


Figure 2. Geographic spread of laboratories sending samples to the Centre during 2023.

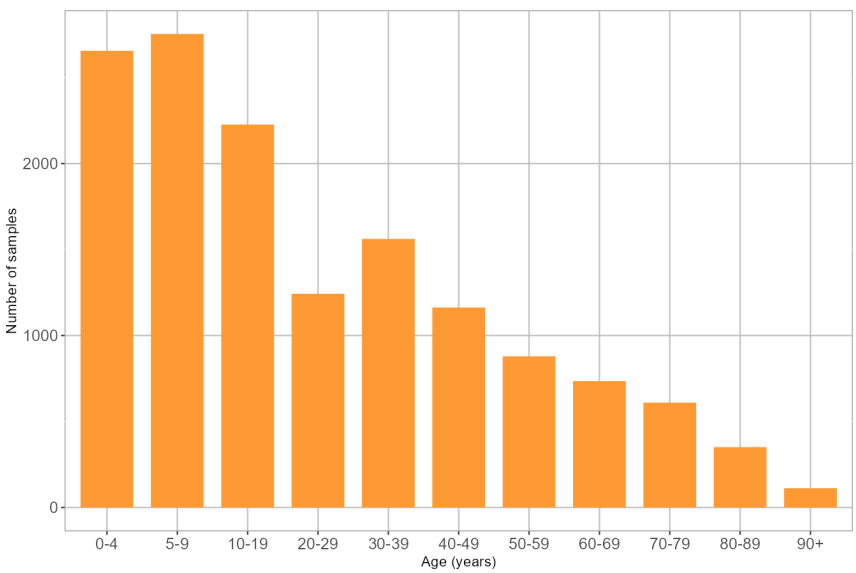


Figure 3. Age distribution of patients from whom samples were received at the Centre in 2023 and the age is known.

Table 1. Samples received by the Centre in 2023, by country.

Country	Samples received				% Samples tested
	Specimens	Isolates	Specimen + Isolate	Other (eg. RNA/DNA/ tissue)	
AUSTRALASIA					
Australia	11714	144	593	5	99.60%
New Zealand	0	372	0	0	100%
EAST ASIA					
Macau SAR, China	0	30	0	0	100%
SOUTH EAST ASIA					
Brunei	281	0	0	0	100%
Cambodia	26	105	0	0	96.90%
Malaysia	0	334	0	0	100%
Philippines	78	0	25	0	100%
Singapore	4	0	145	0	100%
Thailand	11	29	0	0	100%
Timor-Leste	247	0	0	0	100%
SOUTH ASIA					
India	0	40	0	0	100%
Sri Lanka	91	0	0	0	58.20%
SOUTH PACIFIC					
Fiji	663	0	0	0	100%
Kiribati	10	0	0	0	100%
New Caledonia	100	0	0	0	100%
Papua New Guinea	27	0	0	0	82.50%
Samoa	27	0	0	0	92.60%
Solomon Islands	15	0	0	0	100%
Tonga	10	0	0	0	100%
Tuvalu	146	0	0	0	100%
Vanuatu	29	0	0	0	100%
AFRICA					
South Africa	0	0	27	0	100%
Ethiopia	40	0	0	0	92.50%
TOTAL	**13519**	**1054**	**790**	**5**	**99.30%**

Table 2. Samples received from general practitioner-based surveillance systems, namely the Australian Sentinel Practices Research Network (ASPREN), and from the hospital-based Influenza Complications Alert Network (FluCAN) in 2023.

	No. samples received	No. isolates recovered*	Viruses analysed by HI assay
Australian Sentinel Practices Research (ASPREN) Network	352	147	143
Influenza Complications Alert Network (FluCAN)	3064	1705	1660
TOTAL	**3416**	**1852**	**1803**

Table 3. Samples successfully isolated in cell culture and/or RT-PCR assay at the Centre in 2023, 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	4276	1143	558	3267	1214
New Zealand	199	16	0	157	0
EAST ASIA					
Macau SAR, China	15	14	0	1	0
SOUTH EAST					
Brunei	11	66	2	44	11
Cambodia	38	31	0	43	0
Malaysia	35	65	1	207	1
Philippines	51	9	0	15	0
Singapore	36	77	0	35	0
Thailand	6	23	0	10	0
Timor-Leste	25	3	0	25	0
SOUTH ASIA					
India	13	16	0	8	0
Sri Lanka	24	18	0	5	6
SOUTH PACIFIC					
Fiji	204	38	0	205	55
Kiribati	0	5	5	0	0
New Caledonia	71	3	0	25	0
Papua New Guinea	10	0	0	0	0
Samoa	0	0	0	23	2
Solomon Islands	14	0	0	0	1
Tonga	0	0	0	10	0
Tuvalu	24	36	47	6	3
Vanuatu	10	0	0	14	0
AFRICA					
South Africa	0	27	0	0	0
Ethiopia	23	3	0	0	9
TOTAL	5085	1593	613	4100	1302

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

Antigenic Analysis of Influenza Isolates

Background

The antigenic properties of influenza virus 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.

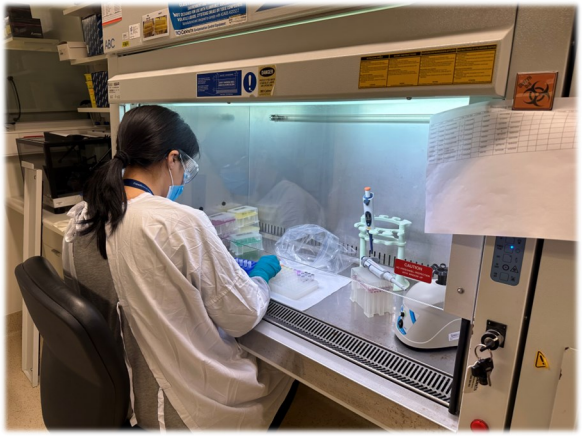


Figure 4. Influenza subtypes and lineages of samples received in 2023 and characterised by antigenic analysis.

Antigenic analyses 2023

A total of 12,666 isolates that were received at the Centre in 2023 were cultured and isolated in MDCK cells. The largest proportion of isolates were A (H1N1)pdm09 viruses (48.2%), followed by B/ Victoria (34%) viruses (Figure 4). In samples received from Africa, A(H3N2) viruses predominated. In Australasia and in the South Pacific region, A(H1N1)pdm09 were most prominent, followed by B/Victoria and then A(H3N2) viruses. In East Asia, approximately half of the isolates were A(H1N1) pdm09, followed by 46.7% A (H3N2) and a small percent of B/Victoria. In South Asia, A(H3N2) viruses were predominant, followed by A(H1N1)pdm09 and then B/Victoria viruses. In South East Asia, B/Victoria viruses were most prominent, followed by A(H3N2) and then (H1N1) pdm09 viruses.

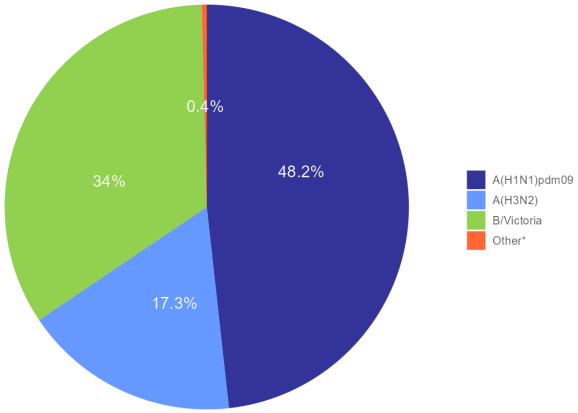
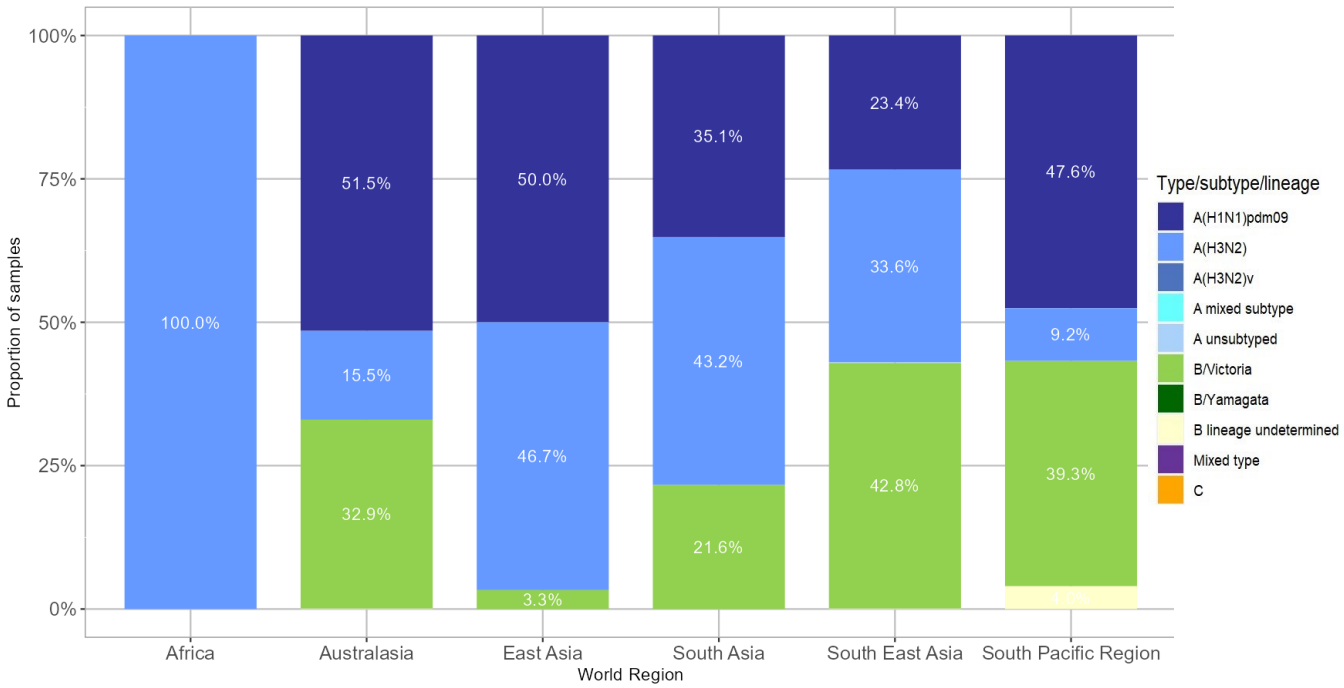


Figure 5. Influenza subtypes and lineages of isolates received from different regions during 2023 as determined by antigenic analysis.



Genetic Analysis of Influenza Viruses

Background

A subset of all influenza viruses analysed at the Centre undergo 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.

In addition to Sanger sequencing, 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. NGS is performed at the Centre using either Illumina or Oxford Nanopore Technologies (ONT) platforms.

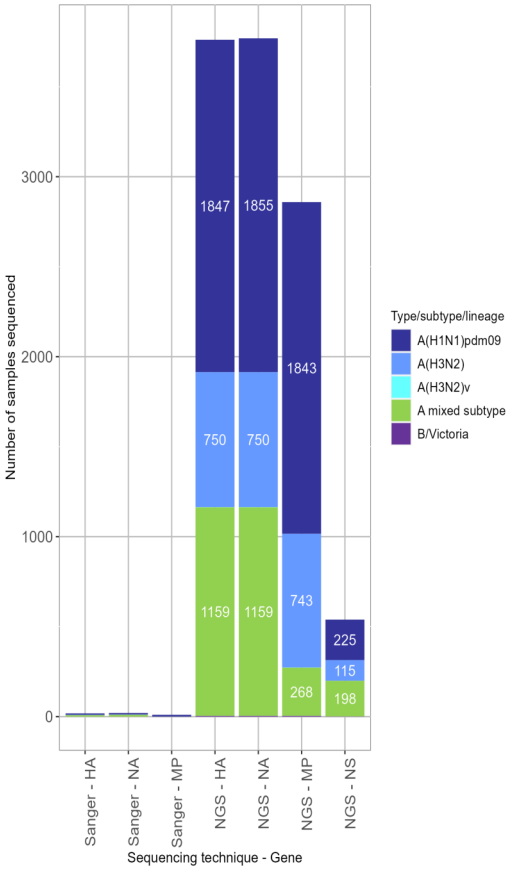


Figure 6. Sequencing of viruses received at the Centre in 2023. Note that some viruses were analysed by Sanger sequencing and NGS, and are therefore represented twice in this figure.

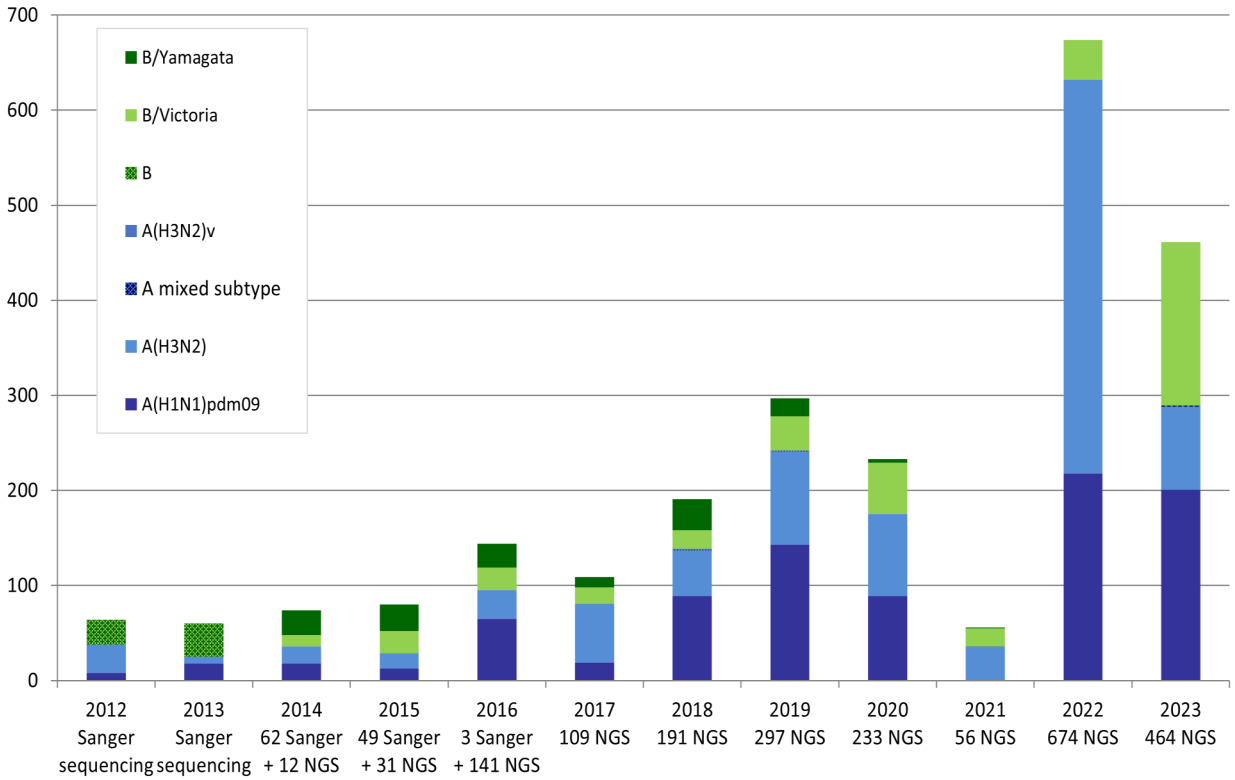
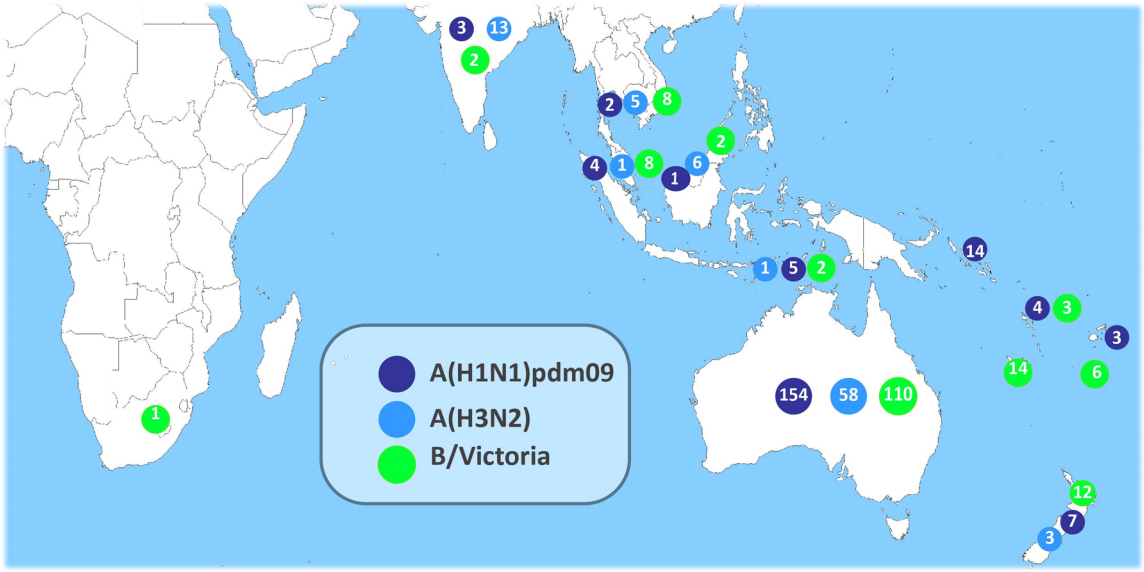


Figure 7. Number of viruses analysed by full genome sequencing 2012-2023 using Sanger sequencing and/or NGS (Illumina or ONT).

Sequencing 2023

In 2023, 3808 HA, 3818 NA, 2884 MP and 544 NS genes from 3818 human viruses received at the Centre were analysed by Sanger sequencing or NGS (Figure 6). Of these viruses, full genome sequencing was performed on 464 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 2023.



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 2023

A total of 11,069 gene sequences from 3753 human influenza viruses were deposited with GISAID in 2023 (Table 4). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 464 influenza viruses (201 A(H1N1)pdm09 viruses, 87 A(H3N2) viruses and 171 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 2023.*

Gene / Type/ Subtype/ Lineage	HA	NA	MP	NS	PB1	PB2	PA	NP	Total
A(H1N1)pdm09	1673	1700	1658	169	140	152	172	166	5830
A(H3N2)	705	706	667	51	47	49	76	49	2350
B/Victoria	995	994	201	142	138	138	140	141	2889
Total	**3373**	**3400**	**2526**	**362**	**325**	**339**	**388**	**356**	**11069**

**Counts include all sequences submitted to GISAID during 2023, which includes viruses received in previous years and viruses sequenced for reference and research purposes.*

Surveillance Results by Influenza Subtype or Lineage

Viruses were analysed by comparison with reference viruses recommended by WHO for the 2023 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 3486 A(H1N1)pdm09 isolates were analysed by HI assay in 2023. A small portion (0.54%) and (0.78%) of viruses received from Australasia and the South Pacific region were antigenically dissimilar to the cell grown vaccine A/Sydney/5/2021(Figure 9,10, Table 5). All viruses from South East Asia, South Asia and East Asia displayed similar antigenic properties to the reference strain.

Haemagglutinin gene sequencing

Sequencing was performed on a total of 1871 HA genes. Phylogenetic analysis showed that the majority of circulating A(H1N1)pdm09 viruses sent to the Centre during 2023 were in subclade 5a.2a (Figure 10). With this in mind, the A(H1N1)pdm09 strain for the 2024 Southern Hemisphere recommended vaccine was updated to A/Victoria/4897/2022 .

A(H1N1)pdm09 reference strain: A/SYDNEY/5/2021		
Region	**Like**	**Low reactor (%)**
Australasia	3156	17(0.54%)
South East Asia	167	0
South Asia	1	0
East Asia	15	0
South Pacific Region	129	1(0.78%)
TOTAL	**3468**	**18(0.52%)**

Table 5 Antigenic characterisation of A(H1N1)pdm09 viruses analysed at the Centre in 2023, compared to the A/Sydney/5/2021 reference virus.

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.

