Annual Report 2021

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 through a funding agreement between the Commonwealth and Melbourne Health, and reports directly to the Department as well as to WHO.

Contact information

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Highlights of 2021

Surveillance

The Centre received and processed **372 samples**, of which **99.6% were tested**. Of viruses tested, approximately **53.8%** were **A(H3N2) viruses.**

Research, publications and grants

The Centre further developed its research program during 2021, with Centre staff involved as authors on **65 papers** in peer-reviewed journals. Centre staff were awarded several research grants and funding, including **USD $200,000** from the **US Centers for Disease Control (CDC)**.

WHO vaccine strains isolated by the Centre

Two vaccine candidate viruses that were originally isolated in eggs by the Centre were selected for **inclusion in the WHO recommended influenza vaccine strains.**

Australian Influenza Symposium

The **14th Australian Influenza Symposium** was held as a virtual forum hosted by ASN Events and attended by **355 delegates**.

Ongoing COVID-19 work

The COVID-19 pandemic has resulted in historically low influenza infection rates. With this in mind, many members of the Centre have participated in various COVID-19 related projects, seminars, and workshops during 2021.

Director's report

I present the 2021 Annual Report of the WHO Collaborating Centre for Reference and Research on Influenza following a very unusual year, with very little influenza activity reported globally. The Centre has continued to fulfil its commitments to the WHO, National Influenza Centres in the region, and the Commonwealth Government and to participate in training and research activities. Centre staff have worked with the WHO to adapt influenza sentinel surveillance systems to include COVID-19.

Coincident with the global spread of COVID-19, reports of influenza activity plummeted to a historic low and typical seasonal influenza did not occur in either the southern or northern hemisphere. As a result of the greatly reduced influenza activity globally, the Centre received and processed only 372 influenza samples from 16 laboratories in Australia and 9 other countries during 2021. The largest proportion (just over 50%) of the samples analysed were influenza A (H3N2) viruses. The Centre continued to conduct antigenic and genetic characterisation of viruses and noted an increase in genetic diversification of the H1, H3, and B/Vic HA genes. The Centre also continued routine testing of viruses for reduced susceptibility to neuraminidase inhibitors and the polymerase inhibitor baloxavir marboxyl.

During 2021 the Centre continued to work on isolation of cell-based and egg-based viruses for vaccine production. Two vaccine candidate viruses that were originally isolated in eggs by the Centre were selected for inclusion in the WHO recommended influenza vaccine strains during 2021. The Centre also continued to monitor potential pandemic influenza viruses and seeks to obtain new viruses as they were detected (such as A(H5) viruses), to check reagents and prepare virus and RNA stocks.

It was not possible to travel and provide training in person in 2021 because of the COVID-19 pandemic. However, Centre staff participated in remote training in several countries including the Pacific Islands, Cambodia, Mongolia, Indonesia, and Mozambique. Centre staff presented remotely at several domestic and international conferences in 2021.

Centre staff contributed to a total of 65 original research papers, reviews and reports in 2021. 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 Mike Catton and Prof Deb Williamson, the outgoing and incoming Director of VIDRL, respectively. We are also very grateful to many other members of VIDRL staff, especially Jane Brewster, Anna Ayres and Dallas Wilson, for their support of the Centre's work at every level during 2021. The continuing support and counsel of the Office of Health Protection in the Australian Government Department of Health are deeply appreciated. Finally, I would like to thank all the staff and students of the Centre for their excellent work through the unusual year that was 2021, and for adjusting to several measures that were instituted to reduce the risk of infection in the work place, including staggered work schedules, distancing and mask wearing. It is a privilege to work with the Centre staff and I look forward to working with our partners in 2022 and onwards.

Prof Kanta Subbarao
Centre Director

Surveillance

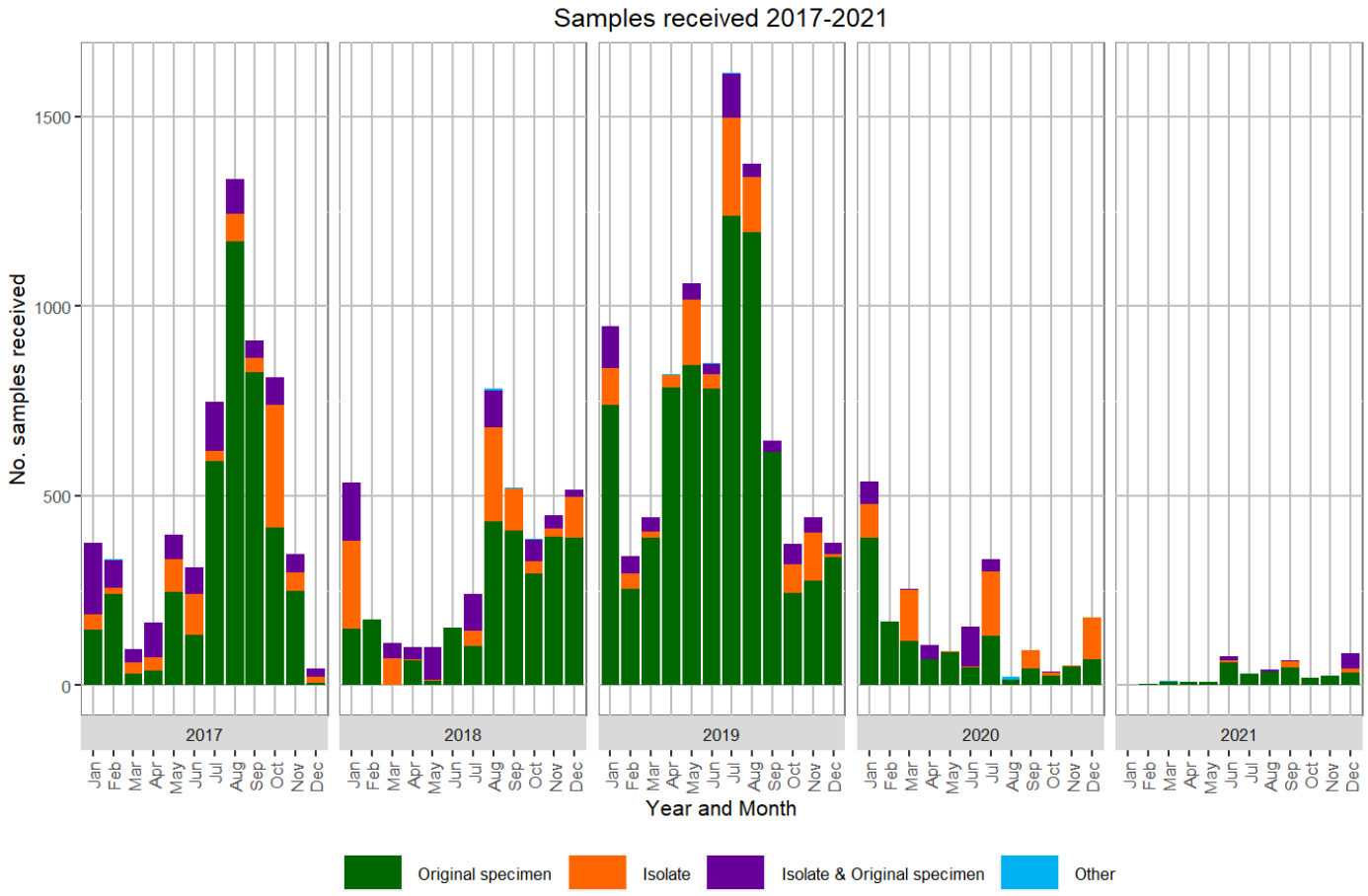
Introduction

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

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

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

Figure 1. Samples received by the Centre, 2017-2021



Receipt of Influenza Viruses

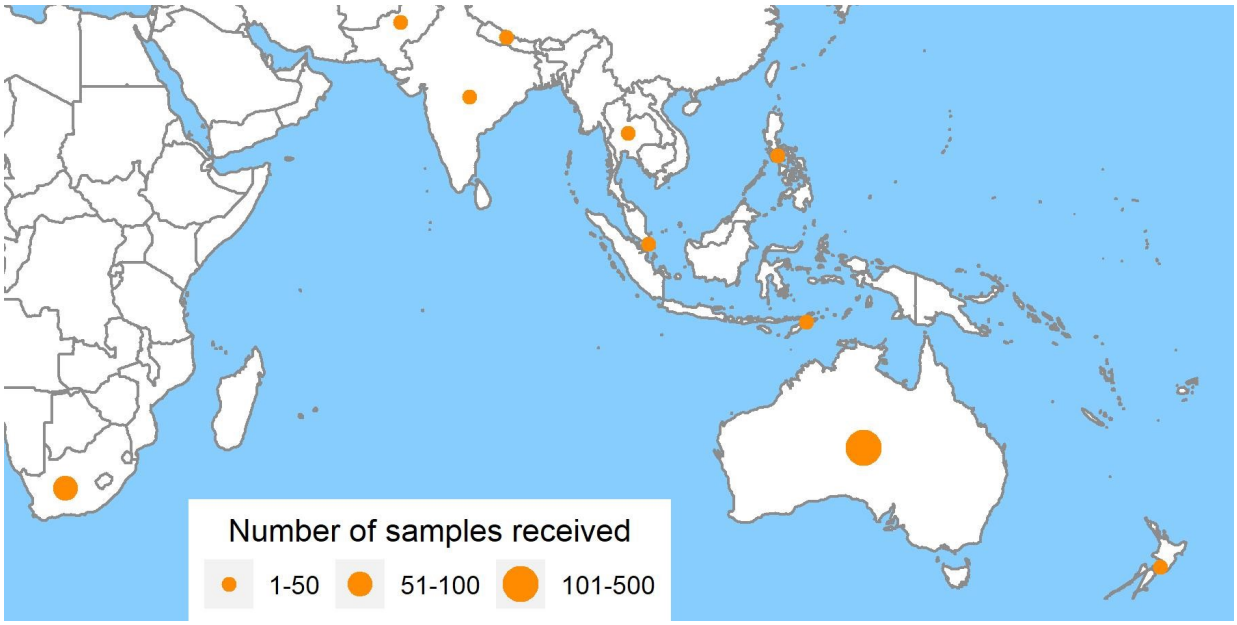
During 2021 the Centre received 372 clinical specimens and/or virus isolates from 31 laboratories in 10 countries (Figures 1 and 2, Table 1). This is significantly lower than the number of samples received by the Centre during 2020, and is consistent with the low number of influenza infections during the 2021 Australian influenza season. This can be attributed to the restrictions in place during most of 2021 against the COVID-19 pandemic. Amongst samples received by the Centre for which the age of the patient was known, the largest number were from subjects aged under 5 years (Figure 3). 1 sample came from Australian general practitioner based surveillance systems (Table 2).

Isolation and analysis of viruses

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

A total of 367 samples (98.7%) were isolated by culture and/or analysed by real-time reverse-transcription polymerase chain reaction (RT-PCR). Samples for which a positive cell culture result was obtained with sufficient titre were further analysed by haemagglutination inhibition (HI) assay. For reporting purposes, subtypes and lineages are based on antigenic analysis of the HA and in some cases are confirmed by genetic analysis of NA. Of the samples for which results could be obtained, 53.8% were identified as A(H3N2) viruses, 18.7% were B/Victoria, and 13.1% were A(H1N1)pdm09 (Table 3).

Figure 2. Geographic spread of influenza laboratories sending viruses to the Centre during 2021.



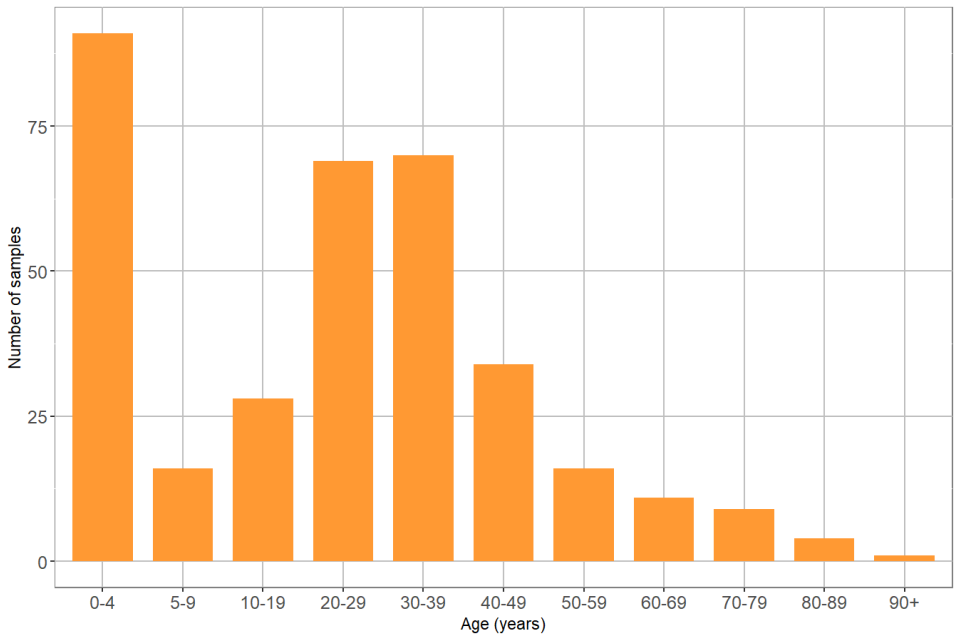


Figure 3. Age distribution of patients from whom samples were received at the Centre in 2021 and the age is known.

Table 1. Samples received by the Centre in 2021, by country.

Country	Samples received				% Samples tested
	Specimens	Isolates	Specimen + Isolate	Other (eg. RNA/ DNA/tissue)	
AUSTRALASIA					
Australia	141	2	1	2	96.6%
New Zealand		4	1		100%
SOUTH EAST ASIA					
Philippines	16		7		100%
Singapore	27				100%
Thailand	10				100%
Timor-Leste	44				100%
SOUTH ASIA					
India		15			100%
Nepal	20				100%
Pakistan	20				100%
AFRICA					
South Africa	1	11	50		100%
TOTAL	**279**	**32**	**59**	**2**	**98.7%**

Table 2. Samples received from general practitioner based surveillance systems in Australia, 2021

	No. samples received	No. isolates recovered*	Viruses analysed by HI assay
Influenza Complications Alert Network (*FluCAN*)	1		
TOTAL	**1**		

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

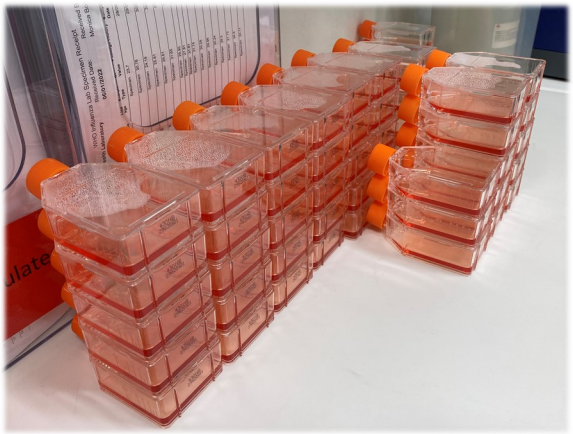
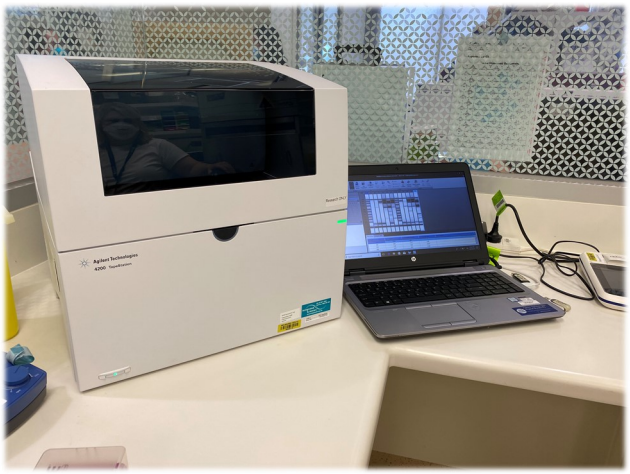


Table 3. Samples successfully tested by cell culture and/or RT-PCR assay at the Centre in 2021, by country.

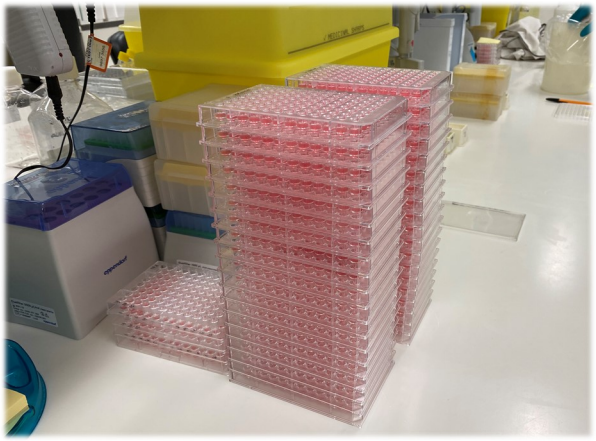
Country	Samples tested by cell culture and/or RT-PCR assay							
	A (H1N1)pdm09	A(H3N2)	A(H3N2)v	A mixed subtype	A unsubtyped	B/Victoria	B lineage undetermined	C
AUSTRALASIA								
Australia	6	68	2	1	22	12	15	3
New Zealand		3				2		
SOUTH EAST ASIA								
Philippines		4				4		
Singapore		3				17		
Thailand		5						
Timor-Leste		43			1			
SOUTH ASIA								
India	6	8						
Nepal	1	15				1		
Pakistan		4						
AFRICA								
South Africa	27	11				21		
TOTAL	**40**	**164**	**2**	**1**	**23**	**57**	**15**	**3**



Antigenic Analysis of Influenza Isolates

Background

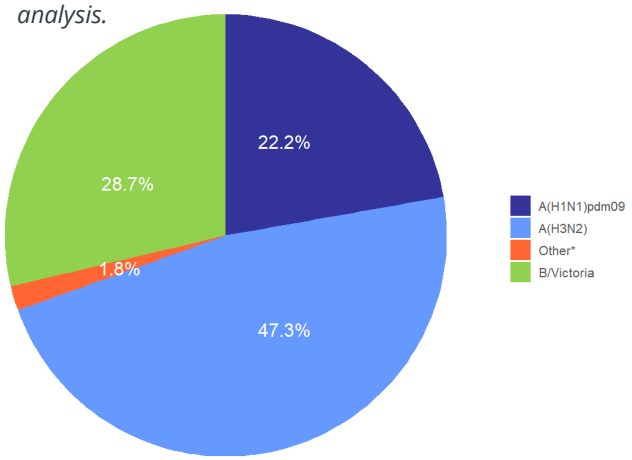
The antigenic properties of influenza viral isolates are analysed using the HI assay, in which viruses are tested for their ability to agglutinate red blood cells in the presence of ferret antisera previously raised against reference viruses. A number of A(H3N2) viruses are also analysed antigenically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