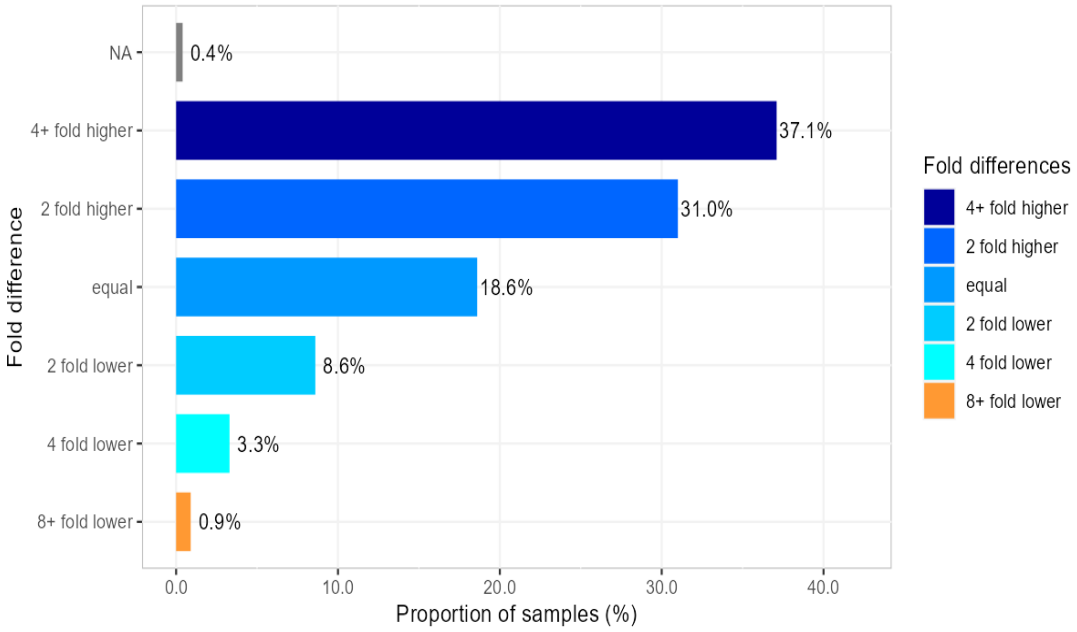


Figure 10. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/Sydney/5/2021 reference virus.

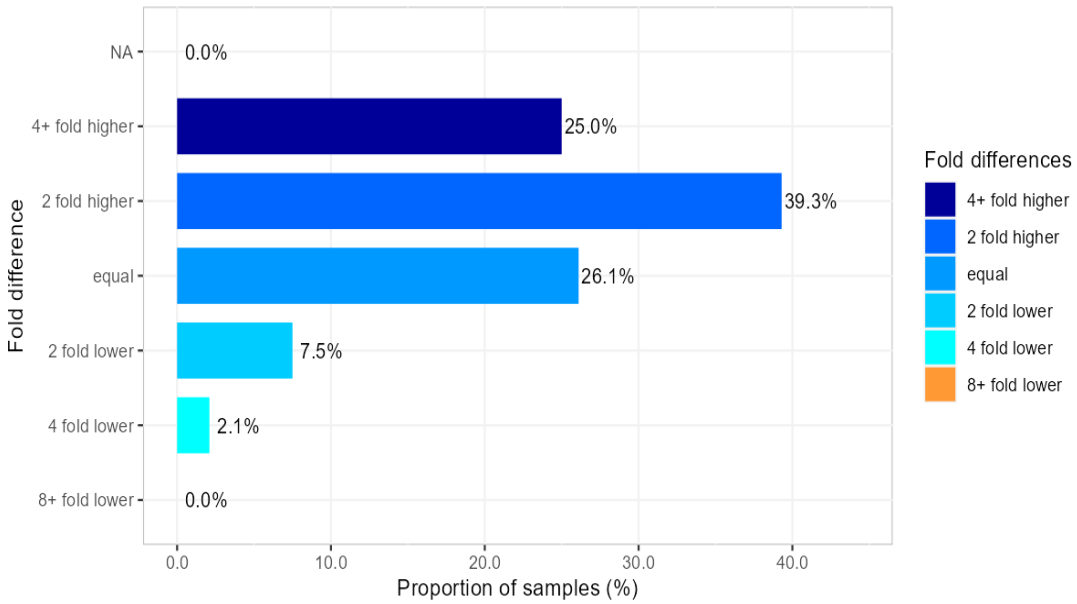
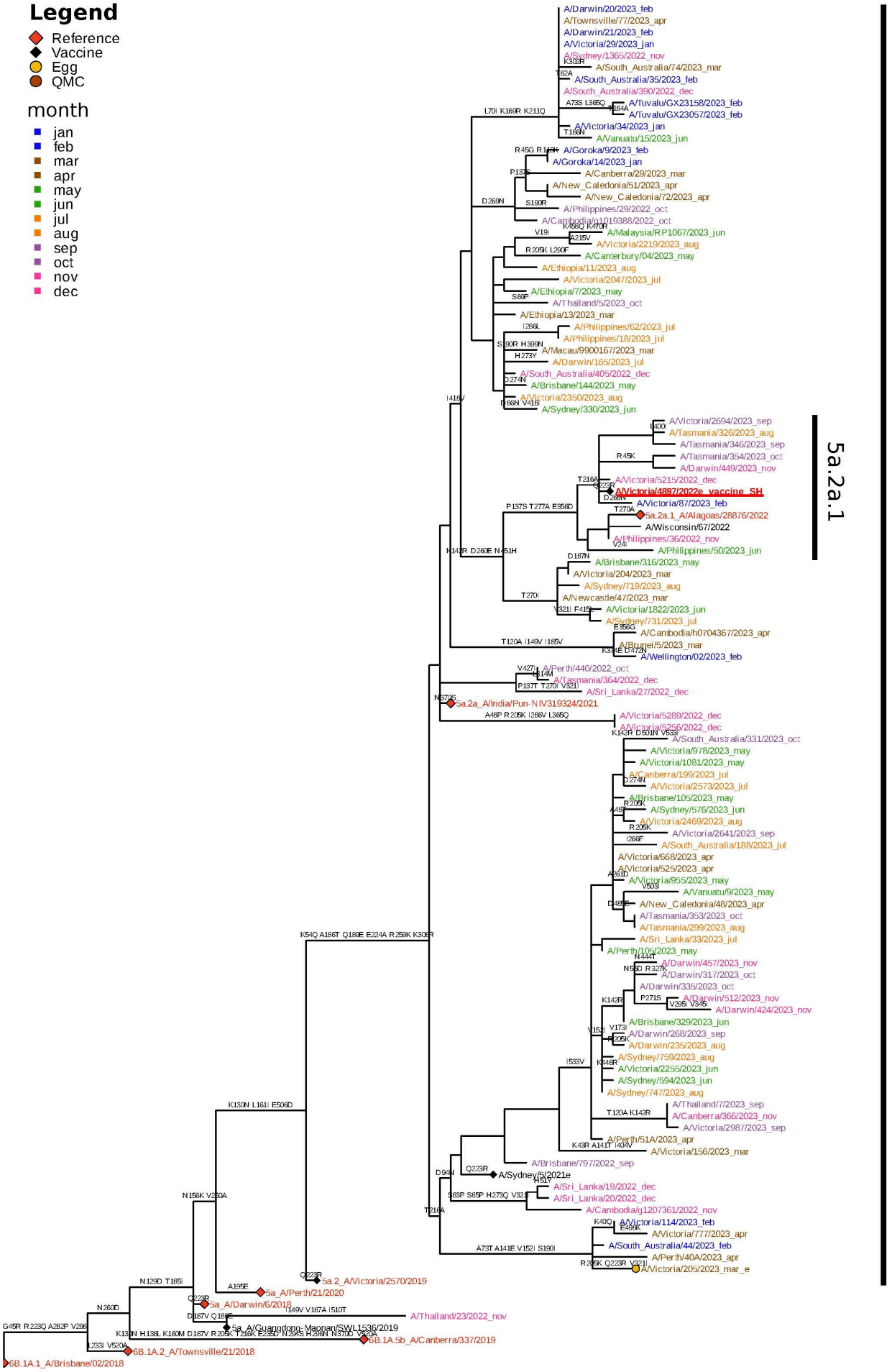


Figure 11. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2023.



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, no FRA-MNs were performed for A(H3N2) viruses that were unable to be analysed by HI assay.

A total of 1404 A(H3N2) subtype isolates were analysed by HI assay in 2023. . A small portion (3.7%, 6.7%, 4.92%, and 1.82% of viruses received from Africa, Australasia, South East Asia and The South Pacific region, respectively, were antigenically dissimilar to the cell-grown vaccine A/Darwin/6/2021(Figure 12, Table 6). All viruses from South Asia, and East Asia displayed similar antigenic properties to the reference strain.

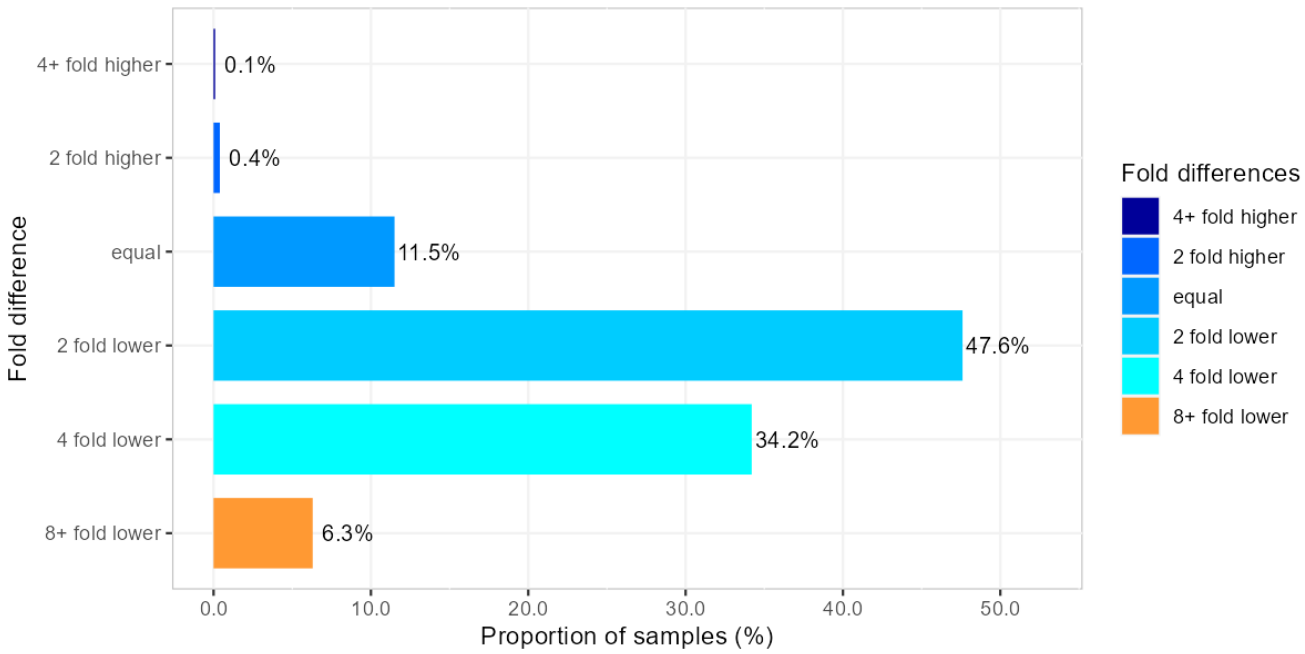
Haemagglutinin gene sequencing

A total of 777 HA genes from A(H3N2) viruses were sequenced. Phylogenetic analysis indicate that most circulating viruses fell into clade 2a.3a.1, which contains the 2023 Southern Hemisphere recommended vaccine strain A/Darwin/6/2021 (Figure 13).

Table 6 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 (%)**
Africa	26	1 (3.7 %)
Australasia	961	69 (6.7 %)
East Asia	14	0
South Asia	16	0
South East Asia	251	13 (4.92 %)
South Pacific Region	54	1 (1.82 %)
TOTAL	**1322**	**84 (5.97 %)**

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.



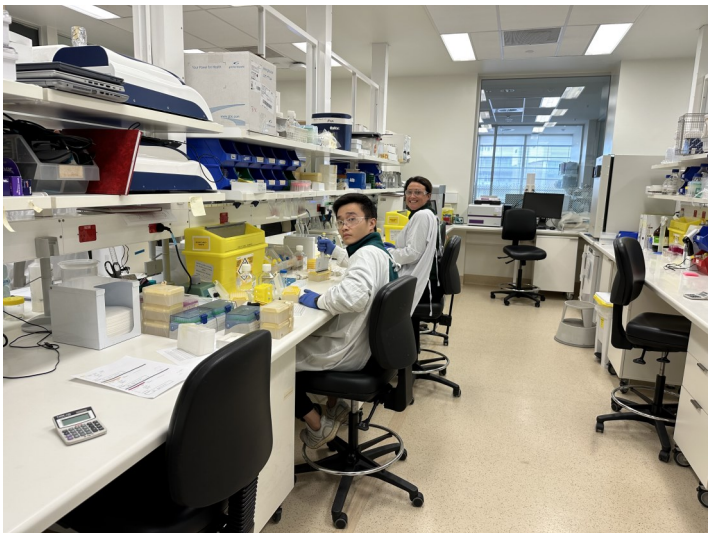
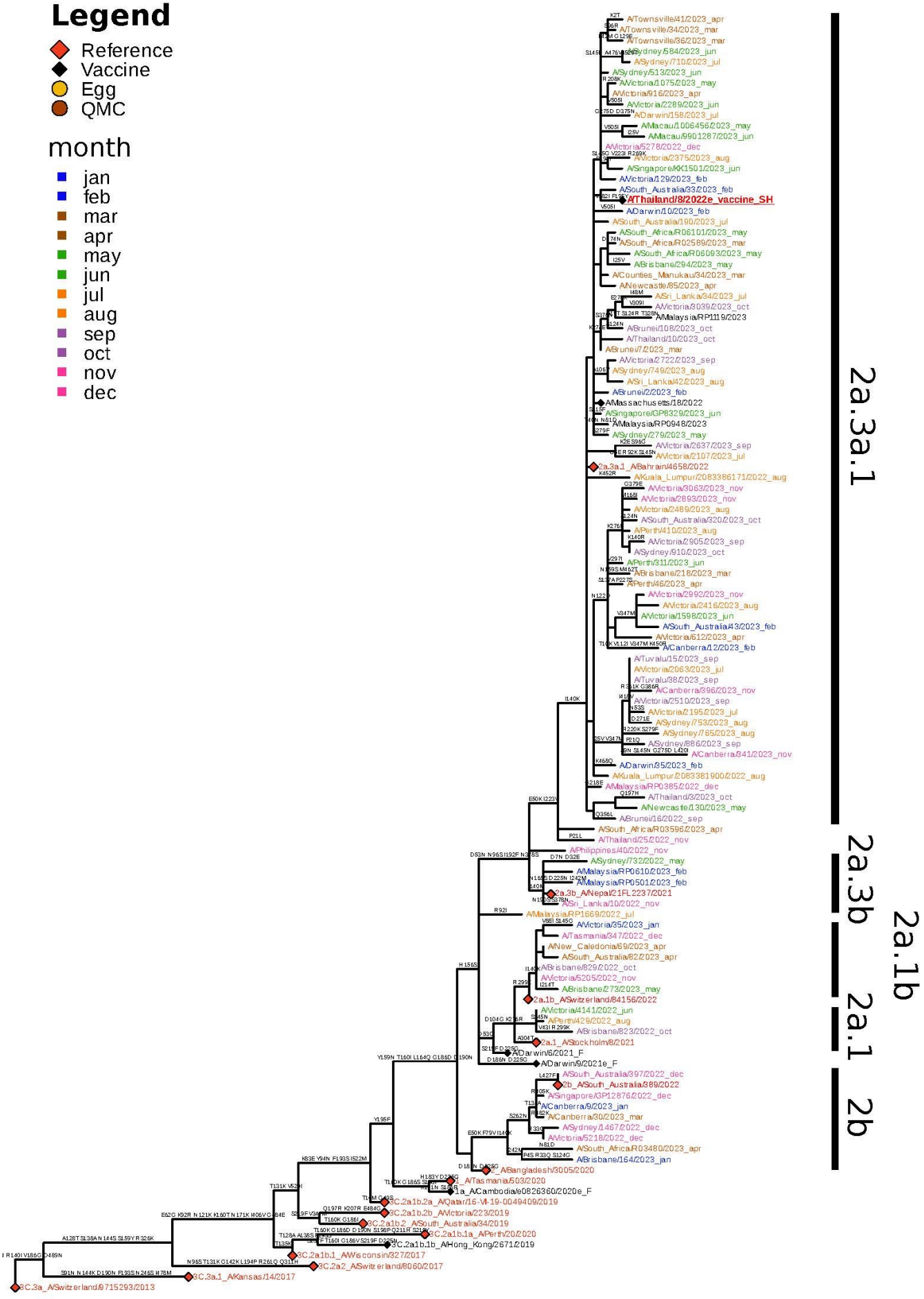


Figure 13. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2023.



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. However, no B/Yamagata lineage viruses with collection dates after March 2020 have been detected globally, and the Centre did not receive any samples containing B/Yamagata viruses in 2023.

Antigenic Analysis

A total of 2768 B/Victoria lineage isolates were analysed by HI assay in 2023. Of these, 2768 samples were tested against the cell-grown recommended vaccine strain for the 2023 Southern Hemisphere B/Austria/1359417/2021(Figure 14, table 7). A small portion (0.05%) and (0.59%) of viruses received from Australasia and South East Asia were antigenically dissimilar to the cell-grown vaccine B/Austria/1359417/2021.

Haemagglutinin gene sequencing

A total of 1179 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 2023 recommended vaccine strain B/Austria/1359417/2021 (Figure 15).

Table 7 Antigenic characterisation of B/Victoria viruses received at the Centre during 2023 compared to the B/Austria/1359417/2021 reference virus.

	B/Victoria lineage reference strain: B/Austria/1359417/2021	
Region	**Like**	**Low reactor (%)**
Australasia	2183	1 (0.05 %)
East Asia	1	0
South Asia	8	0
South East Asia	338	2 (0.59 %)
South Pacific Region	235	0
TOTAL	**2765**	**3 (0.11 %)**

Figure 14. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to B/ Austria/1359417/2021 reference virus.