Antigenic analyses 2021

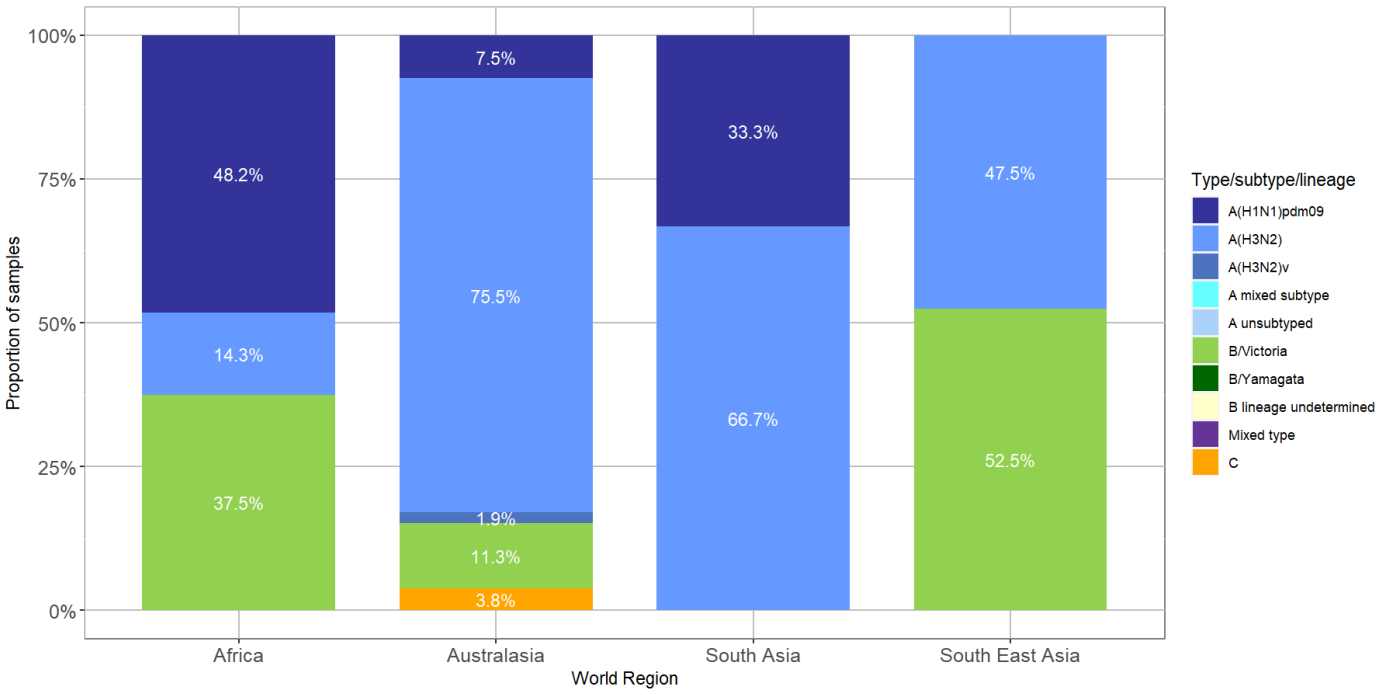
A total of 332 isolates that were received at the Centre in 2021 were cultured and isolated in MDCK cells, of which 167 (50.3%) produced a positive result. The largest proportion of viruses were A(H3N2) (47.3%), followed by B/Victoria viruses (Figure 4). The predominance of A(H3N2) viruses for samples received and successfully isolated at the Centre by cell culture was observed in some world regions (Australasia and South Asia) (Figure 5). In the African region, of viruses that were successfully cultured and isolated in cells, A(H1N1)pdm09 viruses predominated. In South East Asia, there were almost equal proportions of B/Victoria and A (H3N2) viruses.

Figure 4. Influenza sub/types and lineages of samples received in 2021 and characterised by antigenic analysis.



**A unsubtyped, A mixed, C, A(H3N2)v*

Figure 5. Influenza sub/types and lineages of isolates received from different world regions during 2021 as determined by antigenic analysis.



Genetic Analysis of Influenza Viruses

Background

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

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

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

Figure 6. Sequencing of viruses received at the Centre in 2021. Note that some viruses were analysed by both Sanger sequencing and NGS, and are therefore represented twice in this figure.

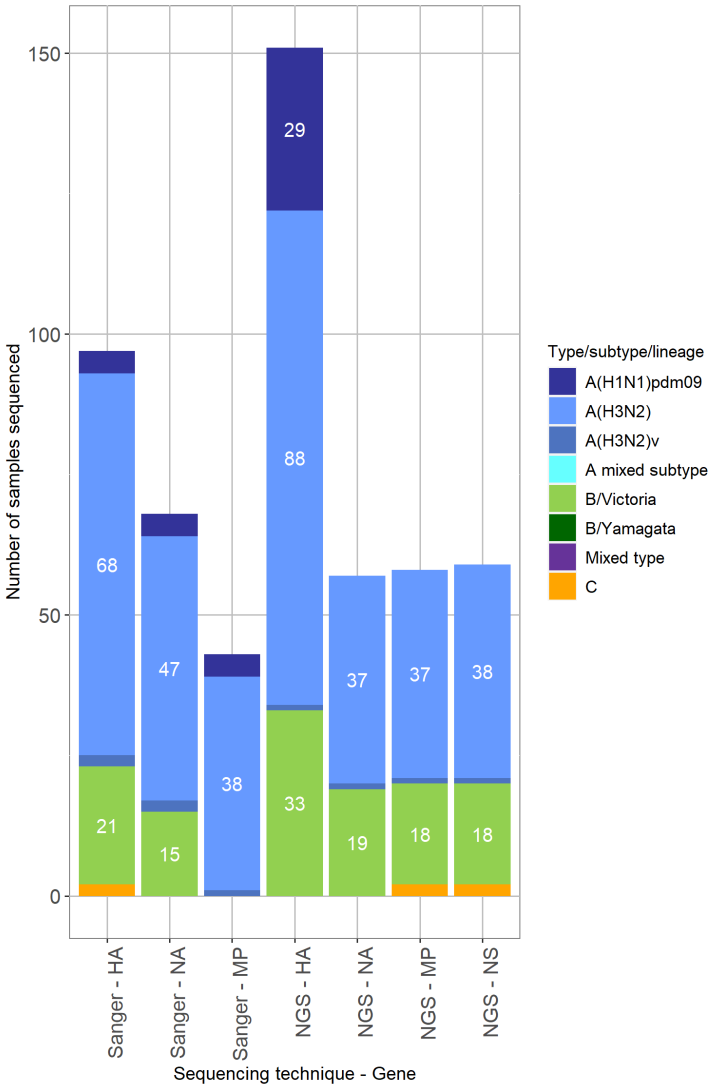
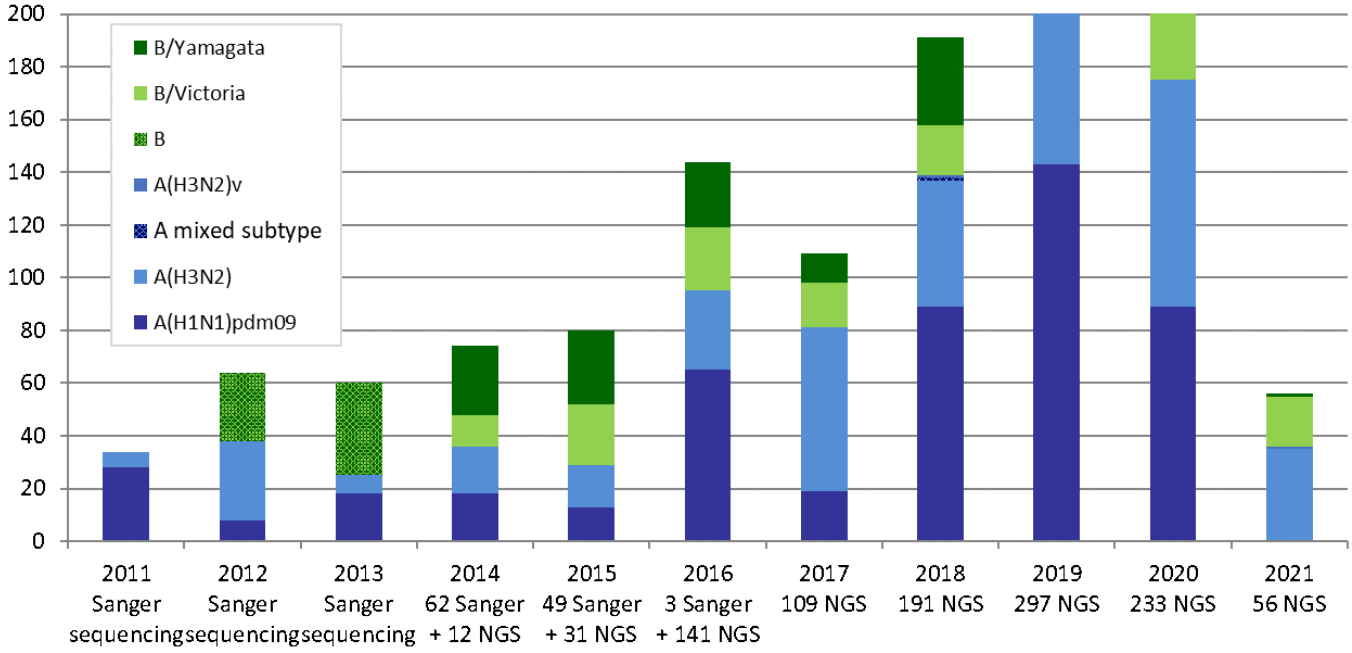


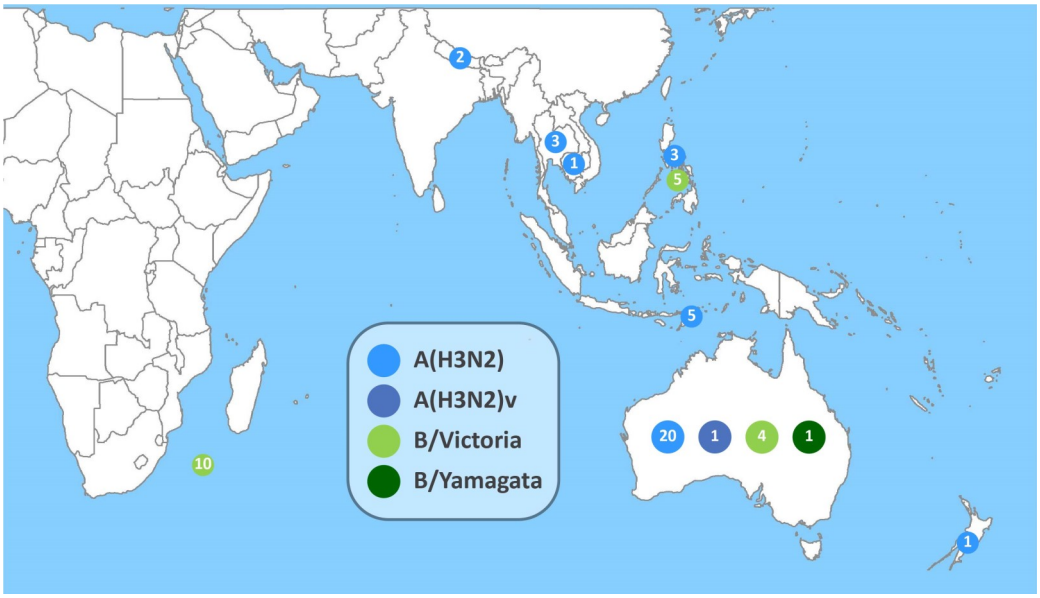
Figure 7. Number of viruses analysed by full genome sequencing 2011-2021 using Sanger sequencing and NGS techniques.



Sequencing 2021

In 2021, 222 HA, 92 NA, 82 MP and 59 NS genes from 224 human viruses received at the Centre were analysed by Sanger sequencing or NGS (Figure 6). Of these viruses, full genome sequencing was performed on 56 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 2021.



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 2021

A total of 977 gene sequences from 84 human influenza viruses were deposited with GISAID in 2021 (Table 4). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 75 influenza viruses (1 A(H1N1)pdm09 viruses, 54 A(H3N2) viruses and 20 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 2021.*

Gene / Type/ Subtype/ Lineage	HA	NA	MP	NS	PB1	PB2	PA	NP	Total
A(H1N1)pdm09	14	14	9	1	1	1	1	1	**42**
A(H3N2)	140	131	99	64	55	58	59	61	**667**
B/Victoria	65	73	22	22	20	20	22	22	**266**
B/Yamagata	1	1							**2**
Total	**220**	**219**	**130**	**87**	**76**	**79**	**82**	**84**	**977**

**Counts include all sequences submitted to GISAID during 2021, 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 2021 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

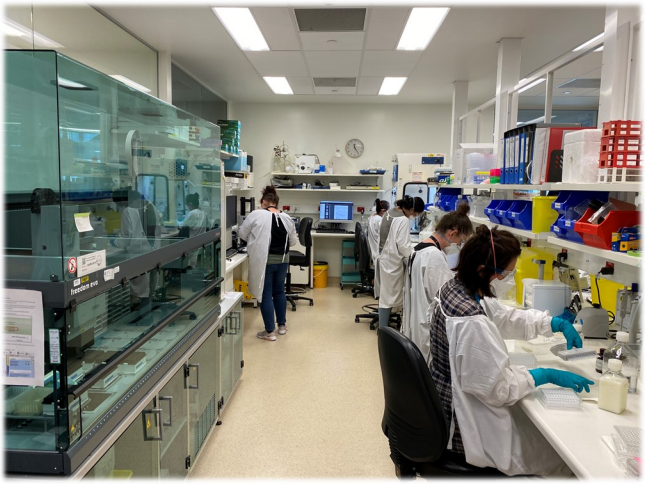
A total of 34 A(H1N1)pdm09 isolates were analysed by HI assay in 2021. A large proportion of viruses (70.59%) received from Africa later in the year were antigenically dissimilar to the cell-grown vaccine reference strain A/Victoria/2570/2019 (Figure 9, Table 5). All viruses from Australasia and South Asia displayed similar antigenic properties to the reference strain.

Haemagglutinin gene sequencing

Sequencing was performed on a total of 32 HA genes. Phylogenetic analysis showed that circulating A (H1N1)pdm09 viruses sent to the Centre during 2021 were in two main subclades. Samples from South Africa were in subclade 6B.1A.5a.1, while others were in subclade 6B.1A.5a.2, which contains the Southern Hemisphere 2021 recommended vaccine strain A/Victoria/2570/2019 (Figure 10).

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

	A(H1N1)pdm09 reference strain: A/Victoria/2570/2019	
Region	**Like**	**Low reactor (%)**
Africa	1	24 (96%)
Australasia	3	0 (0%)
South Asia	3	0 (0%)
TOTAL	**10**	**24 (70.59%)**



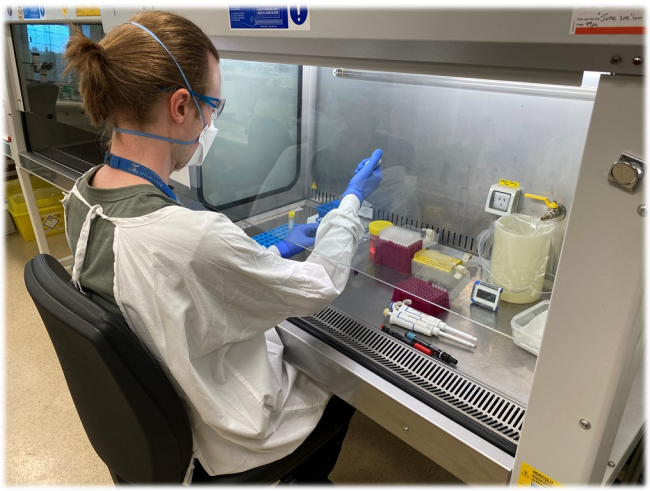
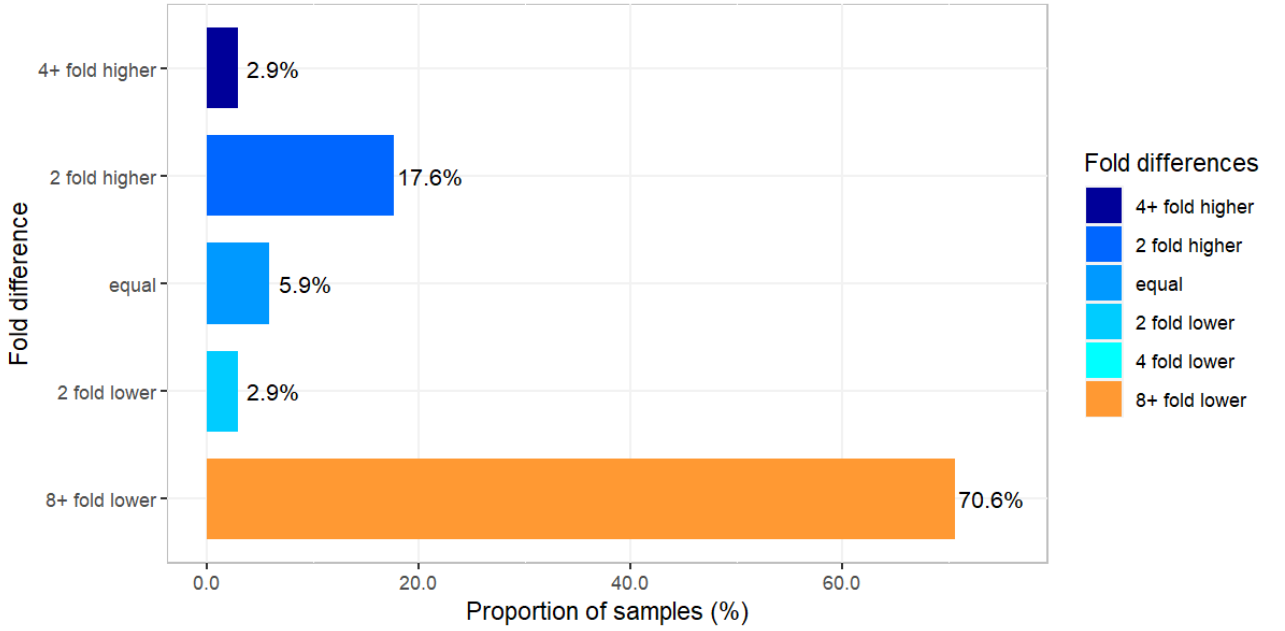
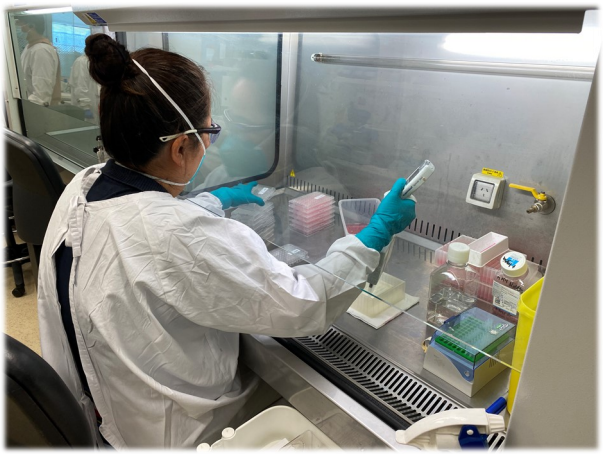
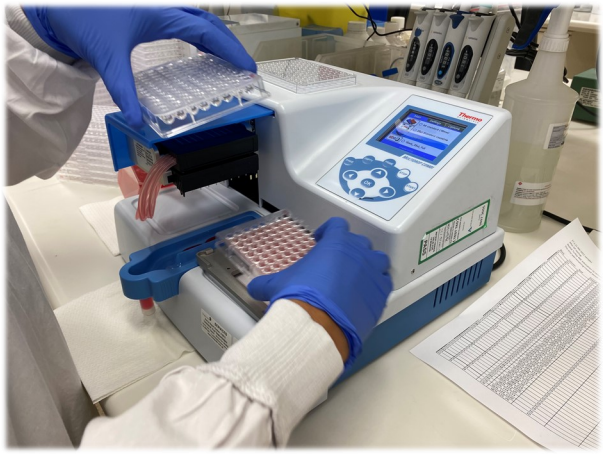