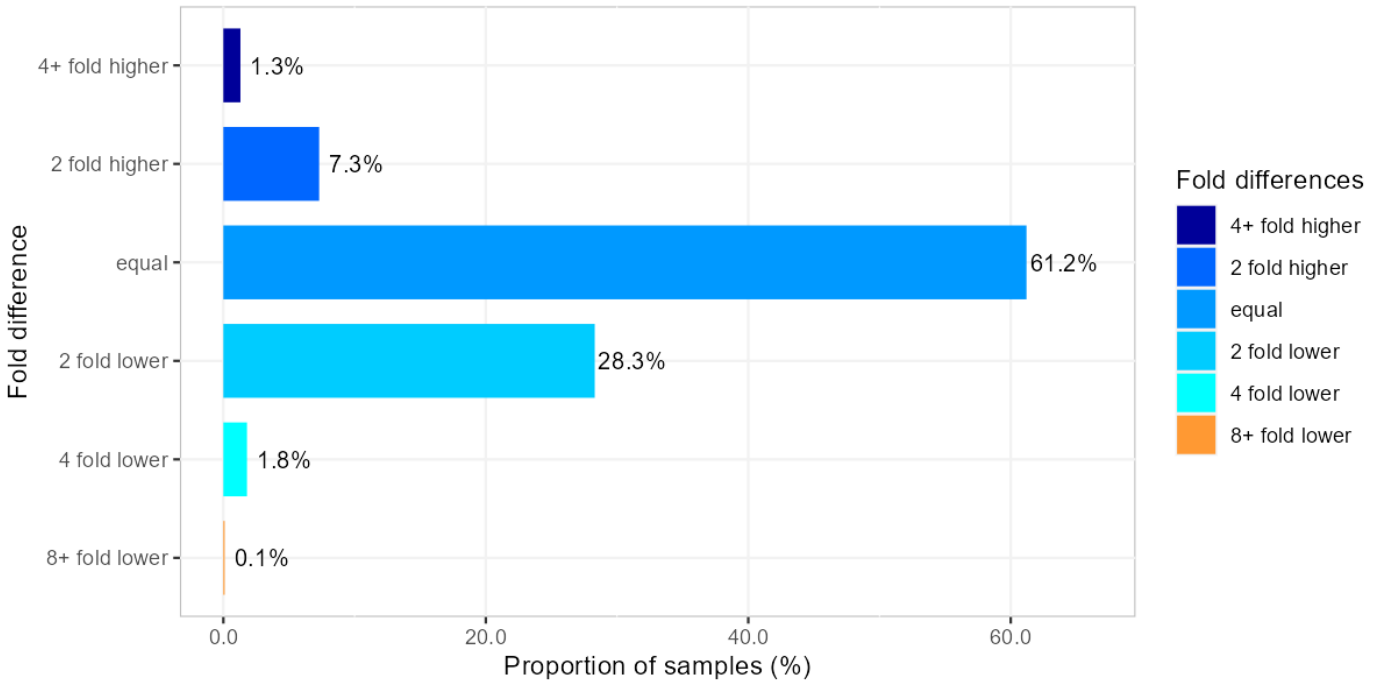
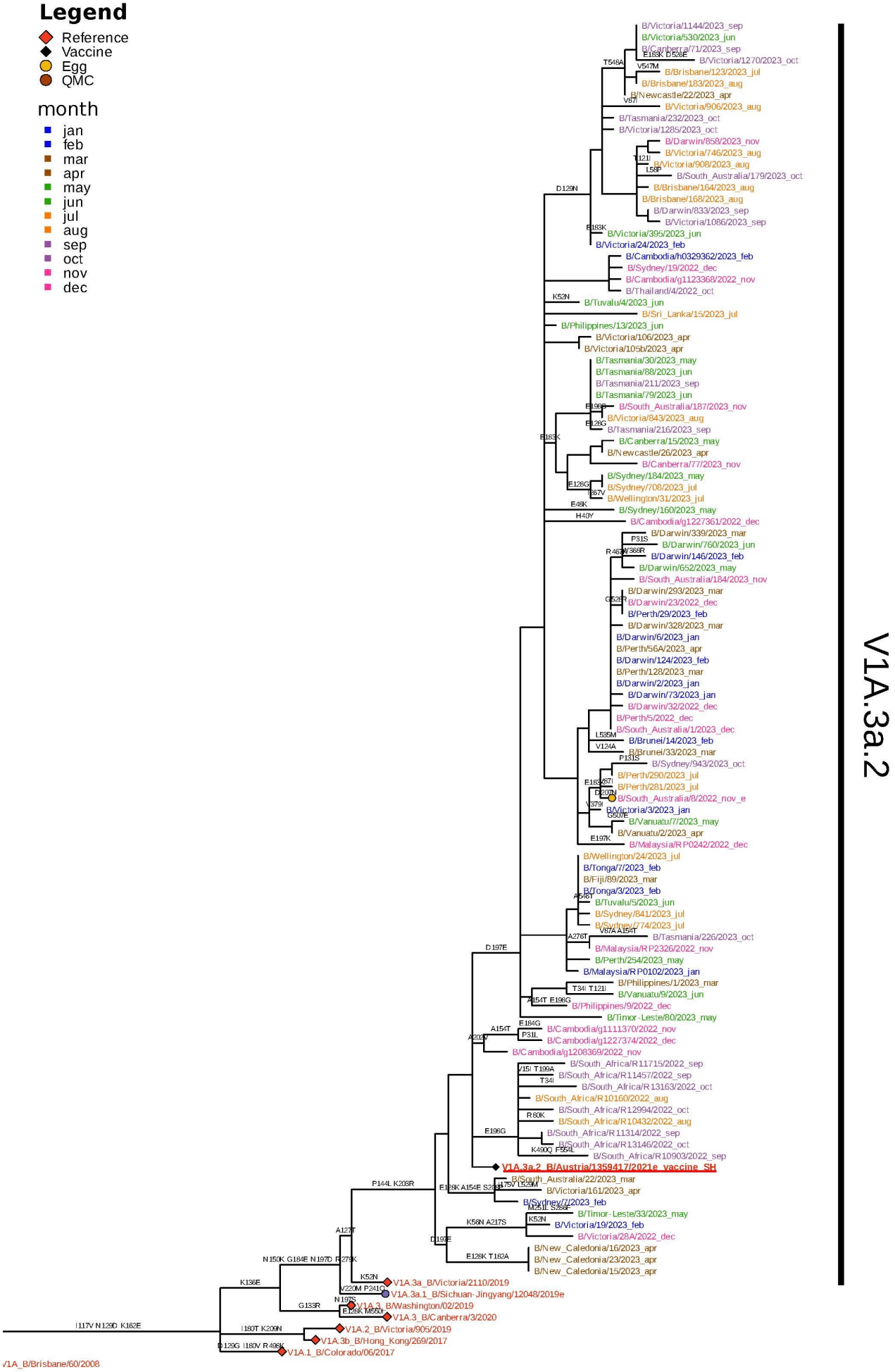


Figure 15. Phylogenetic tree of representative HA genes of B/Victoria viruses received by the Centre during 2023.



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. Laninamivir is not currently approved in Australia but is used in Japan. 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 NAI 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 8. Viruses received by the Centre in 2023 and tested by NAI assay, by country.

	Type/subtype/lineage				
Country	**A(H1N1)pdm09**	**A(H3N2)**	**B/Victoria**	**B lineage undetermined**	**TOTAL**
Australasia					
Australia	2066	738	1307	2	4113
New Zealand	198	14	134	0	346
East Asia					
Macau SAR, China	15	14	1	0	30
South East Asia					
Brunei	11	58	14	0	83
Cambodia	38	31	43	0	112
Malaysia	23	56	115	0	194
Philippines	51	8	13	0	72
Singapore	34	68	35	0	137
Thailand	6	16	9	0	31
Timor-Leste	9	1	12	0	22
South Asia					
India	13	16	8	0	37
South Pacific					
Fiji	115	35	95	0	245
Kiribati	0	5	0	0	5
New Caledonia	71	3	24	0	98
Papua New Guinea	10	0	0	0	10

*Table 8. Continued below**

Country	A(H1N1)pdm09	A(H3N2)	B/Victoria	B lineage	TOTAL
Samoa	0	0	6	0	6
Tonga	0	0	9	0	9
Tuvalu	13	12	5	0	30
Vanuatu	10	0	9	0	19
Africa					
South Africa	0	27	0	0	27
TOTAL	**2683**	**1102**	**1839**	**2**	**5626**

Antiviral resistance analyses 2023

NAI assays were used to analyse 5626 viruses for reduced inhibition by the NAIs (Tables 8 and 9). 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 reduced inhibition by NAIs.

A total of 18 viruses (17 A(H1N1)pdm09 and 1 B/Victoria) showed 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 were associated with the reduction of inhibition by NAIs (Table 10). For example, it is well established that a histidine to tyrosine substitution at position 275 (H275Y) in the NA protein of A(H1N1) pdm09 viruses reduces inhibition by oseltamivir, as does the equivalent H273Y mutation in B viruses.

*Table 9. Neuraminidase inhibitor sensitivity of viruses received by the Centre in 2023**.

Type/Subtype/ Lineage	No. tested	Oseltamivir		Peramivir		Laninamivir		Zanamivir	
		RI	HRI	RI	HRI	RI	HRI	RI	HRI
A(H1N1) pdm09	2683	1 (0.04%)	17 (0.63%)	4 (0.15%)	15 (0.56%)	2 (0.07%)	0	3 (0.11%)	0
A(H3N2)	1102	0	0	0	0	0	0	0	0
B/Victoria	1839	0	0	2 (0.11%)	1 (0.05%)	0	0	1 (0.05%)	0
B lineage	2	0	0	0	0	0	0	0	0
TOTAL	**5626**	**1 (0.02%)**	**17 (0.3%)**	**6 (0.11%)**	**16 (0.28%)**	**2 (0.04%)**	**0**	**4 (0.07%)**	**0**

Based on IC50, the NAI sensitivity of each strain is classified as the following: **Normal inhibition = IC50 values are within or close to the median IC50 of type/subtype-matched viruses tested at the Centre during the past year. **Reduced inhibition** (RI) = IC50 values are 10 to 100 fold above the median value of viruses with normal inhibition (5 to50 fold for influenza B viruses). **Highly reduced inhibition (HRI)** = IC50 values are greater than 100 fold above the median value of viruses with normal inhibition (above 50 fold for influenza B viruses).*

Table 10. Characteristics of viruses received by the Centre during 2023 with highly reduced inhibition by NAIs.

Type/Subtype/ Lineage	Country of submitting laboratory	NAI(s) with highly reduced inhibition (marked with *)				Mutations Detected
		Oseltamivir	Peramivir	Laninamivir	Zanamivir	
A(H1N1)pdm09	India	*	*			H275Y
A(H1N1)pdm09	Australia	*				H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*				H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
A(H1N1)pdm09	Australia	*	*			H275Y
B/Victoria	Fiji		*			H134Y

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. In 2023, 461 viruses which had been characterized by whole genome sequencing were screened for known antiviral substitutions in the PA gene associated with reduced susceptibility to Baloxavir Marboxil. No antiviral resistance substitutions for Baloxavir were detected.

Screening for baloxavir resistance in 2023

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 606 viruses by pyrosequencing or sequencing did not identify any viruses with mutations in the I38 position of the PA endonuclease (Table 11).

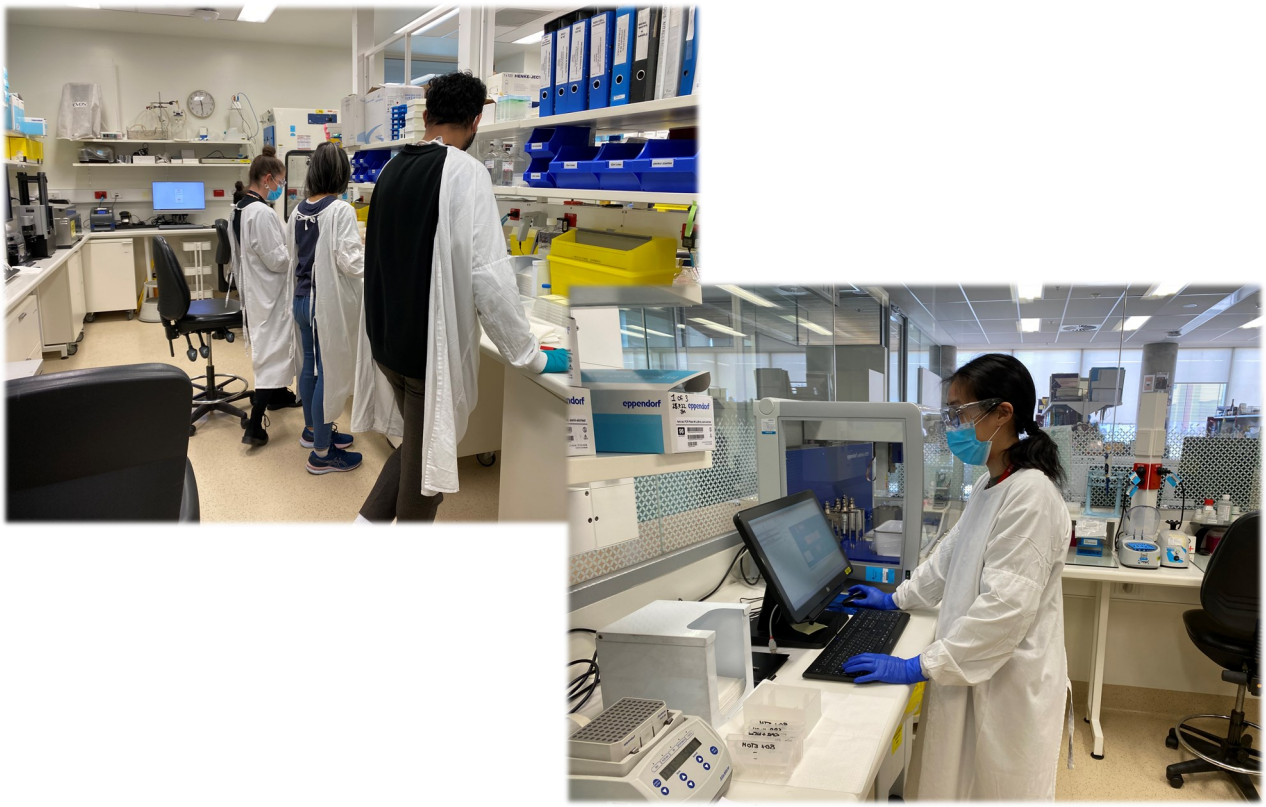


Table 11. Viruses screened for reduced susceptibility to baloxavir during 2023 by sequencing/pyrosequencing.

	Pyrosequencing/ sequencing			
Type/subtype/ lineage / Country	A(H1N1)pdm09	A(H3N2)	B/Victoria	TOTAL
Australasia				
Australia	218	82	13	434
New Zealand	9	8	12	29
South East Asia				
Brunei	1	6	2	9
Cambodia	2	0	0	2
Malaysia	4	1	12	17
Thailand	2	7	8	17
Timor-Leste	5	1	2	8
South Asia				
India	5	13	3	21
South Pacific				
Fiji	3	0	0	3
New Caledonia	1	0	14	15
Samoa	0	0	3	3
Solomon Islands	14	0	0	14
Tonga	0	0	8	8
Tuvalu	12	0	0	12
Vanuatu	4	0	3	7
Africa				
South Africa	0	6	1	7
TOTAL	**280**	**124**	**20**	**606**

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, a serine to alanine substitution at position 31 (S31N), in the influenza A M2 protein.

Screening for adamantane resistance in 2023

Real-time PCR or sequencing was used to analyse 2227 influenza A viruses, which were representative of those submitted to the Centre during 2023 (Figure 16). All of the tested influenza A viruses carried the S31N mutation, indicating that they would be resistant to adamantanes.

Figure 16. Geographic spread of viruses received at the Centre during 2023 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 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 2023

In 2023, a total of 28 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 61.0% (Tables 12 and 14).

Table 12. Virus isolation in eggs at the Centre in 2023.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	22	13	59.1%
A(H3N2)	21	13	61.9%
B/Victoria	3	2	66.7%
Total	**46**	**28**	**61.0%**

Isolation of viruses in cells in 2023

In 2023, a total of 38 viruses were successfully isolated in qualified cells at the Centre, representing an overall isolation rate of 63% (Tables 13 and 15).

Table 13. Virus isolation in cells at the Centre in 2023.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	21	11	52%
A(H3N2)	26	19	73%
B/Victoria	13	8	62%
Total	**60**	**38**	**63%**

Table 14. Potential candidate vaccine strains isolated in eggs at the Centre in 2023.

A(H1N1)pdm09	A(H3N2)
A/Canberra/46/2023	A/Darwin/2472/2022
A/Sydney/44/2023	A/Brisbane/837/2022
A/Victoria/205/2023	A/Victoria/5290/2022
A/Victoria/201/2023	A/South Australia/389/2022
A/Darwin/7/2023	A/Singapore/GP12876/2022
A/Victoria/380B/2023	A/South Australia/82/2023
A/South Australia/83/2023	A/Darwin/2/2023
A/Canberra/50/2023	A/Sydney/4/2023
A/Tasmania/44/2023	A/Sydney/316/2023
A/Newcastle/107/2023	A/Victoria/196/2023
A/Victoria/650/2023	A/Victoria/260/2023
A/New Caledonia/48/2023	A/Darwin/344/2023
A/New Caledonia/33/2023	A/Sydney/856/2023

B/Victoria
B/South Australia/8/2022
B/Victoria/3/2023

Table 15. Potential candidate vaccine strains isolated in cells at the Centre in 2023.

A(H3N2)
A/Brunei/42/2022
A/South Australia/372/2022
A/Brisbane/841/2022
A/Victoria/5218/2022
A/Victoria/5222/2022
A/South Australia/389/2022
A/Victoria/5290/2022
A/Singapore/GP12876/2022
A/South Australia/62/2023
A/Sydney/160/2023
A/South Australia/48/2023
A/Tasmania/16/2023
A/Victoria/188/2023
A/Sydney/252/2023
A/Brisbane/265/2023
A/Brisbane/273/2023
A/South Africa/R04452/2023
A/Victoria/2374/2023
A/Perth/401/2023

A(H1N1)pdm09
A/Victoria/185/2023
A/Sydney/44/2023
A/Victoria/205/2023
A/South Australia/70/2023
A/Victoria/267/2023
A/South Australia/83/2023
A/South Australia/85/2023
A/Brisbane/13/2023
A/Victoria/380B/2023
A/Victoria/2463/2023
A/Tasmania/326/2023

B/Victoria
B/Victoria/7/2023
B/Darwin/74/2023
B/South Australia/12/2023
B/Fiji/95/2023
B/Brisbane/2/2023
B/Victoria/178/2023
B/Victoria/194/2023
B/Darwin/494/2023

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 2023, 1 candidate vaccine virus that had been received from other WHO Collaborating Centres and laboratories was passaged in eggs at the Centre (Table 16).

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

H5N1
IDCDC-RG78A (A/American wigeon/South Caro-

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 17).

Serum panel analyses in February 2023

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 yeas), older adults (51-64 years), and elderly adults (>65 years) who had received the 2022-2023 Northern Hemisphere seasonal quadrivalent inactivated egg, cell-based, or recombinant influenza vaccine, in the USA. The Centre also analysed serum panels for paediatric (1-10 years), adults (18-64 years) and elderly adults (>65 years) that had received the 20222023 Northern Hemisphere seasonal quadrivalent inactivated egg vaccine in China, and one panel of adults (18- 64 years) that had the Northern Hemisphere seasonal quadrivalent inactivated egg vaccine in the UK.

A(H1N1)pdm09: When compared to post vaccination geometric mean HI titres (GMT) against either egg-propagated A/Victoria/2570/2019 or cell-propagated A/Wisconsin/588/2019-like vaccine antigens, there were significant reductions in most serum panels against most recent A(H1N1)pdm09 viruses of subclades 5a.2a and 5a.2a.1, as well as some viruses of 5a.1.

Serological Analyses (continued)

A(H3N2): Using HI and virus neutralisation (VN) assays, when compared to GMTs against cell culture propagated A/Darwin/6/2021-like viruses post-vaccination GMTs against recent A(H3N2) viruses belonging to clades 2a (2a.1b, 2a.3a.1), 2b and 1a.1 were not significantly reduced in most panels. Reductions of GMTs were observed when compared to egg-propagated A/Darwin/9/2021-like reference viruses

B/Victoria: Post vaccination HI GMTs against recent B/Victoria lineage viruses in the 3a.2 clade were not significantly reduced when compared to either cell or egg-propagated B/Austria/1359417/2021-like viruses. Significant reductions in GMTs were observed in some sera panels for B/Victoria lineage viruses in the 1A.3 clade.
B/Yamagata: No serology studies were performed for B/Yamagata viruses

Serum panel analyses in September 2023

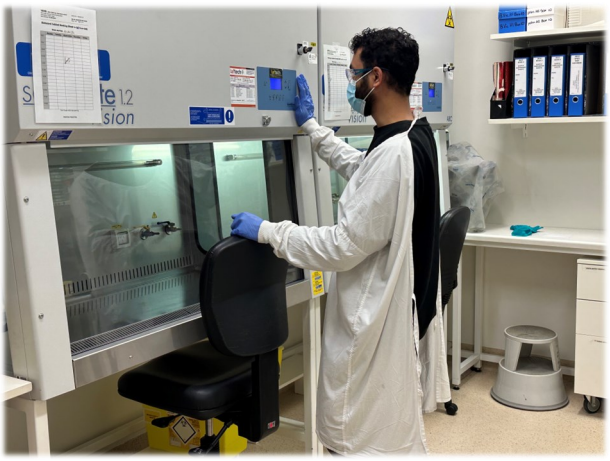
In September, the Centre analysed serum panels from a paediatric cohort (1-10 years), adults (18-64 years) and elderly (>65 years) who had received either the 2023 Southern Hemisphere seasonal quadrivalent inactivated egg or cell-based vaccine in Australia.

A(H1N1)pdm09: Human serology studies using these serum panels showed no significant reductions in post-vaccination HI geometric mean titres (GMTs) for the majority of recently circulating, representative A (H1N1)pdm09 5a.2a viruses when compared to egg- or cell culture-propagated A/Sydney/5/2021-like viruses. There were significant reductions in post vaccination GMTs in some sera panels against recent A (H1N1)pdm viruses belonging to subclade 5a.2a.1

A(H3N2): When compared to GMTs against cell culture-propagated A/Darwin/6/201-like vaccine viruses, there were significant reductions in some sera panels against A(H3N2) viruses in the more recent 2a.1b, 2a.3a.1, and 2b subclades. These reductions were more pronounced when compared to egg-propagated A/Darwin/9/2021 vaccine virus.