Figure 9. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/ Victoria/2570/2019 reference virus.







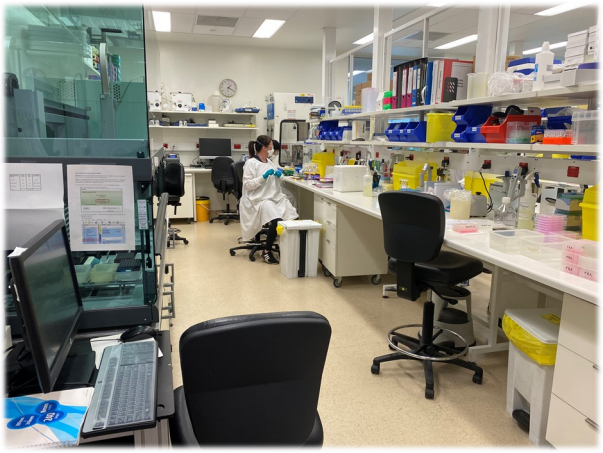
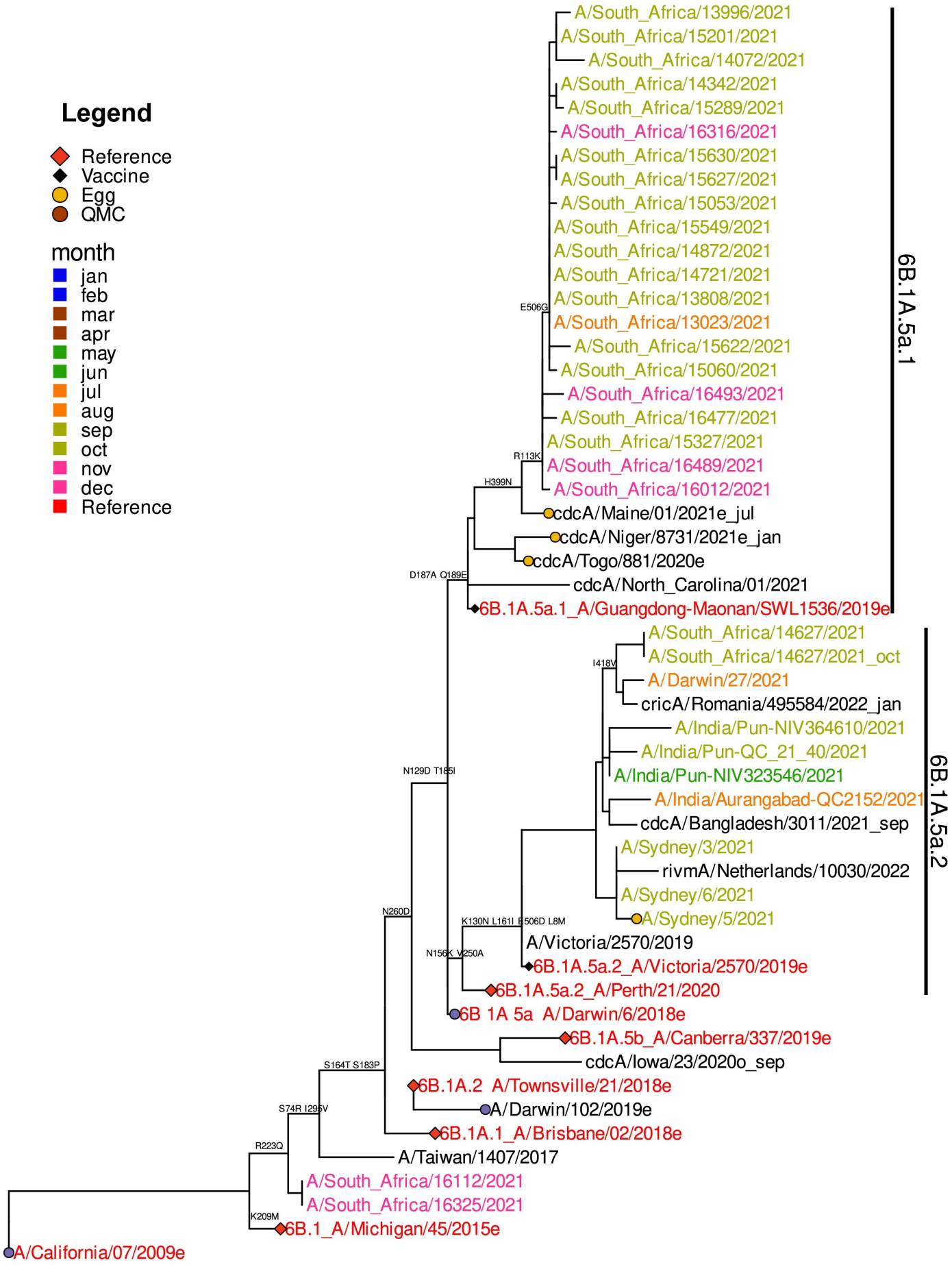


Figure 10. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2021.



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. During 2021, however, while 32 FRA-MNs were performed during 2021, no FRA-MNs were performed for A(H3N2) viruses that were unable to be analysed by HI assay.

Of 56 A(H3N2) subtype isolates analysed by HI assay compared to the cell-propagated reference strain A/Darwin/726/2019 (cell equivalent of A/Hong Kong/2671/2019) (Figure 11, Table 6), the majority were low reactors. With this in mind, the A(H3N2) component was updated to the A/Darwin/9/2021 virus for the 2022 Southern Hemisphere vaccine.

Haemagglutinin gene sequencing

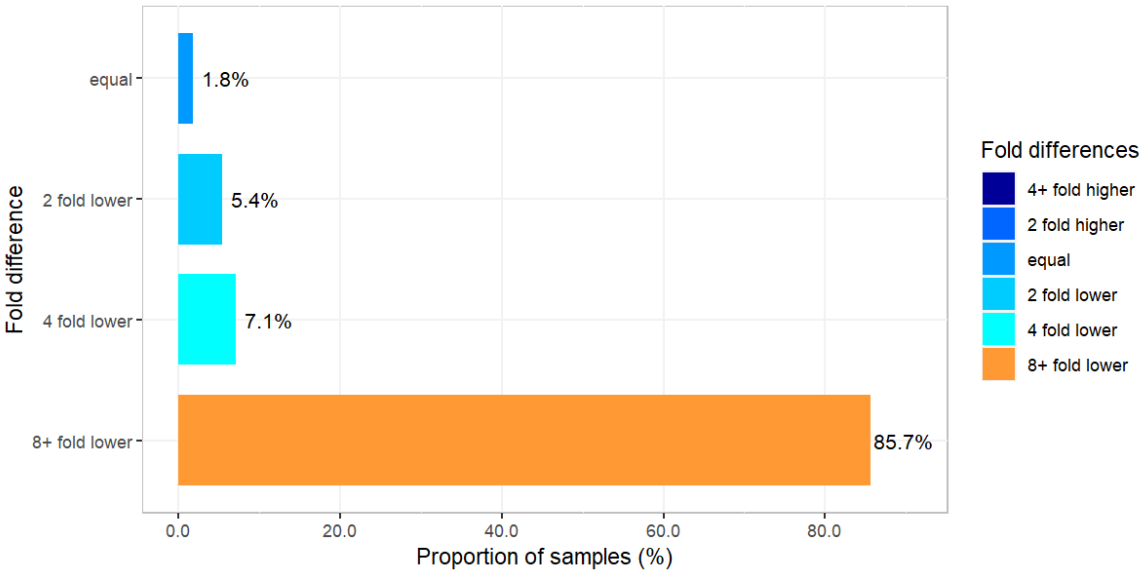
A total of 128 HA genes from A(H3N2) viruses were sequenced. Phylogenetic analysis indicate that most circulating viruses fell into clade 3C.2a1b.2a, which contains the new Southern Hemisphere 2022 recommended vaccine strain A/Darwin/9/2021 (Figure 12).

	A(H3N2) reference strain: A/Darwin/726/2019*	
Region	**Like**	**Low reactor (%)**
Africa	2	6 (75%)
Australasia	3	26 (89.66%)
South Asia		4 (100%)
South East Asia	3	12 (80%)
TOTAL	**8**	**48 (85.71%)**

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

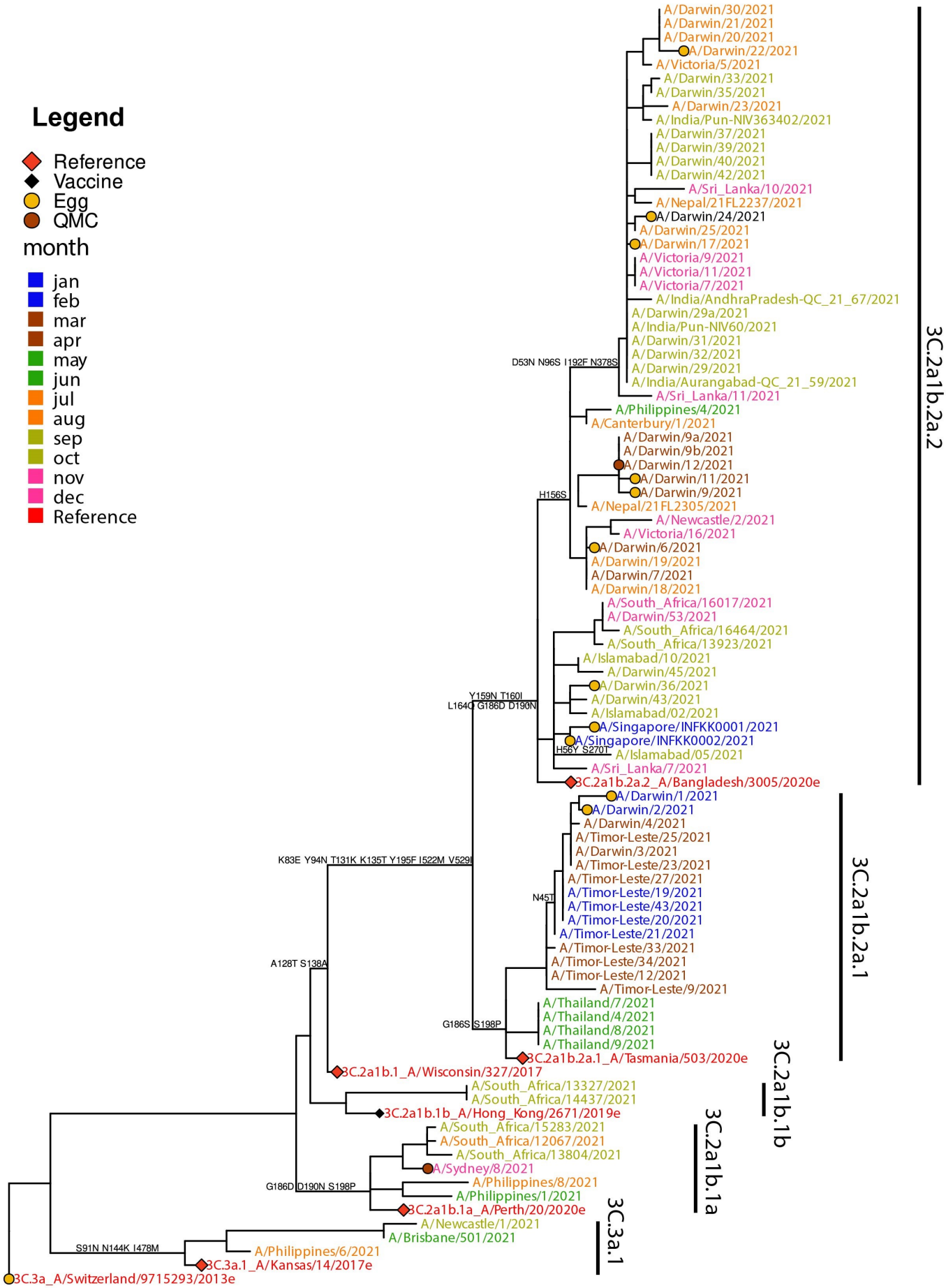
Table 6. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the cell-grown A/Darwin/726/2019 reference virus.*

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



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

Figure 12. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2021.



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 2021 vaccine strain, B/Washington/02/2019), and the B/Yamagata/16/88 lineage (represented by the 2021 vaccine strain B/Phuket/3073/2013). Until 2001, B/Victoria lineage viruses had been restricted to Asia where they tended to alternate in predominance with the B/Yamagata lineage. In 2002 the B/Victoria lineage became the predominant influenza B lineage in most parts of the world. This trend was reversed in 2003 and 2004 when the B/Yamagata lineage predominated. Since then both lineages have co-circulated, with alternating cycles of predominance every few years. During 2021 there were no B/Yamagata lineage viruses detected globally, and the Centre did not receive any samples of these viruses.

Antigenic Analysis

A total of 41 B/Victoria viruses were analysed by HI assay. Almost half of all viruses were low reactors to the cell-grown reference virus B/Washington/02/2019 (Table 7, Figure 13). With this in mind, the B/Victoria component was updated to the B/Austria/1359417/2021 virus for the 2022 Southern Hemisphere vaccine.

Haemagglutinin gene sequencing

A total of 44 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 new Southern Hemisphere 2022 recommended vaccine strain B/Austria/1359417/2021 (Figure 14).

Table 7. Antigenic characterisation of B/Victoria viruses received at the Centre during 2021 compared to the B/Washington/02/2019 reference virus.

	B/Victoria lineage reference strain: B/Washington/02/2019	
Region	**Like**	**Low reactor (%)**
Africa	6	11 (64.71%)
Australasia	3	0 (0%)
South East Asia	14	7 (33.33%)
TOTAL	**23**	**18 (43.9%)**

Figure 13. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to B/Washington/02/2019 reference virus.

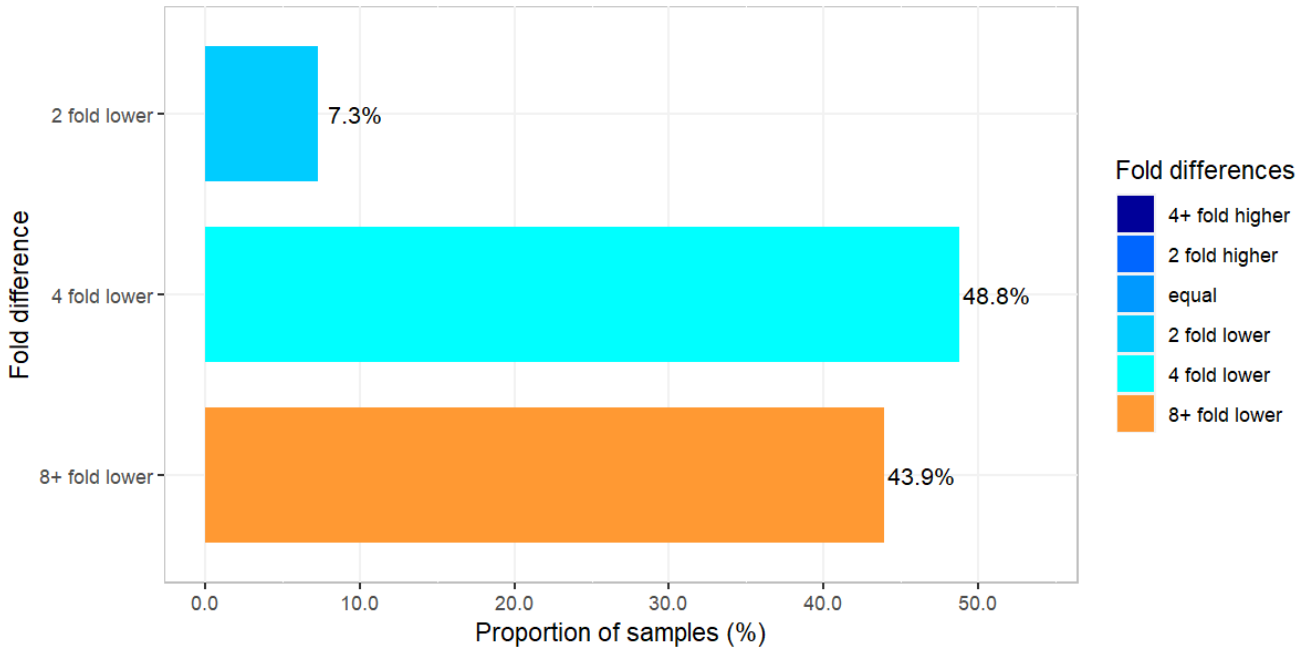
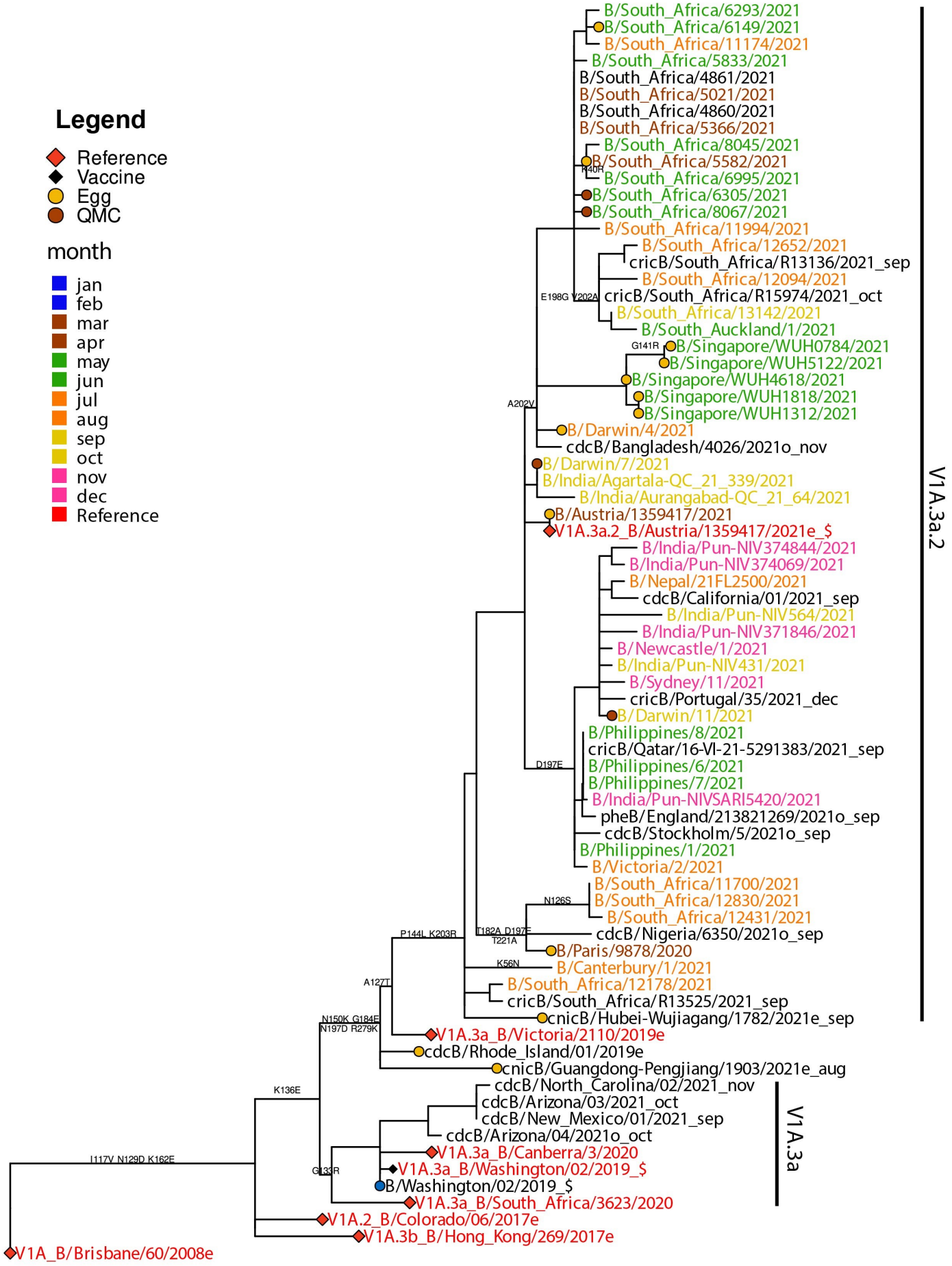