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.

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



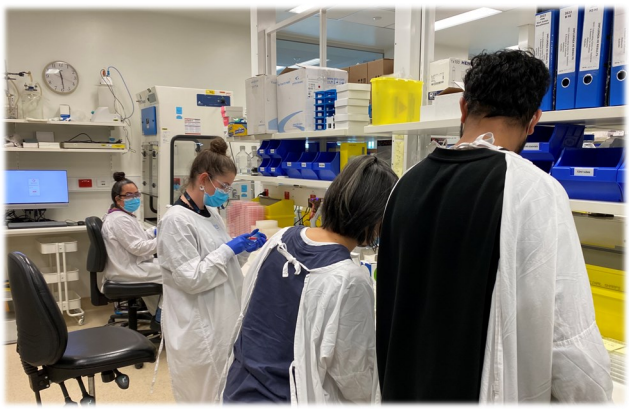


Table 17. Representative and vaccine candidate strains used for serological analyses during 2023.

FEBRUARY	SEPTEMBER
A(H1N1)pdm09	**A(H1N1)pdm09**
A/Brisbane/782/2022 (C)	A/Darwin/23/2023 (C)
A/Delaware/55/2019 (C)	A/Darwin/7/2023 (C,E)
A/Ghana/2711/2022 (C)	A/Sydney/44/2023 (C,E)
A/Sydney/1300/2022 (C)	A/Sydney/5/2021 (C,E)
A/Sydney/5/2021 (C)	A/Tasmania/29/2023 (C)
A/Victoria/2570/2019 (E)	A/Victoria/4897/2022 (C)
A/Victoria/4897/2022 (C)	A/Wisconsin/47/2022 (C)
A(H3N2)	**A(H3N2)**
A/Brisbane/841/2022 (C)	A/Darwin/9/2021 (C)
A/Darwin/11/2021 (C)	A/Canberra/79/2023 (C)
A/Darwin/9/2021 (E)	A/Darwin/11/2021 (C)
A/Thailand/8/2022 (C,E),	A/Darwin/9/2021 (E)
A/Victoria/5290/2022 (C)	A/Newcastle/113/2023 (C)
	A/South Australia/48/2023 (C)
	A/Thailand/8/2022 (C,E)
	A/Victoria/260/2023 (C)
B/Victoria	**B/Victoria**
B/Austria/1359417/2021 (C,E)	B/Austria/1359417/2021 (E)
B/Darwin/16/2022 (C)	B/Darwin/772/2023 (C)
B/Maryland/01/2021 (C)	B/North Carolina/01/2021 (C)
B/Singapore/SAR56364/2022 (C)	B/Perth/43/2023 (C)
	B/Singapore/WUH4618/2021 (C)
	B/Sydney/339/2023 (C)
	B/Victoria/395/2023 (C)

*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 2023 WHO made the recommendations reported below.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2023-2024, Geneva, Switzerland, 24 February 2023

The WHO recommends that trivalent vaccines for use in the 2023-2024 northern hemisphere influenza season contain the following:

Egg-based vaccines

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (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.
-

Cell culture- or recombinant-based vaccines

- an A/Wisconsin/67/2022 (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.

WHO recommends that trivalent vaccines for use in the 2023-2024 influenza season in the northern hemisphere contain the following:

Egg-based vaccines

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Cell culture- or recombinant-based vaccines

- an A/Wisconsin/67/2022 (H1N1)pdm09-like vi;
- an A/Darwin/6/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus

WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2024 Geneva, Switzerland, 29 September 2023

The WHO recommends that **trivalent** vaccines for use in the 2024 southern hemisphere influenza season contain the following:

Egg-based vaccines

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/Thailand/8/2022 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Cell– or recombinant-based vaccines

- an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;
- an A/Massachusetts/18/2022 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

For quadrivalent egg- or cell culture-based or recombinant vaccines for use in 2024 southern hemisphere influenza season, the WHO recommends inclusion of the following B/Yamagata lineage component:

- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

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 2023 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/4897/2022 (Feb, Sep)	
A(H3N2)	A/Thailand/8/2022 (Sep) A/Brisbane/837/2022 (Sep)	A/Sydney/1304/2022 (Feb, Sep)
B/Victoria		B/Singapore/WUH4618/2021(Feb. Sep))
B/Yamagata	B/Phuket/3073/2013 (Feb, Sep)	B/Singapore/INFTT-16-0610/2016 (Feb, Sep) B/Singapore/INFKK-16-0569/2016 (Feb/Sep) B/Brisbane/9/2014 (Feb/Sep)

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 12 October 2023 and recommended that the following viruses be used for influenza vaccines in the 2024 Southern Hemisphere influenza season:

Egg-based quadrivalent vaccines:

• an A/Victoria/4897/2022 (H1N1)pdm09-like virus;

• an A/Thailand/8/2022 (H3N2)-like virus; and

• a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Cell- or recombinant-based quadrivalent influenza vaccines:

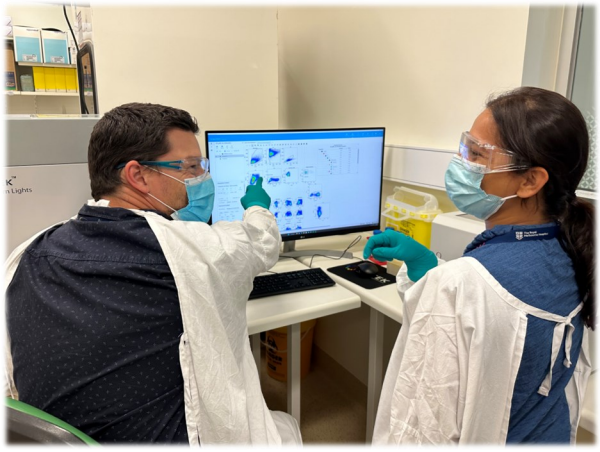
• an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;

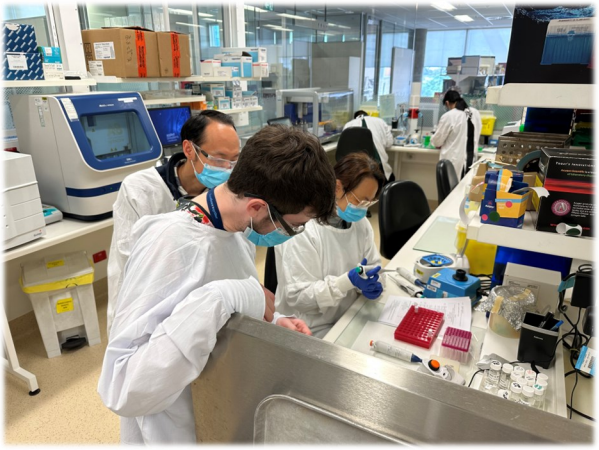
• an A/Massachusetts/18/2022 (H3N2)-like virus; and

• a B/Austria/1359417/2021 (B/Victoria lineage)-like virus;

The recommendation for the B/Yamagata lineage component of quadrivalent influenza vaccines remains unchanged from previous recommendations:

. a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.





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

Yi-Mo Deng has been involved on an ad hoc basis with the establishment and review of online NGS courses for the WHO Headquarters from March 2023.

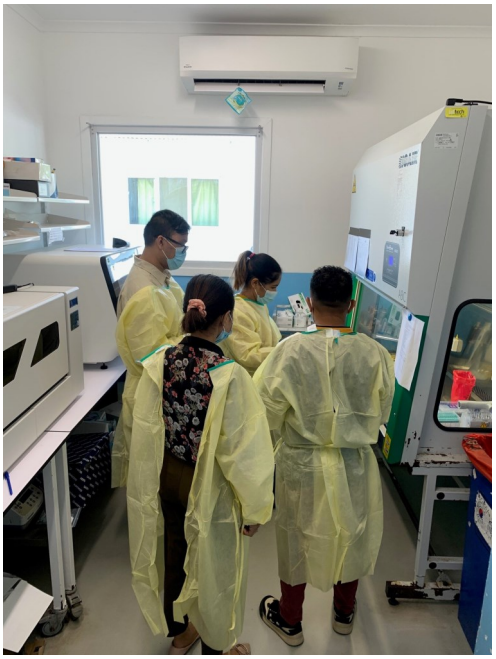
Patrick Reading continued as a Consultant and Advisor to the Australia Indonesia Health Security Partnership. This role involves working with different partner agencies to provide advice and support to diagnostic laboratories within Indonesia.

Patrick Reading participated in assessment of the National Virology Laboratory in Brunei Darassalam (Nov 13-16, 2023) for designation as a National Įn¸ uenza Centre (NĮC) He is involved in continued mentoring of the laboratory to address gaps identi´ed during the assessment.

Patrick Reading continued to work with WHO South Paci´c OWce and the Paci´c Community (SPC) to coordinate implementation and training of Paci´c Įsland laboratories in multiplex RT-PCR for detection of in¸ uenza viruses and SARS-CoV-2 using reagents from the Įnternational Reagent Resource (ĮRR: https://www.internationalreagentresource.org). Reagents delivery and distribution and preparation of validation panels is to be coordinated by the Centre.

Patrick Reading and Navin Karan from the Victorian Įnfectious Diseases Reference Laboratory (VĮDRL) ´nalised Agreement of Performance of Work (APW) with WPRO Division of Technical Support (DPS), Paci´c Health Security and Communicable Diseases Section (PSC) to (i) establish and implement maintenance plan across 6 Paci´c Įsland Countries (PĮCs) to ensure accuracy and maintenance of pipettes for molecular testing, (ii) organise in-country re-certi´cation of Class ĮĮ biosafety cabinets (BSCĮĮ) and maintenance of PCR cabinets, and (iii) provide technical support and in-country training for the implementation of multiplex PCR tests for respiratory pathogens (2024-2027).

Presa Chanthalavanh and **Patrick Reading** conducted a one week assessment and training at Vila Central Hospital, Port Vila, Vanuatu between November 27 December 1, 2023. Training was conducted for Flu-SC2 multiplex PCR (FluA/ B/SARS-CoV-2/human RNase P), as well as subtyping (A/H3, A/H1pdm) and lineage (B/ Yam, B/Vic) sin- gleplex assays for influenza viruses. Additional training in the use of a dengue/chikungunya/ zika multiplex PCR from DNAture (supplied by SPC) was also conducted. The serological and molecular test- ing capacities of hos pital laboratory were also assessed to inform future support by WHO CC, VIDRL, DFAT and other partners.

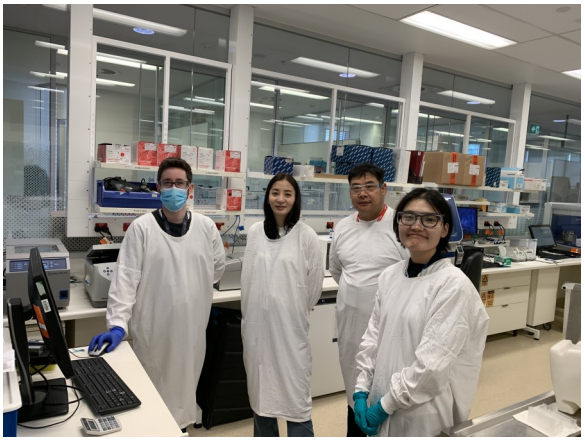


Presa Chanthalavanh and **Patrick Reading** conducted a one week training at the National Health Laborato- ry, Dili Timor Leste between May 17-22, 2023. Training was provided in multiplex PCR, as well as in biosafety procedures and establishment of appropriate standard operating procedures (SOPs) for the molecular labora- tory. This training and mentoring aimed to strengthen laboratory capacity as the National Health Laboratory worked to- ward designation as a WHO National Influenza Centre.

Centre-based Training

Steven Edwards, Olivia Lay, Patrick Reading, and **Natalie Spirason** were involved in training scientists from the National Referral Hospital Molecular Laboratory, Honiara, Solomon Islands, and Villa Central Hospital Molecular Laboratory, Port Villa, Vanuatu, between 27 February - 3 March 2023. The workshop involved training in RT-PCR techniques for the detection of influenza viruses from clinical samples.

Presa Chanthalavanh, Clyde Dapat, Joelle Dharmakumara, Steven Edwards, Olivia Lay, Pina Iannello, Patrick Reading, Cleve Rynehart, Natalie Spirason, Paul Whitney, and **Tasoula Zakis** were involved in delivering a training workshop for scientists from Laboratorio Nacional da Saúde Timor-Leste between 5-16 June 2023. This workshop covered techniques in the cultivation of influenza virus in eggs, as well as RT-PCR and Nanopore techniques and bioinformatics (NGS data analysis, phylogenetic analysis, GISAID and NextStrain databases).



Clyde Depat, Steven Edwards, Xiaomin Dong, , Patrick Reading, Presa Chanthalavanh and **Natalie Spirason** were involved in training scientists from the National Influenza Centre in Ultaantbaatar, Mongolia, between 17 – 27 October 2023. The workshop focussed on the use of Illumina and Nanopore technologies for whole genome sequence of influenza and RSV in clinical samples. Training in bioinformatics was also provided.

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

Saira Hussain (started April 2023), Harry Stannard, Nikita Deshpande, Sook Kwan Leah Brown (until February 2023), Paulina Koszalka (until January 2023), Patrick Reading, Ian Barr, Kanta Subbarao

Research overview

Our research mainly focuses on the evaluation of the effectiveness of approved and investigational influenza antivirals as well as the risk of the emergence of drug resistant viruses which may spread widely amongst the community. We also study the viral fitness of different drug resistant variants. This information provides insights into the likelihood that such viruses could spread amongst the community.

Collaborators

Smitha Georgy (Faculty of Veterinary and Agricultural Sciences, University of Melbourne); Lorena Brown, Jessica Neil, Brad Gilbertson, Matthew Gartner, Charlie-McKenzie Kludas, Rubaiyea Farrukee and Sarah Londrigan (University of Melbourne); Regis Grailhe (Translation Research Division, Institute Pasteur Korea); Andrew Mehle (University of Wisconsin); Seema Lakdawala (Emory University School of Medicine), Paul Digard (The Roslin Institute, University of Edinburgh), Elena Govorkova (St Jude's Childrens Research Hospital, US), Aus Bio Ltd. (Australia), F. Hoffmann-La Roche Ltd, SK Bioscience (Republic of Korea).

Highlights and developments 2023

Development of investigational antivirals

Paulina Koszalka concluded work here at the Centre in January 2023, but continues to work with the group on an upcoming paper on the antiviral efficacy of molnupiravir in the ferret model. This work extends the pre-clinical assessment of molnupiravir as an influenza treatment option, assessing the efficacy of molnupiravir alone or in combination with oseltamivir at reducing viral shedding, viral load in the lungs and aerosol transmission.

Under the supervision of Mariana Baz (the previous head of the antivirals group, Harry Stannard conducted in vitro antiviral efficacy studies and pre-clinical assessment in ferrets of a novel naturally sourced polyphenol compound in green tea (EGCG). This work has now been published.

The antivirals group, along with collaborators from Aus Bio Ltd. and The University of Melbourne, were successful in obtaining funding through the Pandemic Antiviral Discovery initiative (PAD) from the Novo Nordisk foundation (NNF) to complete the preclinical development of the lead candidate as a long- acting pan-influenza antiviral drug for both prevention and treatment of influenza, with a focus on countering influenza strains with pandemic potential. The project is led by Kanta Subbarao and co-investigators from the Centre are Ian Barr and Saira Hussain. The antiviral group will be working to determine antiviral efficacy in vitro and in vivo (ferrets) of the Aus Bio compounds compared with licensed influenza antivirals as well as performing drug resistance studies. The group would also contribute to pharmacokinetics (PK) and pharmacodynamics (PD) studies performed by Aus Bio Ltd. The group will on-board new staff in 2024 to work on this project.

Harry Stannard began his PhD in July 2023, with his thesis titled, 'Further development of the ferret model of influenza A virus infection and its utility to explore novel therapeutic treatments.' Under the supervision of Patrick Reading, Saira Hussain and Ian Barr, Harry will explore multiple avenues for the improvement of the ferret model for influenza antiviral efficacy studies, with a particular focus on exploring lower respiratory tract viral load and disease kinetics in A(H1N1)pdm09, as well as in A (H3N2) and B/Victoria lineage viruses.

Antivirals and Viral Fitness (continued)

Antiviral resistance and virus fitness studies

An on-going study to assess the effects of substitutions in the viral polymerase on the antiviral susceptibility of baloxavir marboxil in collaboration with F. Hoffmann-La Roche Ltd has progressed in 2023. Saira Hussain and Harry Stannard continued work that Paulina Koszalka and Sook Kwan Brown had previously commenced to create reverse genetics viruses based on contemporary seasonal influenza strains bearing mutations in PA protein which show reduced susceptibility to baloxavir. The group were successful in creating 2x seasonal H1pdm09 and 2x H3N2 and 1 x B/Yamagata-lineage reverse genetics (RG) viruses bearing several PA resistance markers. In 2024, we will continue this with work with B/Victoria-lineage viruses, using an RG virus from 2008 which grows well in our laboratory and creating an RG virus backbone for a recent B/Victoria-strain. In order to assess susceptibility to baloxavir, Saira has set up a luciferase reporter-based polymerase assay in the WHOFLU laboratory. In 2024, work is planned to set up a baloxavir phenotypic virus neutralisation assay using the CDC, USA method, called IRINA (Influenza Replication Inhibition Neuraminidase-based Assay). For genotyping baloxavir resistance, the group uses next generating sequencing and has been working on adapting a previously established pyrosequencing protocol for the PyroMark 96 machine (QIAGEN) to the newly purchased PyroMark 48 machine. This is expected to be completed in 2024. The group will continue to work with Roche for assessing baloxavir resistance in 2024.

During 2023, Harry Stannard has continued to work on a study with seasonal influenza A(H1N1)pdm09 viruses, to identify more contemporary influenza virus strains that demonstrate robust influenza disease, transmission, and lower respiratory tract involvement in the ferret and can be used for future antiviral studies. Harry Stannard presented this work as a poster at the 9th European Scientific Working Group on Influenza (ESWI) conference in September 2023.

Assays/Tools development for future antiviral and virus fitness studies

Saira Hussain was successful as co-investigator on a grant obtained from the Cumming Global Centre Foundation Grants for the development of a comprehensive suite of human and animal in vitro respiratory tract models for evaluating viruses with pandemic potential. The project is in collaboration with Jessica Neil, Kanta Subbarao and other investigators at the University of Melbourne, Monash University and the University of Adelaide. Specifically, Saira Hussain and the antivirals group will work on developing ferret precision cut lung slices (PCLS) as a surrogate model for influenza infection and antiviral efficacy studies.

In 2024, Harry Stannard will work on setting up live imaging of influenza infection in ferrets. The project is a collaboration between the Centre and Regis Grailhe (Institute Pasteur Korea), and aims to develop a world-leading live-imaging device for ferrets, enabling quantification and location of fluorescent or bioluminescent tagged influenza viruses during the infection, and is funded by SK Bioscience. The aim of this project is to provide improved empirical readouts of influenza viral kinetics in the animal, while reducing the number of animals required in each study. Additionally, collaborations with Andrew Mehle (University of Wisconsin) and Seema Lakdawala (Emory University School of Medicine) have enabled the sharing of labelled influenza viruses for use in our live-imaging system, specifically NanoLuciferase (bioluminescence) and mRuby (fluorescent) tagged influenza viruses, respectively.

Publications

Stannard, H.; Koszalka, P.; Deshpande, N.; Desjardins, Y.; Baz, M. Pre-Clinical Evaluation of the Antiviral Activity of Epigalocatechin-3-Gallate, a Component of Green Tea, against Influenza A(H1N1)pdm Viruses. Viruses 2023, 15, 2447. https://doi.org/10.3390/v15122447

Diefenbach-Elstob TR, Lay O, Zakis T, Deshpande N, Soppe S, Peck H, Hussain S, Deng Y, Dapat C, Subbarao K, Barr IG. Report on influenza viruses received and tested by the Melbourne WHO Collaborating Centre for Reference and Research on Influenza during 2023. Submitted.

Grants

“Development of a Novel Long Acting Pan-Influenza Antiviral Drug” funded by the Pandemic Antiviral Discovery (PAD) initiative and the Novo Nordisk Foundation. Award ($AUD) 3,034,704 (2 years). Investigators from WHOFLU centre: Kanta Subbarao (Lead), Ian Barr, Saira Hussain

“Development of human and animal in vitro respiratory tract models for risk assessment of viruses with pandemic potential” Cumming Global Centre Foundation Grants. Award ($AUD) 587,011 (3 years).Investigators from WHOFLU centre: Kanta Subbarao, Saira Hussain

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.

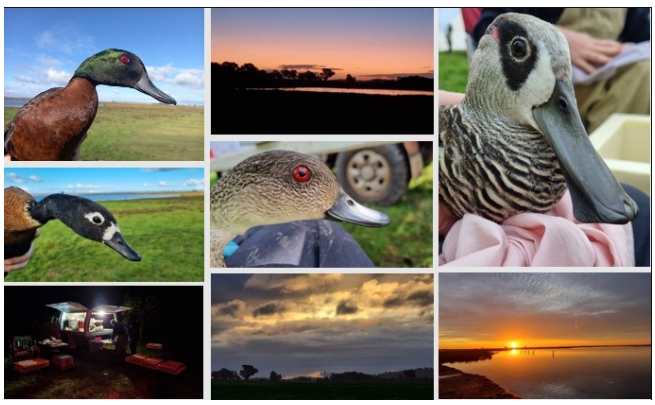
Collaborators

Marcel Klaassen (Deakin University, Victoria); 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 2023

In 2023, we collected and screened 1508 paired swab and serum samples from wild Anseriformes (ducks) and Charadriiformes (shorebirds and terns) in Victoria, New South Wales, Tasmania and Western Australia, with 20 influenza A virus detections. Through sequencing, the viruses were shown to comprise, H2, H4, H5 (low pathogenic), H6, H8 and H11, the vast majority of which 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 (2024). Our enhanced surveillance program was funded by Department of Agriculture, Fisheries and Forestry One Health Investigation Fund, administered by Wildlife Health Australia.



Birds tested (left) play an important role in the maintenance of AIV in Australia. Anseriform (right) were sampled as part of heightened surveillance . 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. Utilizing 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 2023

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 2023, we have extended this work into new areas, aiming to use mRNA-mediated delivery of particular putative restriction factors as a novel antiviral treatment.

We have also 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 2023 research contributed to five peer-reviewed publications, in EBiomedicine, Science Advances, Pathogens (x2) and Immunology and Cell Biology. 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 aspects of innate immunity to infection.

Epidemiology

Centre staff

Sheena Sullivan (Until December 2023) , Tanya Diefenbach-Elstob, Arseniy Khvorov (University of Melbourne, UoM), Leslie Dowson (UoM), Hasanthi Abeykoon (UoM), Christy Vu (UoM), Hadrien Moffroid (UoM), Catherine Pendrey (MAE student; ANU) , Jessie Goldsmith (PhD student, UoM).

Research overview

Our work primarily focuses on 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 provide ongoing estimates to government and WHO. During the pandemic, this work extended to COVID-19 vaccine effectiveness. Studies on COVID-19 have included estimating vaccine effectiveness using administrative health data held by departments of health, and examining outcomes following infection and vaccination among pregnant women. We also conduct various simulation studies and meta-analysis/meta-regression to understand the validity of study designs used to estimate vaccine effectiveness.

The team also collaborate on studies exploring the immunological responses to vaccination that explain waning vaccine effectiveness, lower vaccine effectiveness in people who are repeatedly vaccinated and responses to vaccination in immunocompromised patients. To that end we work closely with the immunology research team on several sero-epidemiology studies, and with the Peter MacCallum Cancer Institute examining vaccination schedules for people with haematological malignancies.

The team continues to work closely with the WHO and other partners on influenza burden of disease studies, providing technical support to member states in the SEAR and WPR. As part of her PhD, Jessie Goldsmith is examining the validity of thresholds used to determine excess influenza-associated mortality.

Leslie Dowson has been involved in studies to understand 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 2023

We continued to work with the Australian Sentinel Practices Research Network (ASPREN) and the Influenza Complications Alert Network (FluCAN), to evaluate the effectiveness of Australian quadrivalent inactivated seasonal influenza vaccines in 2023. HI assay and sequencing data generated by the Centre were used to inform vaccine effectiveness (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, 72% of 2023 FluCAN samples were received, reflecting ongoing enhanced efforts to ensure these samples are included in the Centre's virological surveillance, and to improve the quality of VE 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 2024.

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. Christy Vu together with Hadrien Moffroid and Jessie Goldsmith have been leading a systematic review and meta -analysis to understand the underlying sources of heterogeneity in vaccine effectiveness studies .

Dr Sullivan continues 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.

Dr Sheena Sullivan and Annette Fox (Immunology unit) and Adam Kucharski (London School of Hygiene and Tropical Medicine) continued to lead 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. This work was presented at several national and international meetings in 2023.

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.

1. Regan AK. et. al. 2022. Paediatric and Perinatal Epidemiology.

2. Regan AK. et. al. 2021. J Infect Dis.

3. Jones-Gray et al. 2023. Lancet Resp Med.

4. Muleme M, McNamara BJ, Ampt FH, Baptista M, Dittmer J, Osborne A, Ahmed H, Hales G, Kabwe M, Main S, Moreira C, Silverstein S, Sotheran E, Athan E, Johnston PD, O'Brien DP, Sullivan SG. Severity of COVID-19 among Residents in Aged Care Facilities in Victoria, Australia: A Retrospective Cohort Study Comparing the Delta and Omicron Epidemic Periods. J Am Med Dir Assoc. 2023. doi: 10.1016/j.jamda.2023.01.006. PMCID: PMC9852301. Published online: 2023/02/23.

5. Sullivan SG, Sadewo GRP, Brotherton JM, Kaufman C, Goldsmith JJ, Whiting S, Wu L, Canevari JT, Lusher D. The spread of coronavirus disease 2019 (COVID-19) via staff work and household networks in residential aged-care services in Victoria, Australia, May-October 2020. Infect Control Hosp Epidemiol. 2022:1-8. doi: 10.1017/ice.2022.243. Published online: 2022/10/21.

Immunity to Respiratory Viruses

Centre staff and student

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

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

Adam Kucharski (London School of Hygiene and Tropical Medicine),Barnaby Young (National Centre for Infectious Diseases (NCID) and Tan Tock Seng Hospital, Singapore) ,Andrew Ward (Scripss, San Diego, USA), 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 2023

Influenza vaccine immunogenicity in health care workers

During 2023 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). The primary aims of the study are to determine the effect of repeated influenza vaccination on vaccine immunogenicity and to investigate immunological mechanisms underlying effects. A secondary objective was to investigate effects of repeated vaccination on vaccine effectiveness. Participants were recruited from 6 hospitals across Australia. They were asked to self-report their history of vaccination during five years prior to enrolment and to provide blood before and after vaccination and at the end of the influenza season. 1134 participants were enrolled in 2023 of whom 1071 provided pre- and post-vaccination sera giving a total of 3808 pairs of pre and post vaccination sera collected over the 4 years of the study (Figure 1A).

Immunity to Respiratory Viruses (continued)

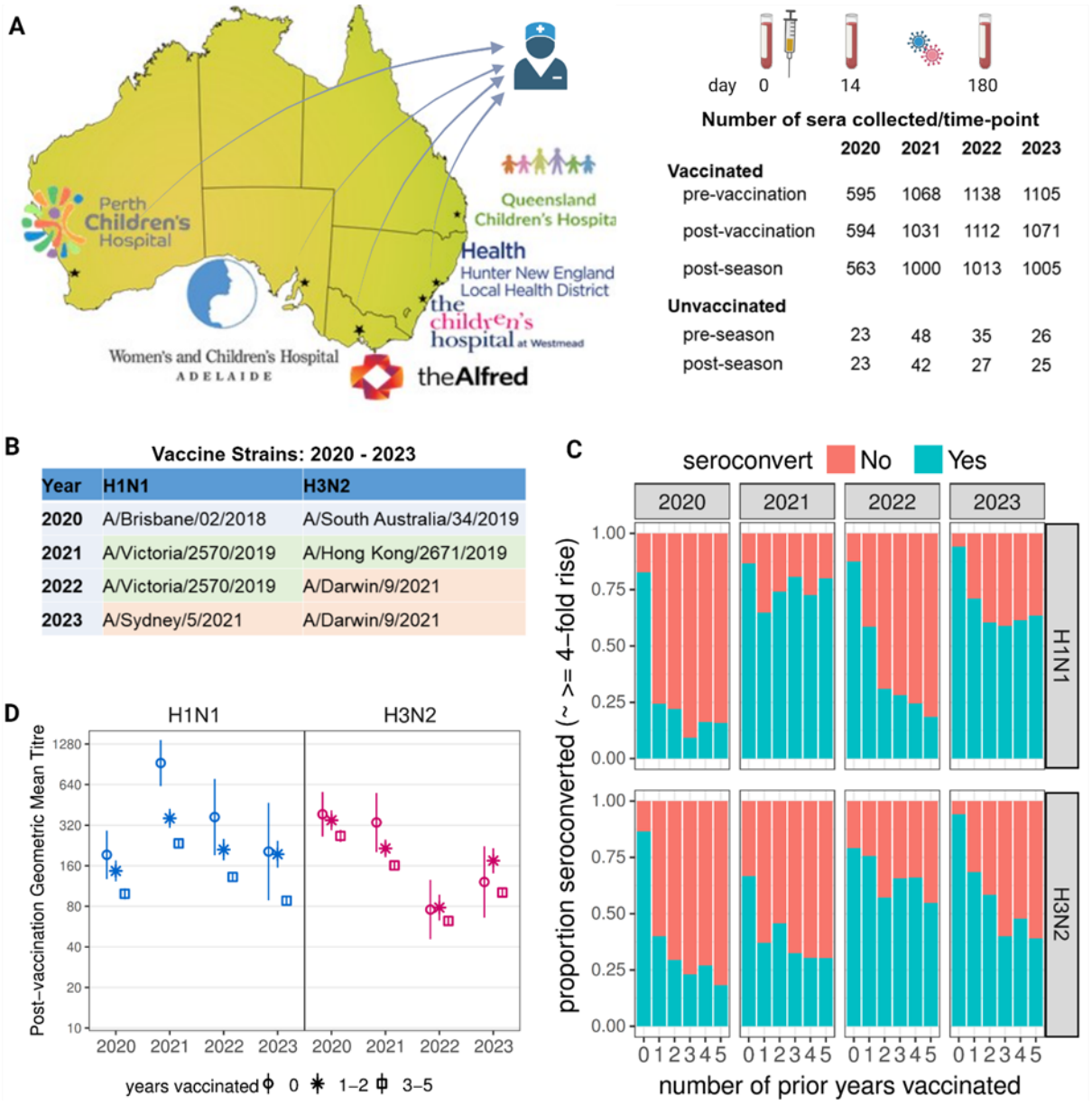


Figure 1. Health Care Worker Influenza Vaccination Study Overview. (A) Study Design and numbers of participants and sera collected. (B) Influenza A strains included in vaccines each year and used for serology. (C) Proportions seroconverting against vaccine strains by year, subtype and number of prior years vaccinated. Proportions seroconverting decreased with increasing prior vaccination with weaker trends in years when there was substantial antigenic change to vaccine strains. (D) Post-vaccination geometric means titres against influenza A strains in each years vaccine by prior vaccination category. Created with Bioender.

Sera were titrated by hemagglutination inhibition (HI) assays against viruses representing egg and cell-grown equivalents of the A(H1N1), A(H3N2), and B/Victoria strains in vaccines administered each year (Figure 1B). A (H1N1) vaccine strains changed in 2021 and 2023 and A(H3N2) strains changed in 2021 and 2022. Proportions of participants who seroconverted against vaccine strains decreased with increasing prior vaccination (Figure 1C). This trend was stronger in years when there was little or no antigenic change from previous vaccine strains. The impact of prior vaccination on seroconversion reflected lower post-vaccination titres among participants vaccinated 3-5 prior years, particularly compared to participants vaccinated 0 of 5 prior years (Figure 1D). Antibody titre fold-rise was also declined with increasing prior years vaccinated (data not shown).

Immunity to Respiratory Viruses (continued)

To explore effects of repeated vaccination on vaccine effectiveness participants were asked to report respiratory illness and provide self-collected respiratory swabs for diagnostic testing. Confirmed influenza illnesses were not detected among participants during 2020 and 2021 when there was negligible virus transmission in Australia due to COVID-19 control measures. We detected 37 confirmed influenza A illnesses in 2022 and 35 in 2023. Six participants developed illness with confirmed influenza B infection, all in 2023. Analysis of data for 2022 and 2023 combined indicates that confirmed influenza illness occurred more often among unvaccinated participants (10.4%) compared to vaccinated participants (3.1%, Chi-square p value with Yates correction = 0.003). Among vaccinated participants illness occurred most often among those vaccinated 3-5 years previously consistent with lower post-vaccination titres in this group. Numbers of participants receiving vaccine for the first time in 2022 or 2023 were too small to determine significance. Moreover, even if vaccine influenza illness was more common among repeated compared to first-time vaccinees, it was less common (3.3%) than among unvaccinated participants (10.4%, p = 0.005), indicating that vaccination protected a substantial proportion of repeatedly vaccinated participants. Analysis is ongoing to understand how antibody titres induced following vaccination contribute to differences in protection between vaccination groups.

Table 1. Detection of confirmed influenza illness during 2022 and 2023 by current and prior influenza vaccination status

	N infected/N (%) Number of prior years vaccinated			
	All	**0**	**1-2**	**3-5**
vaccinated	71/2311 (3.1%)	0/42 (0 %)	4/228 (1.8%)	67/2041 (3.3%)
unvaccinated	7/67 (10.4%)	4/32 (12.5 %)	3/20 (15%)	0/19 (0%)

Taken together results of this influenza vaccination study in hospital workers indicate that vaccine immunogenicity against influenza A components decreases with increasing years of prior vaccination and may reduce but not eliminate protection afforded by vaccination. Our second aim was to investigate mechanisms underlying these effects of repeated vaccination. We first examined whether pre-existing antibodies may mask epitopes so that B cells are not activated. Analysis of antibodies against H1N1 vaccine strains shows that fold-rises decrease with increasing pre-vaccination titre (Figure 2). However, at pre-vaccination titres of 5 to at least 80 titre rise remains lower among previously vaccinated compared to first time vaccinated. Similar trends were observed for H3N2 (data not shown). These results suggest that pre-existing contribute to the attenuating effects of prior vaccination. We also noted that titre fold-rise against H1N1 was greater in 2021 than in 2020 or 2022 (Figure 2) coinciding with substantial antigenic change between the 2021 vaccine strain and prior H1N1 vaccine strains.

Immunity to Respiratory Viruses (continued)

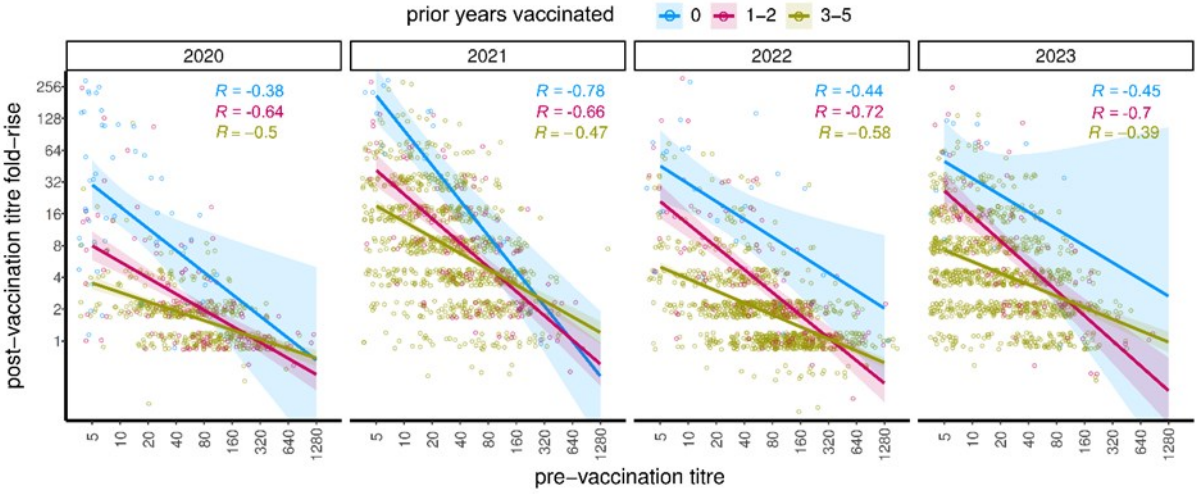


Figure 2. Increasing pre-vaccination antibody titres are associated with decreasing fold-rise in antibodies after vaccination but don't fully account for effects of prior vaccination.

The antibody focusing hypothesis suggests that memory B cells out-compete naïve B cell for resources required to divide and differentiate so that with each new strain encountered antibodies become increasingly focused on epitopes that remain conserved. This may mean that antibodies become focused on non-neutralizing epitopes because mutations arise in neutralizing epitopes due to selection pressure. To determine whether repeated vaccination may drive antibody responses towards non-neutralizing epitopes we measured total Hemagglutinin (HA)-binding antibody titres by ELISA. This showed that H3N2 HA-binding antibody responses were also poor among repeatedly compared to first-time vaccinated participants (Figure 3) indicating that repeated vaccination reduces rather than redirects HA antibody responses. Similarly, vaccination induced little if any rise in HA-reactive B cell frequencies among repeatedly vaccinated participants but induced robust rises among first time vaccinated participants (Figure 4). These results suggest that HA-reactive B cells, including memory B cells, are poorly elicited by vaccination in repeatedly vaccinated participants.

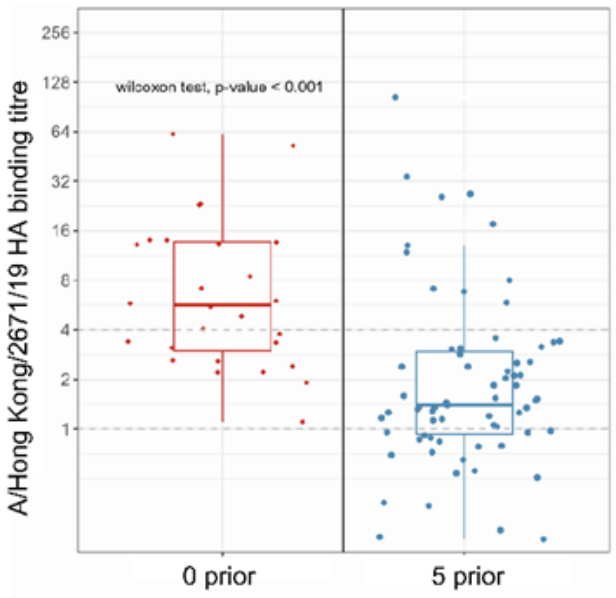


Figure 3. Hemagglutinin (HA) binding antibody titre rise after vaccination among health care workers by number of prior years vaccinated.