Figure 14. Phylogenetic tree of representative HA genes of B/Victoria viruses received by the Centre during 2021.



Antiviral Drug Resistance Testing

Sensitivity to Neuraminidase Inhibitors (NAIs)

Background

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

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

Table 8. Viruses received by the Centre in 2021 and tested by NAI assay, by country.

Type/ subtype/ lineage / Country	A(H1N1) pdm09	A(H3N2)	A(H3N2)v	B/Victoria	TOTAL
Australasia					
Australia	4	37	1	4	**46**
New Zealand		3		1	**4**
South East Asia					
Philippines		4		4	**8**
Singapore		3		17	**20**
Thailand		4			**4**
Timor-Leste		8			**8**
South Asia					
India	6	8			**14**
Pakistan		4			**4**
Africa					
South Africa	27	8		21	**56**
TOTAL	**37**	**79**	**1**	**47**	**164**

Antiviral resistance analyses 2021

NAI assays were used to analyse 164 viruses for reduced inhibition by the NAIs (Table 8). Normally, viruses showing highly reduced inhibition to one or more NAIs undergo further analysis to determine the presence of amino acid substitutions in the NA protein associated with the reduction of inhibition by NAIs.

Of the viruses tested, 37 were A(H1N1)pdm09 viruses, 79 were A(H3N2) viruses, 1 was a A(H3N2)v virus, and 47 were B/Victoria viruses. No virus had highly reduced inhibition by one or more of the NAIs. Normally viruses with highly reduced inhibition would undergo further analysis to determine the presence of amino acid substitutions in the NA protein that associated with the reduction of inhibition by NAIs, for example histidine to tyrosine at position 275 (H275Y) of the neuraminidase protein of A (H1N1)pdm09 viruses, which reduces inhibition by oseltamivir, or the equivalent H273Y mutation in B viruses.

Resistance to Baloxavir Marboxil

Background

Baloxavir marboxil (XofluzaTM) is an antiviral drug which has had regulatory approval for use in the treatment of influenza in Japan and the USA since 2018. 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. In 2019, this assay was implemented on a routine basis at the Centre for the first time.

A subset of viruses received at the Centre are selected as temporally and geographically representative viruses and analysed using a phenotypic focus reduction assay (FRA-BX) to detect reduced sensitivity to baloxavir.

Viral isolates showing a significant change in antiviral drug susceptibility in the FRA-BX assay are further analysed by sequencing or pyrosequencing of the PA endonuclease gene for known or novel mutations associated with reduced sensitivity to baloxavir, for example for a change in amino acid position 38 of the PA endonuclease from isoleucine to other residues such as threonine or methionine which is known to confer resistance to baloxavir.

Selected viruses are also screened for mutations in the I38 position of the PA endonuclease, either by whole genome sequencing conducted as part of the Centre's routine genetic analysis, or pyrosequencing.

Screening for baloxavir resistance in 2021

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 reporting periods to detect any known or novel mutations associated with reduced sensitivity to baloxavir. Genetic screening of 345 viruses (Table 9) by pyrosequencing or sequencing did not identify any viruses with mutations in the I38 position of the PA endonuclease.

Resistance to Adamantanes

Background

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

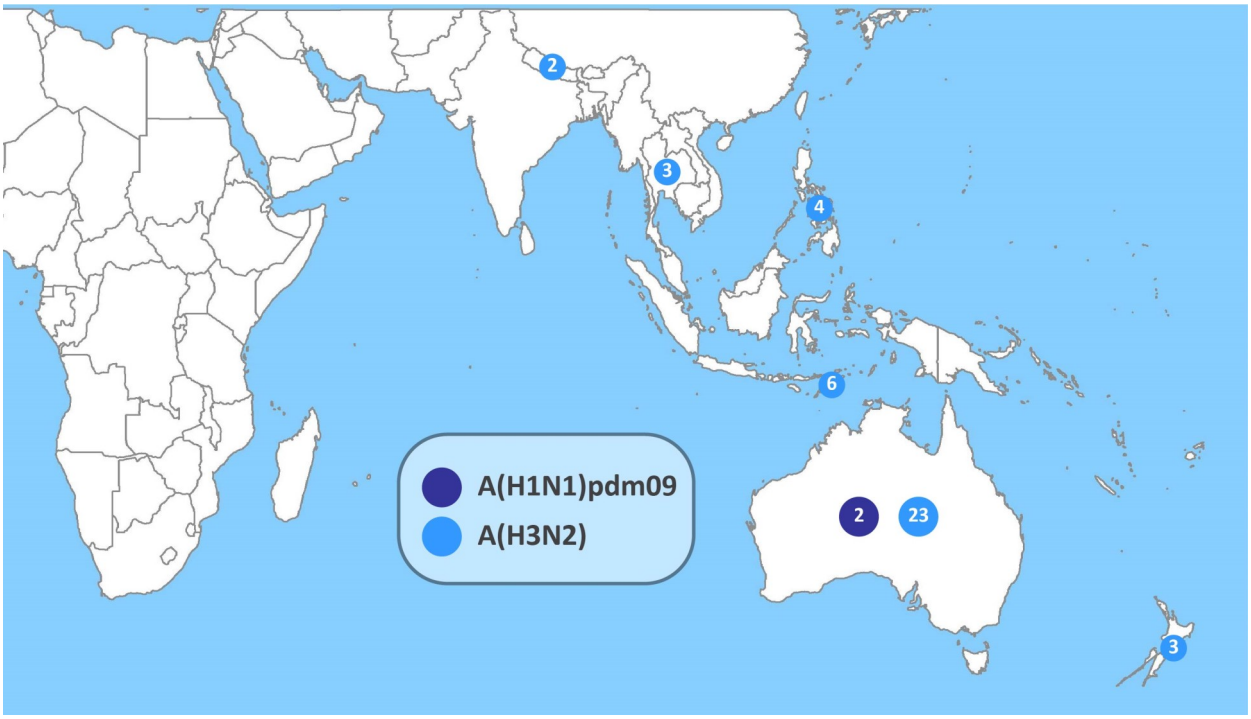
Screening for adamantane resistance in 2021

Real-time PCR or sequencing was used to analyse 43 influenza A viruses, which were representative of those submitted to the Centre during 2021 (Figure 15). All of the tested influenza A viruses carried the S31N mutation, indicating that they would be resistant to adamantanes.