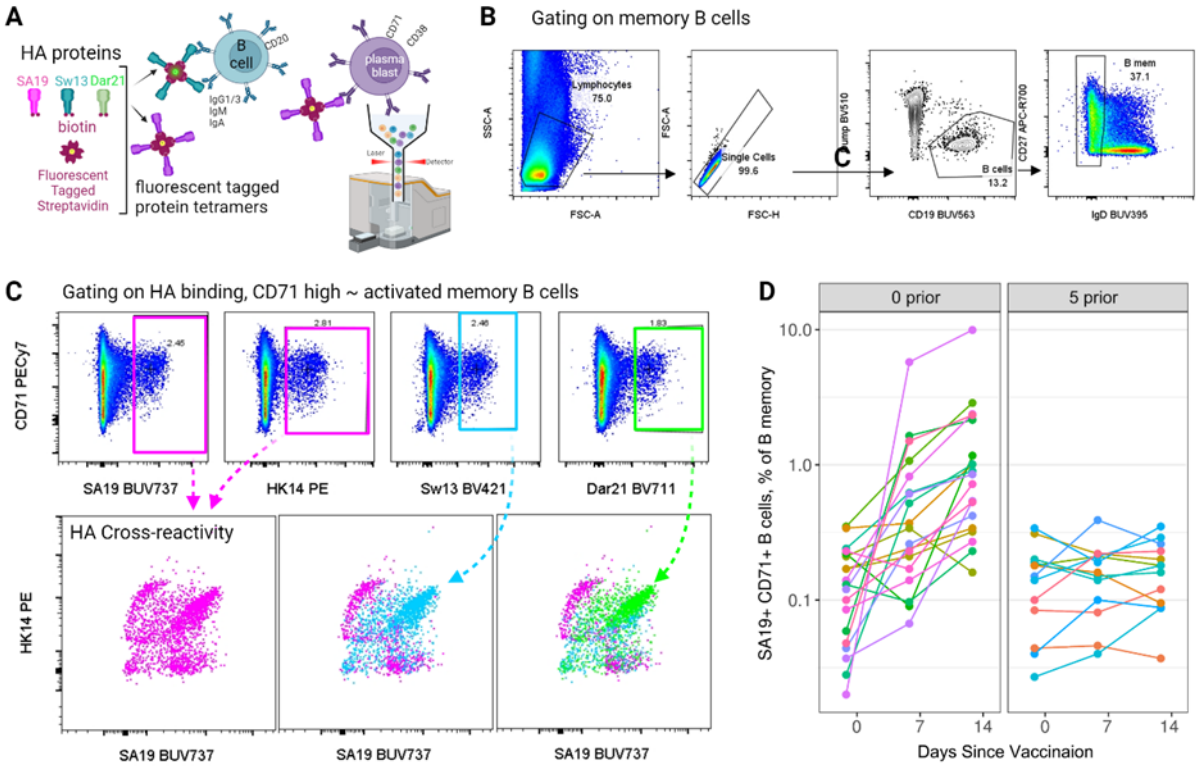


Figure 4. Hemagglutinin (HA) reactive B cell frequencies induced by vaccination among health care workers who have been vaccinated 0/5 versus 5/5 years previously.

Schematic of the method used to detect B cells that bind HA's representing a range of A(H3N2) vaccine strains. (B) Gating used to identify memory B cells. (C) Representative plots of memory B cells in one sample showing binding to HA's representing four different A(H3N2) strains (x -axis) and expression of CD71 activation marker (y-axis). HA cross-reactivity of HA binding B cells is shown in the bottom panels. (D) Summary of HA binding B cell frequencies detected over the course of vaccination in 2020, comparing participant vaccinated 0/5 versus 5/5 prior years. Created using Biorender.

Although B cell and antibody responses were generally poor among repeatedly compared to first time vaccinated, vaccination in 2021 led to improved B cell and antibody responses to A(H1N1) in this group. We are currently performing single cell analysis of gene expression and B cell receptor gene use to explore whether vaccination in 2021 induced a greater de novo response and clones that were not induced in 2020. Initial experiments demonstrate that we are able to associate individual B cells gene expression and B cell receptor gene use with their HA binding profile using oligo-tagged HA's (Figure 5).

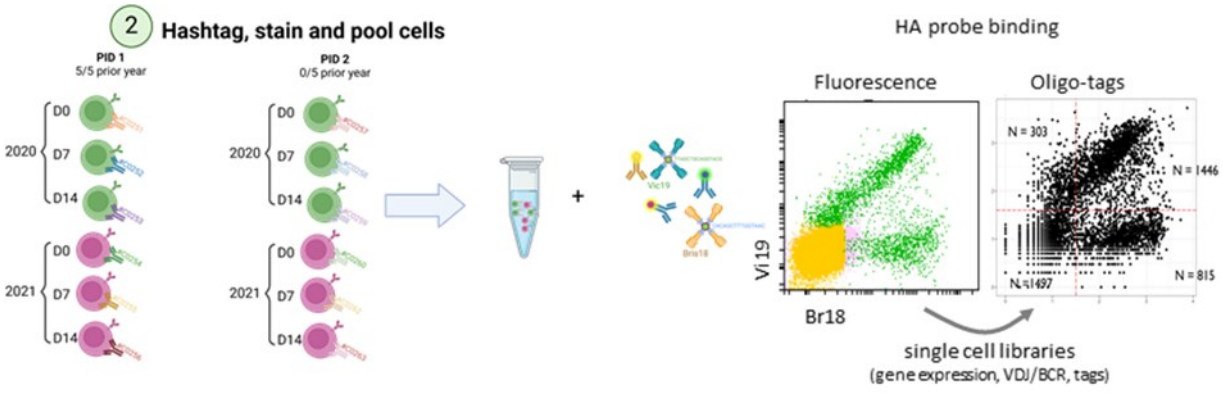


Figure 5. Single cell analysis of HA reactive B cell gene expression and B Cell Receptor (BCR) gene use. Schematic of study design and validation that HA specificity can be defined using oligo-tagged HA tetramers.

Immunity to Respiratory Viruses (continued)

Health Care Worker Study – Supplemental Studies of COVID-19 vaccination and infection.

As previously reported results of a study comparing immune responses to COVID-19 mRNA versus vector vaccines in health care workers. The study showed that surrogate virus neutralizing test antibody titres were substantially high among participants who received mRNA compared to vector vaccinee due to greater B cell expansion and targeting of the RBD. In 2023 we performed single cell sequencing and used mathematical models to follow-up these findings. Fluorochrome and oligo-tagged spike and RBD reactive B cells were sorted from PBMCs collected 7 and 14 days after vaccination from 5 participants each who received mRNA and vector vaccines. Single-cell gene expression, BCR-VDJ gene and surface protein libraries were generated, sequenced and de-multiplexed. BCR were assigned to clones then clones sizes and average somatic hypermutation rate were compared. The results suggest that the mRNA vaccine induced a broader repertoire of B cells to undergo greater clonal expansion than the vector vaccine. This could reflect differences in innate immune signals induced since the mRNA vaccine induced greater interferon-alpha gene expression differed. B cells from vector vaccine recipients have undergone more somatic hypermutation compared to B cells from mRNA vaccine recipients consistent with a longer average interval between doses of vector (90 days) compared to mRNA vaccine (21 days) allowing more time for affinity maturation.

Study of early life imprinting of influenza immunity

During 2023 we extended serology for an early life influenza imprinting study to include neuraminidase (NA) inhibiting (NAI) antibody titres. NAI antibody titres were measured against H6NX viruses containing N1 of A/Michigan/45/2015 or A/Victoria/2570/2019 and N2 of A/Louisiana/32/2017 or A/South Australia/34/2019. We found that vaccination induced NI antibodies in all influenza primed children, and that NI antibody responses against A (H3N2) but not A(H1N1) were greater among children primed by infection compared to vaccination (Figure 6). Plasma has also been sent to Andrew Wards lab at Scripps to map were antibodies bind to HA and NA via electron microscopy. Preliminary results confirm the presence of NA binding antibodies and indicate that vaccination induces antibodies that bind a diverse array of epitopes on the HA.

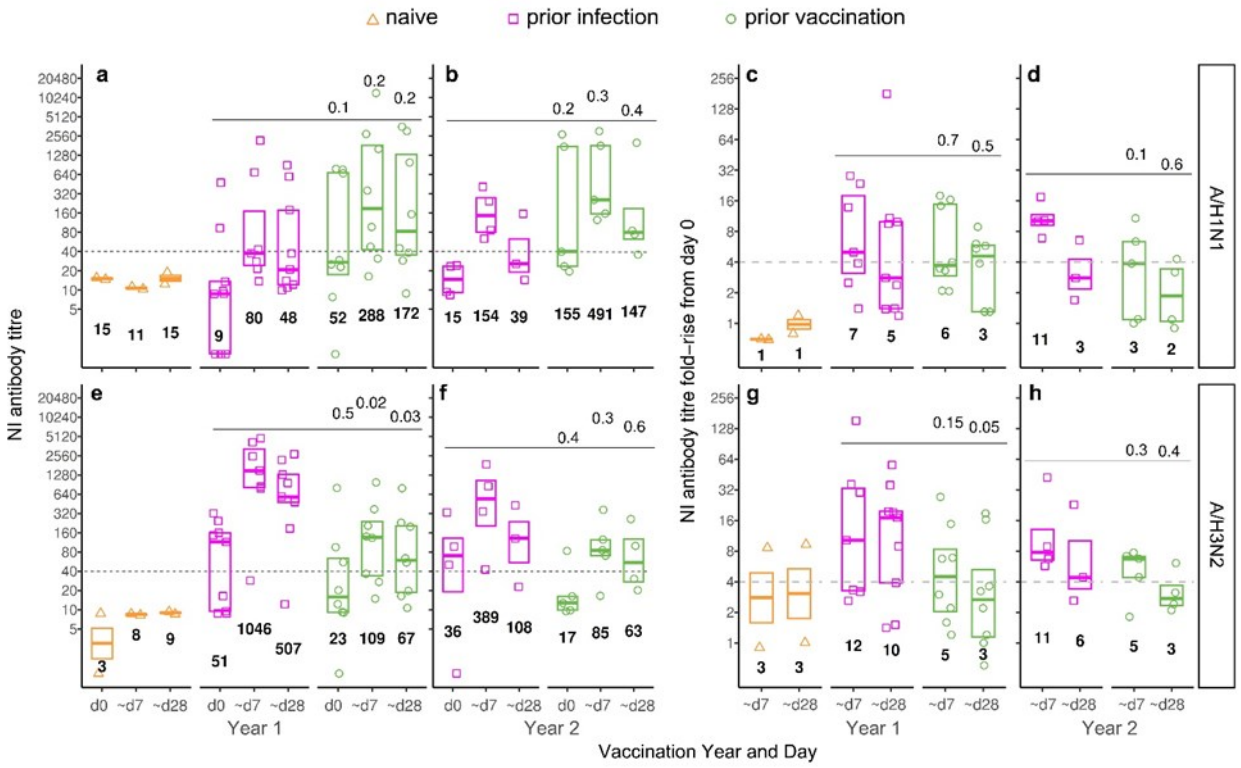


Figure 6. Influenza vaccination induces robust Neuraminidase Inhibiting (NI) antibody responses in children aged 12-54 months who have previously been infected or vaccinated with prior infection significantly augmenting NI antibody production against A(H3N2). (a-d) NI antibody titres and titre fold-rises to A(H1N1) vaccine strains in year 1 (all children) and year 2 (a subset of children continued). (e-g) NI antibody titres and titre fold-rises to A(H3N2) vaccine strains in year 1 and year 2. Results are shown for two children with no prior exposure, nine with prior influenza infection and eight with prior influenza vaccination (colours as per legend). Symbols show data for each child tested and boxplots summarize medians and interquartile ranges. P values are shown for wilcox tests comparing equivalent time-points for children with prior infection and vaccination. Numbers in bold below each boxplot are geometric means for each group.

Immunity to Respiratory Viruses (continued)

Clinical Trial Comparing the Immunogenicity of Three Influenza Vaccine Formulations in Healthy Adults With Infrequent Versus Frequent Prior Vaccination

In collaboration with Barnaby Young from Singapore we initiated a clinical trial to compare3 influenza vaccine formulations with different manufacturing processes:: 1) egg-grown; 2) cell-grown; and 3) recombinant protein. Healthy adults were recruited in Singapore and stratified into two groups by their influenza vaccination history:) frequently vaccinated (3 or more vaccinations) and B) infrequently vaccinated (0 or 1 prior vaccinations). Following stratification participants were randomized to one of the three vaccines. A total of 362 participants were enrolled between September and December 2022, 120+/vaccine of whom 60 each per vaccine were infrequently and frequently vaccinated. Bleeds were performed pre-vaccination and ~ 14, 180 and 365 days after vaccination. Follow-up was completed by December 2023. A total pr 1400 sera were collected and sent to our lab. Sera are currently being assessed by HI assay to determine the magnitude and breadth of antibody responses induced by each vaccine. Five participants had a lab confirmed influenza illness during the season following vaccination. Viruses have been shipped to our lab and sequences have been determined.

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) (2012-2023)

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 2023:

An egg isolate of A(H1N1)pdm09 was derived at the Centre (A/Victoria/4897/2022) was recommended in September 2023 for inclusion the Southern Hemisphere (SH) influenza vaccine in 2024 and was used as the A(H1N1)pdm09 egg-derived vaccine component.

An egg isolate of A(H3N2) was derived at the Centre (A/Thailand/8/2022 (H3N2)) was recommended in September 2023 for inclusion the Southern Hemisphere (SH) influenza vaccine in 2024 and was used as the A(H3N2) egg-derived vaccine component for the SH influenza vaccine in 2024.

For the full recommendation for the SH 2024 vaccine, click here.

For the full recommendation for the NH 2023-2024 vaccine, click here.

Collaborative Research and Development Agreement with Seqirus Ltd (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 2023:

A qualified cell isolate of A(H3N2) that was derived at the Centre (A/Sydney/1304/2022) was an approved A(H3N2) cell-derived vaccine component that was made available for the SH influenza vaccine in 2024.

Research Funding and Awards

Centre staff members are Chief, Co-, or Associate Investigators in grants administered across 2023 (includes those awarded outside of 2023):

Annette Fox, Sheena Sullivan and Adam Kucharski (London School of Hygiene and Tropical Medicine) are Principal Investigators and Project Directors on a US National Institute of Allergy and Infectious Diseases (NIAID), **National Institute of Health (NIH) grant project** "Does repeated influenza vaccination constrain influenza immune responses and protection?" The grant, totaling USD $4.2 million is awarded for the period 3 July 2019 – 30 June 2024. The grant is administered by the University of Melbourne and the work is 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.

Sheena Sullivan is Co-Investigator for the USD $1,277,429 **NIH project grant (R01)** titled, 'Uptake, Safety and Effectiveness of COVID-19 Vaccines during Pregnancy' shared with Annette Regan at the University of San Francisco, for the period 8 April 2022 - 31 March 2025.The grant is administered through the University of Melbourne and work is undertaken at the Centre.

Kanta Subbarao is Chief Investigator for the $1,800,000 **NHMRC Investigator Grant** titled, 'Translating virus biology and host immunity for influenza control' for the period 2020-2025. The grant is administered by the University of Melbourne.

Annette Fox is the is the project lead for the US $549,030 **NIH/NIAID via the NIAID Centers of Excellence for Influenza Research and Response (CEIRR)** titled 'Dissecting influenza antibody evolution through successive exposures in early life' for the period 2023-2025. The grant is administered by The Royal Melbourne Hospital and Scripps.

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.

Kanta Subbarao is Co-Investigator for the $2,911,774.24 **NHMRC Medical Research Future Fund (MRFF)** project titled, 'Bringing Optimised COVID-19 vaccine Schedules To ImmunoCompromised populations (BOOST-IC)', for the period 2022-2024. The grant is administered by the University of Melbourne.

Kanta Subbarao is Lead Investigator and **Sheena Sullivan** is Co-Investigator for the $998,339 **NHMRC MRFF** project titled, 'Aerosol Infection Research: Better mOdels to Reduce iNdoor Exposure (AIRBORNE)' within the MRFF 2021 program 'COVID-19 Treatment Access and Public Health Activities', for the period 2022-2025. The grant is administered by the University of Melbourne.

Kanta Subbarao is Associate Investigator for the $4,157,377.94 **NHMRC Medical Research Future Fund (MRFF)** project titled, 'The Platform trial In COVID-19 vaccine BOOsting (PICOBOO)', for the period 2022-2026. The grant is administered by the University of Melbourne.

Kanta Subbarao is Co-Investigator for the $500,000 **Victorian Department of Health and Human Services grant titled**, 'Evaluating direct and indirect effects of SARS-CoV-2 on multiple organ systems using stem cell-derived tissues' for the period 2020-2023. The grant is administered by the University of Melbourne.

Kanta Subbarao is a Lead Investigator and Ian Barr and Saira Hussain Co-Investigator for the $3,034,704 by **the Pandemic Antiviral Discovery (PAD) initiative and the Novo Nordisk Foundation** project titled "Development of a Novel Long Acting Pan-Influenza Antiviral Drug" for the period 2024-2026. The grant is administered by the University of Melbourne and the Royal Melbourne

Kanta Subbarao and Saira Hussain are Co-Investigator for the $587,911 by **Cumming Global Centre Foundation Grants** project titled "Development of human and animal in vitro respiratory tract models for risk assessment of viruses with pandemic potential " for the period 2024-2027. The grant is administered by the University of Melbourne and the Royal Melbourne

Research Students

PhD Candidates

Ms Jessie Goldsmith continued her PhD candidature from July 2022 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 completed her Masters of Science (Bioinformatics) project with the University of Melbourne. Her project was titled, 'Understanding COVID-19: BCR analysis workflow for studying asymptomatic patients', under the supervision of **Annette Fox**, **Ammar Aziz**, and **Stephany Sanchez**. April 2022—October 2023

Dr Catherine Pendrey completed her Masters of Philosophy in Applied Epidemiology (MAE) with the Australian National University (ANU). Her projects cover the 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 was supervised by **Sheena Sullivan** and Rezanur Rahaman (ANU). February 2022 - December 2023

Heran Zhang continued his Master of Biomedical Science research project with the University of Melbourne under the supervision of Linda Wakim and **Patrick Reading**, titled 'The impact of staphylococcal superantigens on the fate and protective capacity of lung tissue resident memory T cells'. June 2021 – July 2023.

Rachel Wordsworth commenced a Masters of Infectious Diseases research project with the University of Western Australia titled, 'Whole Genome Sequencing (WGS) of Respiratory Syncytial Virus (RSV) using Nanopore Third Generation Sequencing Technology', under the supervision of **Yi-Mo Deng and Xiaomin Dong.** February 2023 – October 2023.

Honours students

There were no Honours students at the Centre during 2023

Work experience students

Ruth Pinczewski (Fentona Girls High School) was at the Centre on 13 June 2023 as part of a wider VIDRL work experience program.

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 70 original research papers, reviews and reports in 2023.

Centre Publications 2023

1. Anderson, G. P., L. B. Irving, A. Jarnicki, K**. Kedzierska, M**. Koutsakos, S. Kent, **A. C. Hurt,** A. K. Wheatley, T. H. O. Nguyen, N. Snape and J. W. Upham (2023). "Prime-boost, double-dose influenza vaccine immunity in COPD: a pilot observational study." ERJ Open Res **9**(2).
2. Asante, I. A., S. O. Nyarko, Y. Awuku-Larbi, R. A. Obeng, G. M. Sarpong, E. A. A. Amenuvor, M. Adusei-Poku, L. Boatemaa, V. Magnusen, J. Wutsika, S. Ago, L. Kwasah, J. Wordui, R. A. Tackie, D. O. Laryea, F. Asiedu-Bekoe, W. Asiedu, D. L. Mingle, E. O. Nyarko, **A. Fox,** S. C. Nimo-Paintsil, N. Attram, T. Sanders and W. K. Ampofo (2023). "Decreased influenza activity during the COVID-19 pandemic in Ghana, 2020." Front Public Health **11**: 1290553.
3. Bailie, C. R., J. K. C. Ghosh, M. D. Kirk and **S. G. Sullivan** (2023). "Effect of ambient PM(2.5) on healthcare utilisation for acute respiratory illness, Melbourne, Victoria, Australia, 2014-2019." J Air Waste Manag Assoc **73**(2): 120-132.
4. Barrios, M. H., S. Nicholson, R. A. Bull, M. Martinello, W. Rawlinson, M. Mina, J. J. Post, B. Hudson, N. Gilroy, A. R. Lloyd, P. Konecny, F. Mordant, M. Catton, **K. Subbarao,** L. Caly, J. Druce and H. J. Netter (2023). "Comparative Longitudinal Serological Study of Anti-SARS-CoV-2 Antibody Profiles in People with COVID-19." Microorganisms **11**(8).
5. Bodle, J., K. Vandenberg, K. Laurie, **I. G. Barr, Y.** Zhang and S. Rockman (2023). "An ELISA-based assay for determining haemagglutinin potency in egg, cell, or recombinant protein derived influenza vaccines." Front Immunol **14**: 1147028.
6. Cable, J., J. Sun, I. S. Cheon, A. E. Vaughan, I. A. Castro, S. R. Stein, C. B. López, K. M. Gostic, P. J. M. Openshaw, A. H. Ellebedy, A. Wack, E. Hutchinson, M. M. Thomas, R. A. Langlois, D. Lingwood, S. F. Baker, M. Folkins, E. F. Foxman, A. B. Ward, M. Schwemmle, A. B. Russell, C. Chiu, K. Ganti, **K. Subbarao,** T. P. Sheahan, P. Penaloza-MacMaster and T. Eddens (2023). "Respiratory viruses: New frontiers-a Keystone Symposia report." Ann N Y Acad Sci **1522**(1): 60-73.
7. Canevari, J. T., A. C. Cheng, L. Wu, S. L. Rowe, D. E. Wollersheim, D. West, S. S. Majumdar and **S. G. Sullivan** (2024). "The relative effectiveness of three and four doses of COVID-19 vaccine in Victoria, Australia: A data linkage study." Vaccine **42**(1): 53-58.
8. Chappell, K. J., F. L. Mordant, A. A. Amarilla, N. Modhiran, B. Liang, Z. Li, D. K. Wijesundara, J. A. Lackenby, P. Griffin, J. K. Bennet, L. Hensen, W. Zhang, T. H. O. Nguyen, M. H. Tran, P. Tapley, J**. Barnes, P. C. Reading,** K. Kedzierska, C. Ranasinghe, **K. Subbarao**, D. Watterson, P. R. Young and T. P. Munro (2023). "Long-term safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2 in adults aged 18-55 years or ≥56 years: 12-month results from a randomised, double-blind, placebo-controlled, phase 1 trial." EBioMedicine **97**: 104842.
9. Chen, J., J. A. Neil, J. P. Tan, R. Rudraraju, M. Mohenska, Y. B. Y. Sun, E. Walters, N. G. Bediaga, G. Sun, Y. Zhou, Y. Li, D. Drew, P. Pymm, W. H. Tham, Y. Wang, F. J. Rossello, G. Nie, X. Liu, **K. Subbarao** and J. M. Polo (2023). "A placental model of SARS-CoV-2 infection reveals ACE2-dependent susceptibility and differentiation impairment in syncytiotrophoblasts." *Nat Cell Biol* 25(8): 1223-1234.
10. Chen, J., J. A. Neil, J. P. Tan, R. Rudraraju, M. Mohenska, Y. B. Y. Sun, E. Walters, N. G. Bediaga,

Centre Publications 2023 (continued)

G. Sun, Y. Zhou, Y. Li, D. Drew, P. Pymm, W. H. Tham, Y. Wang, F. J. Rossello, G. Nie, X. Liu**, K. Subbarao** and J. M. Polo (2023). "Author Correction: A placental model of SARS-CoV-2 infection reveals ACE2-dependent susceptibility and differentiation impairment in syncytiotrophoblasts." Nat Cell Biol 26(2), 305

11. Cowling, B. J., M. Y. W. Kwan, C. Murphy, E. L. Y. Chan, J. S. C. Wong, **S. G. Sullivan**, M. Peiris and S. L. Lee (2023). "Influenza Vaccine Effectiveness Against Influenza-Associated Hospitalization in Hong Kong Children Aged 9 Months to 17 Years, March-June 2023." J Pediatric Infect Dis Soc 12 (11): 586-589.
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Gartner, W. S. Lee, J. McAuley, P. Vaz, F. Sainsbury, M. D. Tate, J. Sinclair, A. Imrie, S. Rawlinson, A. Harman, J. M. Carr, E. A. Monson, M. Hibma, T. J. Mahony, T. Tu, R. J. Center, L. B. Shrestha, R. Hall, M. Warner, V. Ward, D. E. Anderson, N. S. Eyre, N. E. Netzler, A. J. Peel, P. Revill, M. Beard, A. R. Legione, A. J. Spencer, A. Idris, J. Forwood, S. Sarker, D. F. J. Purcell, N. Bartlett, J. M. Deerain, B. J. Brew, S. Asgari, H. Farrell, A. Khromykh, D. Enosi Tuipulotu, D. Anderson, S. Mese, Y. Tayyar, K. Edenborough, J. M. Uddin, A. Hussain, C. J. I. Daymond, J. Agius, K. N. Johnson, P. Shirmast, M. Abedinzadeshahri, R. MacDiarmid, C. L. Ashley, J. Laws, L. L. Furfaro, T. D. Burton, S. M. R. Johnson, Z. Telikani, M. Petrone, J. A. Roby, C. Samer, A. Suhrbier, A. Van Der Kamp, A. Cunningham, C. Donato, J. Mahar, W. D. Black, S. Vasudevan, R. Lenchine, K. Spann, D. J. Rawle, P. Rudd, J. Neil, R. Kingston, T. P. Newsome, K. W. Kim, J. Mak, K. Lowry, N. Bryant, J. Meers, J. A. Roberts, N. McMillan, L. I. Labzin, A. Slonchak, L. E. Hugo, B. Henzeler, N. D. Newton, C. T. David, **P. C. Reading,** C. Esneau, T. Briody, N. Nasr, D. McNeale, B. McSharry, O. Fakhri, B. A. Horsburgh, G. Logan, P. Howley and P. Young (2023). "Statement in Support of: "Virology under the Microscope-a Call for Rational Discourse"." mBio 14(3): e0081523.

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Centre Publications 2023 (continued)

samples obtained pre and post-influenza vaccination reveals a poor boosting of seasonally-relevant, hemagglutinin-specific antibodies." Front Immunol 14: 1154782.

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70. Zheng, M. Z. M., T. K. Tan, F. Villalon-Letelier, H. Lau, Y. M. Deng, S. Fritzlar, S. A. Valkenburg, H. Gu, L. L. M. Poon, **P. C. Reading,** A. R. Townsend and L. M. Wakim (2023). "Single-cycle influenza virus vaccine generates lung CD8(+) Trm that cross-react against viral variants and subvert virus escape mutants." Sci Adv 9(36): eadg3469.

Presentations

Centre staff members presented talks and posters at numerous events during 2023, including national and international conferences, WHO meetings, educational lectures and research seminars.

ORAL PRESENTATIONS

Event/Institute; Location, date	SPEAKER, Title(s)
Immunisation Coalition Annual Scientific Meeting 2023; Melbourne, 5-6 February 2023.	IAN BARR: Influenza 2022 and 2023.
Immunisation Coalition Annual Scientific Meeting 2023; Melbourne, 5-6 February 2023.	KANTA SUBBARAO: Influenza and SARS-CoV-2: Lessons from Pandemic Respiratory Viruses.
ISIRV Correlates of Protection for Next Generation Influenza Vaccines: Lessons Learnt From the COVID Pandemic; Seattle, USA, 1-3 March 2023.	KANTA SUBBARAO: Mucosal data from LAIV.
ISIRV Correlates of Protection for Next Generation Influenza Vaccines: Lessons Learnt From the COVID Pandemic; Seattle, USA, 1-3 March 2023.	STEPHANY SANCHEZ: Influenza vaccine responses to A(H1N1)pdm09 antigens in 2020 and 2021 among repeatedly vaccinated healthcare workers.
ISIRV Correlates of Protection for Next Generation Influenza Vaccines: Lessons Learnt From the COVID Pandemic; Seattle, USA, 1-3 March 2023.	STEPHANY SANCHEZ: Transcriptomic profiling of vaccination versus Post-Influenza infection.
ISIRV Correlates of Protection for Next Generation Influenza Vaccines: Lessons Learnt From the COVID Pandemic; Seattle, USA, 1-3 March 2023.	SHEENA SULLIVAN: Influenza Vaccine Effectiveness.
Cell Symposium: Viruses in health and disease; Sitges, Spain, 19-21 March 2023.	KANTA SUBBARAO: Rational treatment strategies for SARS-CoV-2 derived from studies in human pluripotent stem cell models.
Doherty Public Health Laboratory seminar; Melbourne, 18 April 2023.	PATRICK READING: Molecular testing for viral respiratory diseases in the Pacific - recent progress and where to next?
The XVIth International Nidovirus Symposium; Montreux, Switzerland, 14/18 May 2023.	KANTA SUBBARAO: The implications of SARS-CoV-2 virus evolution on vaccines.
13th WHO working group for the molecular detection and subtyping of influenza viruses and the use of next generation sequencing in GISRS; Rio de Janeiro, Brazil, 5-7 June 2023.	YI-MO DENG: Updates on General Genetic Surveillence work at WHO CC Melbourne in 2022.
13th WHO working group for the molecular detection and subtyping of influenza viruses and the use of next generation sequencing in GISRS; Rio de Janeiro, Brazil, 5-7 June 2023.	YI-MO DENG: Updates on NGS work at WHO CC Melbourne in 2022.

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
13th WHO working group for the molecular detection and subtyping of influenza viruses and the use of next generation sequencing in GISRS; Rio de Janeiro, Brazil, 5-7 June 2023.	YI-MO DENG: New development of NGS technology.
Career Pathways in Science, Future's Networking Seminar Series, University of Melbourne; Melbourne, 6 June 2023.	PATRICK READING: A career balancing act – basic research, laboratory capacity building and regional support.
12th WHO working group on surveillance of antiviral susceptibility of influenza viruses for GISRS; Rio de Janeiro, Brazil, 7-9 June 2023.	SAIRA HUSSAIN: Update on influenza antiviral susceptibility testing at WHO CC Melbourne (June 2022 -May 2023).
Vaccine Effectiveness, Burden and Impact Studies meeting (VEBIS, I-MOVE meeting); Stockholm, Sweden, 7-9 June 2023.	SHEENA SULLIVAN: Use of electronic health registries in COVID-19 VE estimation in Australia; and then participation in the subsequent plenary/panel discussion on EHR in VE estimation.
Vaccine Effectiveness, Burden and Impact Studies meeting (VEBIS, I-MOVE meeting); Stockholm, Sweden, 7-9 June 2023.	SHEENA SULLIVAN: What to do about correlated covid/influenza/RSV vaccination status.
PROPHECY Annual Symposium 2023; Melbourne, 13 June 2023.	KANTA SUBBARAO: The effect of virus evolution on COVID-19 vaccines.
Vaccines and Related Biological Products Advisory Committee June 15, 2023 Meeting Announcement; Virtual Forum, 15 June 2023.	KANTA SUBBARAO: Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC): Statement on the antigen composition of COVID-19 vaccines.
Communicable Diseases & Immunisation Conference 2023; Perth, 19-21 June 2023.	CATHERINE PENDREY: The re-emergence of influenza following the COVID-19 pandemic in Victoria, Australia.
Doherty Institute Computational Sciences Initiative (CSI) Seminar Series; Melbourne, 19 June 2023.	MICHELLE WILLE: Evolutionary genetics of avian influenza in Australia, and use of phylogenomics to illuminate spread of HPAI.
Communicable Diseases & Immunisation Conference 2023; Perth, 19-21 June 2023.	SHEENA SULLIVAN: Repeated influenza vaccination is associated with attenuated antibody responses in healthcare workers.
Communicable Diseases & Immunisation Conference 2023; Perth, 19-21 June 2023.	SHEENA SULLIVAN: Responses to influenza A(H1N1) pdm09 vaccines show recall of seasonal A(H1N1) epitopes.
International Society for Influenza and Other Respiratory Diseases (ISIRV); , 20 June 2023.	MICHELLE WILLE: Leveraging surveillance of LPAI to prepare for HPAI in Australia.
WHO Workshop on Estimation of RSV Disease Burden based on RSV Surveillance of GISRS; Geneva, Switzerland, 21-22 June 2023.	STEVEN EDWARDS: Experiences and Challenges in RSV Genomic Data Generation.

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
National Microbiology webinar speaker (virtual), Royal College of Pathologists of Australasia, 26 July 2023.	KANTA SUBBARAO: What's new with influenza in 2023?
Australian Society for Microbiology (ASM) Annual General Meeting Seminar, 22 August 2023.	MICHELLE WILLE: Leveraging surveillance of LPAI to prepare for HPAI in Australia.
New South Wales Health, Virology Research Seminar, 1 August 2023.	MICHELLE WILLE: Leveraging surveillance of LPAI to prepare for HPAI in Australia.
Keynote speaker, Australian Academy of Health and Medical Sciences symposium, Melbourne, 19 August 2023.	KANTA SUBBARAO: Life as a Clinician-Scientist.
Burnet Institute Seminar, Melbourne, VIC, 22 August 2023.	KANTA SUBBARAO: SARS-CoV-2 infection in human pluripotent stem cell models.
Keynote speaker, Duke-NUS Early Career Scientists Association (DUNES) symposium, Duke-NUS, Singapore, 20 October 2023.	KANTA SUBBARAO: My journey as a Physician-Scientist.
Emerging Infectious Disease Department, Duke-NUS, Singapore, 31 October 2023.	KANTA SUBBARAO: SARS-CoV-2 infection in primary and pluripotent stem-cell models of the respiratory tract and beyond.
Individual and Population Immunity to Respiratory Viruses, Hong Kong China, 8-10 November 2023.	ANNETTE FOX: Strain change effects on influenza vaccine immunogenicity.
Individual and Population Immunity to Respiratory Viruses, Hong Kong China, 8-10 November 2023.	ZIHENG (ANNIE) ZHU: Unpacking the attenuating effects of repeated influenza vaccination (A/H3N2).
Victorian Infection and Immunity Network Young Investigators Symposium, 9 November 2023.	A. JESSICA HADIPRODJO: Influenza vaccine responses to A(H1N1)pdm09 antigens in 2020 and 2021 among repeatedly vaccinated healthcare workers.
NIAID NIH Human Influenza Challenge Model Workshop, Bethesda, MD, USA, 14 November 2023.	KANTA SUBBARAO: Controlled human infection with influenza viruses at the Doherty Institute.
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, Brunei Seminar, 17 November 2023.	PATRICK READING: Pandemics, epidemics and the continuing threat of novel influenza viruses entering the human population.
Centre for Vaccinology and the Centre for Emerging Viral Diseases, University of Geneva, Geneva, Switzerland, 6 December 2023.	KANTA SUBBARAO: SARS-CoV-2 biology, antivirals and vaccines.

POSTER PRESENTATIONS	
Event/Institute; Location, date	**SPEAKER, Title(s)**
ESWI,Valencia, Spain. 17-20 September 2023. (Virtual presentation).	HARRY STANNARD. Trends in viral replication and lung pathogenesis of influenza A(H1N1)pdm09 viruses .from 2009 to 2022 in the ferret model.
Africa Network for Influenza Surveillance and Epidemiology (ANISE) 7th Meeting, 11-13 September 2023.	SAIRA HUSSEIN: Results from WHO GISRS Global External Quality Assessment Programme 2020-2022 for molecular detection of SARS-CoV-2 in the WHO African Region.
European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), 22-24 November 2023	SAIRA HUSSEIN: Results from WHO GISRS Global External Quality Assessment Programme (EQAP) 2020-2022 for molecular detection of SARS-CoV-2.

Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2023.

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 and Aged Care), *Committee member*

Influenza and other respiratory viruses, *Editorial Board*

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*

Saira Hussain

WHO Expert Working Group for GISRS Surveillance of Antiviral Susceptibility, *Member*

Katie Milne

Medical Laboratory Quality Network

Victorian Infectious Disease Reference Laboratory NATA Action Group*, Member*

Patrick Reading

Options for the Control of Influenza XII, Brisbane 2024, *Local organising committee*

Influenza and Other Respiratory Viruses, *Editorial board*

Australian Respiratory Virology Meeting, *Organising committee*

Doherty Institute, *Discipline leader, Education and Professional Development*

Influenza and Other Respiratory Viruses, *Editorial board*

Kanta Subbarao

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*

Committees and Advisory Groups (continued)

Doherty Institute Operational Management Committee, *Member*

Human Animal Spillover and Emerging Diseases Scanning (HASEDS) group, *Member*

National Influenza Surveillance Committee (Department of Health), *Member*

Scientific Advisory Board, Singapore Infectious Diseases Translational Research Program, NUS, Singapore, *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*

South African Medical Research Council, Johannesburg, South Africa, *Reviewer*

Taskforce for the development of an R&D roadmap for coronavirus vaccines, *Member*

WHO Technical Advisory Group on COVID-19 Vaccine Composition 2021-2023, *Chair*

Cell, *Advisory Board*

Cell Host and Microbe, *Editorial board*

Journal of Virology, *Editorial board*

Med, *Editorial board*

PLoS Pathogens, *Section Editor*

Sheena Sullivan

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

Antarctic Wildlife Health Working Group. Expert Group for Birds and Marine Mammals. Scientific Committee for Antarctic Research, *Member*

Avian Influenza Virus AUSVETPLAN working group, *Member*

Discover Research Steering Committee for Doherty Computational Sciences Initiative, *Member*

Doherty Institute Green DISCO, *Member*

East Asian Australian Flyway Partnership Avian Disease Working Group, *Member*

eMERGE (Early and Mid-career network Committee, Peter Doherty Institute for Infection and Immunity, *Member*

Global Consortium for highly pathogenic avian influenza viruses in seabirds, *Chair*

High Pathogenicity H5N1 Avian Influenza Intersessional Group, Population and Conservation Status Working Group of the Agreement for the Conservation of Albatrosses and Petrels (ACAP), *Member*

MicroSeq Conference Organising Committee, *Member*

National Avian Influenza Wild Bird Surveillance, *Steering Committee*

Victorian Wader Study Group, *Member*

Committees and Advisory Groups

Wildlife Health Australia, *Member*

PLoS Pathogens, *Editor*

Waterbirds, *Editor*

Virology and Molecular Ecology (special issue), *Editor*

Tanya Diefenbach-Elstob

National Influenza Surveillance Committee (Department of Health and Aged Care), *Member*

Visitors to the Centre

The Centre was pleased to host the following visitors during 2023.

Date	VISITOR and affiliation
7 February 2023	A/PROF AUBREE GORDON; University of Michigan, Michigan, USA; Visiting scientist, Informal meet and greet.
8 February 2023	PROF PAUL THOMAS; St Jude Children's Research Hospital, Memphis, USA; Visiting scientist, Informal discussion on types of studies conducted at the Centre.
27 February - 3 March 2023	MR JEFFERY KALOMAR; Villa Central Hospital Molecular Laboratory, Port Villa, Vanuatu; Visiting scientist, Training in RT-PCR techniques - part of a wider VIDRL training program.
27 February - 3 March 2023	MS ANGELLA MARGARET MANELE; National Referral Hospital Molecular Laboratory, Honiara, Solomon Islands; Visiting scientist, Training in RT-PCR techniques - part of a wider VIDRL training program.
5-16 June 2023	MS ELIZABETH MARIA HORNAY; Laboratorio Nacional da Saúde Timor-Leste, Dili, Timor-Leste; Visiting scientist, Training in virus isolation, serology, sequencing, and NGS techniques for influenza viruses for NIC status.
5-16 June 2023	DR ARI JAYANTI PEREIRA TILMAN; Laboratorio Nacional da Saúde Timor-Leste, Dili, Timor-Leste; Visiting scientist, Training in virus isolation, serology, sequencing, and NGS techniques for influenza viruses for NIC status.
17-28 July 2023	DR SAMUEL WILKS; WHO Collaborating Centre for Modelling, Evolution and Control of Emerging Infectious Diseases, Department of Zoology, University of Cambridge; Collaborator.
22 August 2023	PROF IAN WILSON; Scripps Research Institute, La Jolla, USA; Visiting scientist, Part of a Viral Infectious Diseases Theme seminar and wider Doherty visit.

Visitors to the Centre (continued)

Date	VISITOR and affiliation
2-3 November 2023	DR WILLIAM POMAT; The Director of the PNG Institute of Medical Research. DR VARSHA POTDAR; National Institute of Virology Pune, Scientist, Maharashtra, India. DR RIPEKA KAURASI; Ministry of Health and Medical Services Fiji, visiting Medical Officer. DR RAVINDRAN THAYAN; Institute for Medical Research Kuala Lumpur, Research Officer. DR PILAILUK AKKAPAIBOON OKADA; Head, Thailand National Influenza Centre. DR MAI THI QUYNH LE; National Institute of Hygiene Hanoi Vietnam, Epidemiologist. DR JOAO XIMENES; Ministry of Health Timor Leste Scientist. DR ERIK KARLSSON; Deputy Head of Virology Unit Institut Pasteur du Cambodge, Cambodia. DR JUDE JAYAMAHA; National influenza Centre, Medical Research Institute Colombo, Sri Lanka, Consultant Medical Virologist. DR CATHERINE DACASIN; Research Institute for Tropical Medicine (RITM DOH), Scientist. QUANYI WANG; Vice Director of Vice Director General of Beijing CDC, Professor.
6 December 2023	PROF FU LIN, DR SHUANG LI and YING SHEN, Beijing Center for Disease Prevention and Control (Beijing CDC), Institute for Infectious Disease and Endemic Disease Control and Beijing Office of Center for Global Health. PROF MIN LIU and PROF JUN LIU, Peking University (PKU), School of Public Health.

Engagement in WHO activities

Event; Location, Date	Centre staff involved
WHO Consultation on the Composition of Influenza Vaccines for the northern hemisphere 2023-2024; Geneva, Switzerland, 20-24 February 2023.	Ian Barr, Kanta Subbarao, and Patrick Reading attended.
Joint national and international influenza surveillance review Sentinel Surveillance & Laboratory assessment); Male, Maldives, 5-9 March 2023.	Patrick Reading was part of the review panel.
13th WHO working group for the molecular detection and subtyping of influenza viruses and the use of next generation sequencing in GISRS; Rio de Janeiro, Brazil, 5-7 June 2023.	Yi-Mo Deng attended.
12th WHO working group on surveillance of antiviral susceptibility of influenza viruses for GISRS; Rio de Janeiro, Brazil, 7-9 June 2023.	Saira Hussain attended.
WHO meeting on Severity Assessment for Influenza; Geneva, Switzerland, 12-13 June 2023.	Sheena Sullivan attended.
WHO Workshop on Estimation of RSV Disease Burden based on RSV Surveillance of GISRS; Geneva, Switzerland, 21-22 June 2023.	Steven Edwards attended.
Assessment of the National Virology Laboratory (Nov 13-16, 2023) for designation as National Influenza Centres (NICs); Brunei Darassalam, 13-16 November 2023.	Patrick Reading was part of the review panel.
6th NIC meeting for the WHO African Region; Johannesburg, South Africa, 14-15 September 2023.	Heidi Peck attended and gave a presentation.
16th Bi-Regional Meeting of National Influenza Centres and Influenza Surveillance in the WHO's Western Pacific and South-East Asia Regions; Dhaka, Bangladesh, 1-3 August, 2023.	Ian Barr and Patrick Reading facilitated group work sessions, Saira Hussain also attended.
WHO Technical Advisory Group for Emergency Use Listing (EUL) meeting; Geneva, Switzerland, 5-6 September, 2023.	Kanta Subbarao is a member of the Technical Advisory Group.
Agreement of Performance of Work (APW) with WPRO Division of Technical Support (DPS), Pacific Health Security and Communicable Diseases Section (PSC) Multiplex PCR tests for respiratory pathogens, October 2023.	Written and finalised by Patrick Reading.
Training workshop in whole genome sequencing of respiratory viral pathogens, Bangkok, Thailand, 20 November-1 December 2023.	Yi-Mo Deng, Clyde Dapat, Xiaomin Dong, Steven Edwards, organized and ran the workshop.
WHO Technical Advisory Group on COVID-19 Vaccines (TAG-CO-VAC) meeting, 4-5 December, 2023.	Kanta Subbarao is a member of the Technical Advisory Group.

Other Conference Participation and Professional Engagement

Centre staff members also participated in the following events as attendees and/or in other roles during 2023

Event; Location, date	Centre staff involvement
ISIRV Correlates of Protection for Next Generation Influenza Vaccines; Lessons Learnt From the COVID Pandemic' Melbourne, 5-6 February 2023.	Kanta Subbarao was part of the organising committee, and also participated in a group discussion: Lessons Learned from COVID for Identifying Correlated of Protection and Develop Consensus on Immune Responses to Target, and was session Chair: Next Generation/Universal Influenza Vaccine.
Cell Symposium: Viruses in health and disease; Spain, 19-21 March 2023.	Kanta Subbarao was part of the organising committee and was also Chair for Session 4: Public health in the age of viral pandemics.
Asia-Pacific Vaccine and Immunotherapy Congress (APVIC); Brisbane, 26-28 April 2023.	Heidi Peck attended.
Asia-Pacific Vaccine and Immunotherapy Congress (APVIC); Brisbane, 26-28 April 2023.	Ian Barr attended and was a member of the Scientific Advisory Committee.
Food and Agriculture Organization of the United Nations: Global consultation on Highly Pathogenic Avian Influenza (HPAI); Rome, Italy, 2-4 May 2023.	Michelle Wille participated in panel discussions for two sessions, 'Surveillance for different objectives and associated challenges' and 'Perspectives on the impacts on wild birds'.
FluTracking Australia Surveillance Workshop - Learnings on COVID-19 from participatory surveillance; Newcastle, 8-9 May 2023.	Sheena Sullivan attended.
Communicable Diseases & Immunisation Conference 2023; Perth, 19-21 June 2023.	Ian Barr attended.
Australian Society for Microbiology National Meeting 2023; Perth, 3-6 July 2023.	Megan Triantafilou attended.
National Institute for Biological Standards and Control meeting; United Kingdom, 11-13 July 2023,	Ian Barr attended.
Methods and Implementation Support for Clinical and Health Research Hub/Clinical Epidemiology and Biostatistics Unit workshop; 17-18 July 2023.	Tanya Diefenbach-Elstob and Sheena Sullivan attended.
Pathogen genomics to enhance global health preparedness and response; 15th August 2023.	Xiaomin Dong and Presa Chanthalavanh attended.

Other Conference Participation and Professional Engagement (Cont)

Event; Location, date	Centre staff involvement
Standardizing the Conduct of Nonrandomized, Clinical Cohort Studies in Epidemic Settings; USA,14-15 September, 2023.	Sheena Sullivan attended.
Operation Waterhole at Agribio, Latrobe Uni. 20-21 September 2023.	Ian Barr attended.
AIMS (Advances in mRNA Sciences) Melbourne, 28-29 October 2023.	Ian Barr attended.
Consortium for Standardization of Influenza Seroepidemiology (CONSISE), Hong Kong, 7 November 2023.	Sheena Sullivan and Annette Fox attended.
Individual and population immunity to respiratory viruses; Hong Kong, 8-10 November 2023.	Sheena Sullivan and Annette Fox attended.

Community Engagement

The Director, Deputy Director and other staff members participated in requests from media representatives for interviews and comments throughout 2023.

Ian Barr

- Was interviewed by Guardian Australia in an article titled, ''Pandemic potential': bird flu outbreaks fuelling chance of human spillover', published 12 January 2023; https://www.theguardian.com/environment/2023/jan/12/pandemic-potential-bird-flu-outbreaks-fuelling-chance-of-human-spillover
- Was interviewed in a newsGP article titled, 'Chance of early flu season in 2023', published 23 January 2023; https://www1.racgp.org.au/newsgp/clinical/chance-of-early-flu-season-in-2023
- Was quoted in an article by The Sydney Morning Herald titled, ''It's not hype': COVID vaccine technology to fight another deadly virus, then cancer', published 12 February 2023; https://www.smh.com.au/national/it-s-not-hype-covid-vaccine-technology-to-fight-another-deadly-virus-then-cancer-20230208-p5cisl.html
- Was interviewed by ABC News in an article titled, 'Global H5N1 bird flu outbreak so bad many countries are now considering vaccination', published 17 February 2023; https://www.abc.net.au/news/science/2023-02-17/bird-flu-h5n1-global-pandemic-poultry-vaccination-wild-animals/101972756
- Was quoted in an article by Australian Doctor titled, 'Wave or whimper? What GPs should expect this flu season', published 21 February 2023; https://t.co/sFTpUDiptM
- Participated in an interview with ABC News on the death of an 11 year old child in Cambodia from avian influenza, published 24 February 2023
- Wrote an article on the Doherty Institute website titled, 'The upcoming 2023 influenza season in Australia – What's to come?', published 6 March 2023; https://www.doherty.edu.au/news-events/news/2023-influenza-season-in-australia-whats-to-come
- Was quoted in an article by Australian Doctor titled, 'Flu cases have spiked already — should GPs

Community Engagement (continued)

brace for a bad season?', published 9 March 2023; https://www.ausdoc.com.au/news/flu-cases-have-spiked-early-this-year-should-gps-be-worried/

- Was quoted in an article by NewsGP titled, 'How severe is this year's flu season likely to be?', published 16 March 2023; https://www1.racgp.org.au/newsgp/clinical/how-severe-is-this-year-s-flu-season-likely-to-be
- Co-wrote an article on The Conversation titled, 'Are flu cases already 100 times higher than last year? Here's what we really know about the 2023 flu season', published 17 March 2023; https://theconversation.com/are-flu-cases-already-100-times-higher-than-last-year-heres-what-we-really-know-about-the-2023-flu-season-201559
- Co-wrote an article in Pursuit titled, 'Bird flu, human cases and the risk to Australia', published 20 March 2023; https://pursuit.unimelb.edu.au/articles/bird-flu-human-cases-and-the-risk-to-australia
- Was interviewed on RN Breakfast in a segment titled, 'Is Australia experiencing another early flu season?', published 23 March 2023; https://www.abc.net.au/radionational/programs/breakfast/is-australia-experiencing-another-early-flu-season-/102133366
- Was interviewed by The Age in an article titled, 'Fears of low vaccination rates ahead of "significant" and "unpredictable" flu season, published 2 April 2023; https://www.theage.com.au/national/fears-of-low-vaccination-rates-ahead-of-significant-and-unpredictable-flu-season-20230331-p5cwz1.html
- Was interviewed by Guardian Australia in an article titled, Flu cases are on the rise across Australia. Do I need a winter vaccination?', published 18 April 2023; https://www.theguardian.com/australia-news/2023/apr/18/flu-cases-are-on-the-rise-across-australia-do-i-need-a-winter-vaccination?
- Was interviewed by Sky News Australia in a segment titled, 'Fears bird flu could become the next pandemic', published 29 April 2023; https://www.skynews.com.au/world-news/global-affairs/fears-bird-flu-could-become-the-next-pandemic/video/6260dc17cb719f5d51214169f4677f6b
- Was interviewed by ABC NewsRadio on the current global outbreak of bird flu, published 22 May 2023
- Was interviewed by ABC Western Queensland Rural Report on the current global outbreak of bird flu, published 23 May 2023
- Was interviewed by ABC Radio on the current global outbreak of bird flu, published 23 May 2023
- Was interviewed by RTE Radio 1 in a segment titled, 'Flu in Australia: what it might tell us about the winter ahead', published 6 June 2023; https://www.rte.ie/radio/radio1/clips/22259591/
- Was interviewed by ABC Radio AM in a segment titled, 'Flu cases rise with high rates in children', published 12 June 2023; https://www.abc.net.au/radio/programs/am/flu-cases-rise-with-high-rates-in-children-/102468444
- Was interviewed by The New Daily in an article titled, 'Why America's eyes are on Australia's flu season', published 14 June 2023; https://thenewdaily.com.au/life/2023/06/14/flu-season-australia-us/
- Was featured in a press release by the Doherty Institute titled, 'Doherty Institute and SK bioscience join forces against influenza', published 27 June 2023; https://www.doherty.edu.au/news-events/news/doherty-institute-and-sk-bioscience-join-forces-against-influenza
- Was interviewed by Guardian Australia in an article titled, 'Why are Australian children dying from the flu and what can we do to prevent it?' published 14 July, 2023; https://www.theguardian.com/australia-news/2023/jul/13/why-are-australian-children-dying-from-the-flu-and-what-can-we-do-to-prevent-it
- Was quoted in an article by the Australian Journal of Pharmacy titled, 'Helping in the Fight Against Flu' published 21 July, 2023; https://ajp.com.au/in-depth/longer-read/helping-in-the-fight-against-flu/

Community Engagement (continued)

- Was interviewed by ABC Radio Victoria regarding influenza B cases in children, published 24 July, 2023
- Was interviewed by The Atlantic in an article titled, 'Bird Flu Has Never Done This Before', published 3 August, 2023
- Was quoted in an article by Time News titled, 'Flu Epidemic Hits Australia: Low Vaccination Rates and Impact on Children', published 4 August, 2023
- Was quoted in an article by scimex titled, 'EXPERT REACTION: New RSV vaccine could be potent against future variants, suggests animal study', published 24 August, 2023; https://www.scimex.org/newsfeed/expert-reaction-new-rsv-vaccine-could-be-potent-against-future-variants-suggests-animal-study-science-translational-medicine-
- Was interviewed by ABC Radio Adelaide on the Australian influenza season, published 12 September, 2023

Kanta Subbarao

- Was quoted by The Herald Sun in an article titled, 'How the hunt for antivirals led to surprise heart discovery', published 14 June 2023; https://www.heraldsun.com.au/news/victoria/how-the-hunt-for-antivirals-led-to-surprise-heart-discovery/news-story/a292821759b6dbbfda9161ba7627e26f?btr=b7dd2f38a99ca2791dbdd733e28cc7b3
- Was quoted by TIME in an article titled, 'The COVID-19 Vaccine Is Getting an Update. Here's What to Know', published 15 June 2023; https://time.com/6287732/new-covid-19-vaccine-strains/
- Was featured in a press release by the Doherty Institute titled, 'Doherty Institute and SK bioscience join forces against influenza', published 27 June 2023; https://www.doherty.edu.au/news-events/news/doherty-institute-and-sk-bioscience-join-forces-against-influenza
- Was featured in an article by The National Tribune titled, 'Research reveals how covid-19 virus infects the placenta, and how this can be prevented', published 14 July, 2023; https://www.adelaide.edu.au/newsroom/news/list/2023/07/14/research-reveals-how-covid-19-virus-infects-the-placenta-and-how-this-can-be
- Appeared on ABC News Breakfast in a segment titled, 'Research reveals how COVID-19 infects the placenta', published 14 July, 2023; https://www.abc.net.au/news/2023-07-14/research-reveals-how-covid-19-infects-the-placenta/102601382
- Was featured in an article by The Herald Sun titled, 'How Covid invades placenta: Melbourne team's breakthrough discovery', published 14 July, 2023; https://www.heraldsun.com.au/coronavirus/victorian-and-south-australian-researchers-help-solve-covid-placenta-puzzle/news-story/0d2e3b647656aef41cfe9fb577438a35
- Was quoted iby Pharmacy Daily in an article titled, 'Covid infects placenta', published 17 June 2023; https://pharmacydaily.com.au/news/covid-infects-placenta/106444
- Was featured in an article by India Education Diary titled, 'Study Shows Covid-19 Virus Infects The Placenta, And Its Prevention' published 20 July 2023; https://indiaeducationdiary.in/study-shows-covid-19-virus-infects-the-placenta-and-its-prevention/
- Was interviewed by STAT in an article titled, 'Covid-19, a disease with tricks up its sleeve, hasn't fallen into a seasonal pattern — yet' published 23 August 2023; https://www.statnews.com/2023/08/23/covid-19-has-not-yet-fallen-into-a-seasonal-pattern/#:~:text=%E2%80%9CThere%20just%20isn't%20a,seasonality%20in%20the%20coming%20years.

Community Engagement (continued)

Michelle Wille

- Was interviewed by ABC Science in an article titled, 'Bird flu could wipe out Australian black swans, gene study reveals', published 23 January 2023; https://www.abc.net.au/news/science/2023-01-23/black-swan-gene-study-bird-avian-flu-threat/101875874

- Was quoted in an article by CBC Canada titled, 'Bird flu keeps spreading beyond birds. Scientists worry it signals a growing threat to humans, too', published 2 February 2023; https://www.cbc.ca/news/health/bird-flu-keeps-spreading-beyond-birds-scientists-worry-it-signals-a-growing-threat-to-humans-too-1.6732287

- Was quoted in an article by The Sydney Morning Herald/The Age titled, 'Bird flu is spreading among mammals. How worried should we be?', published 7 February 2023; https://www.smh.com.au/national/bird-flu-is-spreading-among-mammals-how-worried-should-we-be-20230207-p5cig3.html?fbclid=PAAaY2_r0M984QyEeZPt3dzCFuyQ8MGnhC0xYXNfmNmM3fPuECxLxG_d_LUVc

- Was interviewed by ABC News in an article titled, 'Global H5N1 bird flu outbreak so bad many countries are now considering vaccination', published 17 February 2023; https://www.abc.net.au/news/science/2023-02-17/bird-flu-h5n1-global-pandemic-poultry-vaccination-wild-animals/101972756

- Was quoted in an article by Reuters titled, 'Analysis: Why public health officials are not panicked about bird flu', published 24 February 2023; https://www.reuters.com/business/healthcare-pharmaceuticals/why-public-health-officials-are-not-panicked-about-bird-flu-2023-02-23/

- Was interviewed by The Telegraph in an article titled, 'Bird flu kills school girl and infects father – 11 others under observation', published 24 February 2023; https://www.telegraph.co.uk/global-health/science-and-disease/bird-flu-death-cambodian-child-sparks-global-alarm/

- Co-wrote an article on The Conversation titled, 'When should we worry about bird flu making us sick? When we see human-to-human transmission – and there's no evidence of that yet', published 1 March 2023; https://theconversation.com/when-should-we-worry-about-bird-flu-making-us-sick-when-we-see-human-to-human-transmission-and-theres-no-evidence-of-that-yet-200710

- Was quoted in an article by Science News titled, 'Bird flu can jump to mammals. Should we worry?', published 6 March 2023; https://www.sciencenews.org/article/bird-flu-mammals-influenza-pandemic

- Was interviewed by ABC Radio Melbourne in a segment titled, 'How concerned to do we need to be about bird flu?', published 10 March 2023; https://www.abc.net.au/melbourne/programs/theconversationhour/the-conversation-hour/102055014

- Was featured in a Doherty Institute article titled, 'Research confirms bird flu has not entered Australia', published 13 March 2023; https://www.doherty.edu.au/news-events/news/research-confirms-bird-flu-has-not-entered-australia

- Co-wrote an article in Pursuit titled, 'Bird flu, human cases and the risk to Australia', published 20 March 2023; https://pursuit.unimelb.edu.au/articles/bird-flu-human-cases-and-the-risk-to-australia

- Was interviewed by The Atlantic in an article titled, 'Bird Flu Has Never Done This Before', published 3 August, 2023; https://www.theatlantic.com/science/archive/2023/08/avian-flu-vaccine-wild-bird-transmission-endemic/674903/

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 2023, the website was viewed by over 9,000 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 2023. The Centre's Twitter profile gained 102 followers during the year, with a total of 1032 followers by 31 December 2023

Scan to access our Centre video, which was updated in May 2024 and is also available from the Centre website

New and departing staff members

New staff

Dr Saira Hussain

Head Antivirals

Dr Clyde Dapat
Bioinformation

Symone Mercuri

Administrative officer

Departing staff

A/Prof Sheena Sullivan

Head Epidemiologist

Pina Lannello

Medical Scientist

Dr Miku Kuba

Communications Officer

Ammar Aziz

Bioinformation

Management and staff

Director
Prof Kanta Subbarao

Deputy Director
Prof Ian Barr

Administrative officer
Symone Mercuri*

Quality & Regulatory Officer
Katie Milne

Educator/Research scientist
Prof Patrick Reading

Laboratory Manager/ Senior Medical Scientist
Dr Paul Whitney

Communications officer
Miku Kuba (until Sept)

Surveillance

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

GENETIC ANALYSIS
Head: Dr Yi-Mo Deng
Medical scientists:
Dr Xiaomin Dong
Steven Edwards
Pina Iannello (until Dec)
Hilda Lau
Olivia Lay
Presa Chanthalavanh
Natalie Spirason

ANTIVIRAL DRUG SENSITIVITY
Head: Dr Saira Hussain*
Medical scientist: Nikita Deshpande

BIOINFORMATICS
Manager: Dr Clyde Dapat*

Vaccine development

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

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

Research

IMMUNITY TO RESPIRATORY VIRUSES
Senior research scientist:
Dr Annette Fox

Post-Doctoral researchers
Dr Yi Liu
Dr Stephany Sanchez

Research assistant
Louise Carolan
Anastasia Jessica Hadiprojo

ANTIVIRALS AND ANIMAL INFLUENZAS
Senior research scientist:
Dr Saira Hussain*
Post-Doctoral researchers
Dr Michelle Wille
Research assistants:
Harry Stannard
Melkamu Tessema

PhD Candidate:
Paulina Koszalka (Medical Scientist from May)
Malet Aban

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

Epidemiology

Head:
A/Prof Sheena Sullivan (Until Dec)
Epidemiologists:
Tanya Diefenbach-Elstob
Research assistant:
Arseniy Khvorov
PhD Candidate:
Jessie Goldsmith
MAE Candidate:
Catherine Pendrey

**New staff members in 2023*