Table 9. Viruses screened for reduced susceptibility to baloxavir during 2021 by pyrosequencing/sequencing.

	Pyrosequencing/sequencing					
Type/ subtype/ lineage / Country	A(H3N2)	A(H3N2)v	B/Victoria	B/Yamagata	C	TOTAL
Australasia						
Australia	22	1	6	1	3	**33**
New Zealand	1					**1**
South East Asia						
Cambodia	2					**2**
Philippines	3		5			**8**
Thailand	3					**3**
Timor-Leste	6					**6**
South Asia						
Nepal	2					**2**
Africa						
South Africa			10			**10**
TOTAL	**39**	**1**	**21**	**1**	**3**	**65**

Figure 15. Geographic spread of viruses received at the Centre during 2021 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. Regulatory requirements stipulate that viruses used to produce human vaccines are isolated and passaged only in embryonated hens' eggs or primary egg-derived cell cultures. Accordingly, the Centre undertakes primary isolation of selected viruses from clinical samples directly into eggs. These isolates are then analysed by HI assay and genetic sequencing.

Isolation of viruses in eggs in 2021

In 2021, a total of 23 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 54.8% (Tables 10 and 11).

Table 10. Virus isolation in eggs at the Centre in 2021.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	5	1	20%
A(H3N2)	25	14	56%
A(H3N2)v	1		0%
B/Victoria	9	8	88.88%
Total	**40**	**23**	**54.8%**

Table 11. Potential candidate vaccine strains isolated in eggs at the Centre in 2021.

A(H1N1)pdm09	A(H3N2)	B/Victoria
A/Sydney/5/2021	A/Bangladesh/911009/2020	B/South Africa/5582/2021
	A/Bangladesh/4002/2020	B/South Africa/6149/2021
	A/Bangladesh/3011/2020	B/Singapore/WUH0784/2021
	A/Bangladesh/3005/2020	B/Singapore/WUH1312/2021
	A/Darwin/1/2021	B/Singapore/WUH1818/2021
	A/Darwin/2/2021	B/Singapore/WUH4618/2021
	A/Darwin/6/2021	B/Singapore/WUH5122/2021
	A/Darwin/9/2021	B/Darwin/4/2021
	A/Darwin/11/2021	
	A/Singapore/INFKK0001/2021	
	A/Singapore/INFKK0002/2021	
	A/Darwin/24/2021	
	A/Darwin/22/2021	
	A/Darwin/17/2021	

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 2021, 16 candidate vaccine viruses that had been received from other WHO Collaborating Centres and laboratories were passaged in eggs at the Centre (Table 12).

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).

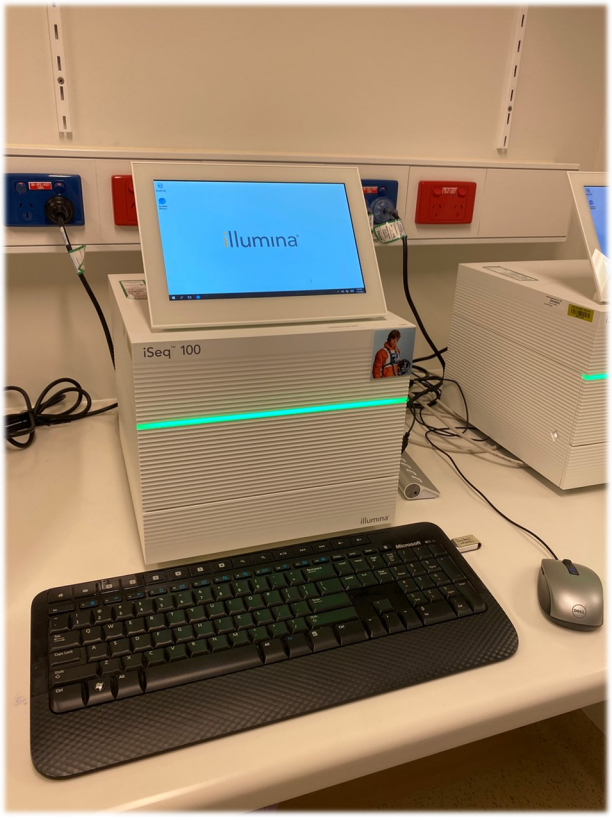


Table 12. Potential candidate vaccine viruses from other WHO Collaborating Centres isolated at the Centre during 2021.

A(H3N2)
NYMC X-355B (A/Tasmania/503/2020)
SAN-007 (A/Tasmania/503/2020)
B/Victoria
B/Yunnan-Qilin/1121/2020
CNIC-2006(B/Sichuan-Jingyang/12048/2019)
B/Paris/9878/2020
B/Austria/1359417/2021
B/Cote d'Ivoire/948/2020
B/Henan-Xigong/1118/2021
B/Hubei-Wujiagang/1299/2021
B/Henan-Shanyang/37/2021
B/Fujian-Zhangpu/34/2021
B/Gansu-Baiyin/1281/2021
CNIC-2006C (B/Sichuan-Jingyang/12048/2019)
H7N9
IDCDC-RG64A (A/Gansu/23277/2019)
H9N2
IDCDC-RG61A (A/Anhui-Lujiang/39/2019)
SJ008 RG A/Hong Kong/308/2014-A/PR/8/34[R] (6+2)

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 13).

Serum panel analyses in February 2021

In February the Centre analysed serum panels from adults (18-64 years), older adults (51-64 years), and elderly adults (>65 years) who had received the 2020-2021 northern hemisphere seasonal quadrivalent inactivated egg- or cell-based vaccine, in the USA.

A(H1N1)pdm09: The combined data from all WHO Collaborating Centres and ERLs showed that geometric mean HI titres (GMT) of anti-HA antibodies against recently circulating A(H1N1)pdm09 viruses from the 5A-187A group were well recognised by the 2020-2021 northern hemisphere vaccine virus (egg-propagated A/Guangdong-Maonan/SWL1536/2019 and cell culture propagated-A/Hawaii/70/2019). However viruses in the 5A-156K group were poorly recognized by this sera. Antisera raised against the 2021 southern hemisphere vaccine viruses (egg-propagated A/Victoria/2570/2019 and cell culture-propagated A/Wisconsin/588/2019) recognised viruses within the 5A-156K group well.

A(H3N2): In VN and HI assays, GMTs of human sera panels showed significant reduction against cell culture-propagated viruses circulating in the 3C.2a1b.1b and 3C.2a1b.2a subclades, but not against those of either 3C.2a1b.1a, 3C.2a1b.2b or the 3C.3a clade. When sera was compared to egg-propagated A/Hong Kong/2671/2019-like reference viruses, almost all serum panels showed significant reduction in GMTs against cell culture-propagated viruses from all HA subclades.

B/Victoria: Post-vaccination GMTs against recent B/Victoria/2/87 lineage viruses representing the dominant 1A.3 HA subclade, including viruses in the 1A.3-150K HA group, were not significantly reduced when compared to titres against cell culture-propagated B/Washington/02/2019. When compared to the egg-propagated B/Washington/02/2019 vaccine virus, GMTs of some serum panels against some cell culture-propagated viruses were somewhat reduced, mostly within the 1A.3-150K HA group that contains additional amino acid changes at V220M and P241Q, or at A127T, P144L and K203R.

B/Yamagata: Post vaccination GMTs against representative B/Yamagata/16/88 lineage viruses were not significantly reduced compared to the cell culture-propagated B/Phuket/3073/2013 vaccine virus.

Serum panel analyses in September 2021

In September, the Centre analysed serum panels from adults (18-64 years) and the elderly (>65 years) who had received the 2021 southern hemisphere seasonal quadrivalent inactivated egg-based vaccine in Australia. In addition, the Centre analysed a paediatric serum panel (0-36m) who had received the 2020-2021 northern hemisphere seasonal quadrivalent inactivated egg-based vaccine in the US.

A(H1N1)pdm09: In serum panels from recipients of 2020-21 northern hemisphere vaccines, when compared to titres against cell culture-propagated A/Hawaii/70/2019 (H1N1)pdm09-like 5A1 vaccine viruses, post-vaccination HI geometric mean titres (GMTs) against cell culture-propagated 5A2 viruses were significantly reduced in almost all serum panels. GMTs against most cell culture-propagated 5A1 viruses were not significantly reduced. In serum panels from recipients of SH 2021 vaccines, when compared to titres against cell culture-propagated A/Wisconsin/588/2019 (H1N1)pdm09-like 5A2 vaccine viruses, post-vaccination HI GMTs against the majority of recent 5A1 and 5A2 cell culture-propagated viruses were not significantly reduced.

A(H3N2): Human serology studies were conducted with serum panels as described above using HI and VN assays. When compared to titres against cell culture-propagated A/Hong Kong/45/2019-like vaccine viruses, post-vaccination GMTs of most serum panels were significantly reduced against the majority of cell culture-propagated 2a1 and 2a2 viruses. Reductions were less pronounced for 1a and clade 3C.3a viruses.

B/Victoria: Serum panels from recipients of both 2020-2021 northern and 2021 southern hemisphere vaccines were compared to titres against cell culture-propagated B/Washington/02/2019-like vaccine virus. Post-vaccination HI GMTs against some cell culture-propagated 3a1 viruses were significantly reduced. With the exception of sera from older adults, reductions in titres to many 3a2 viruses were observed in most other serum panels.

B/Yamagata: GMTs Post vaccination GMTs against representative B/Yamagata/16/88 lineage viruses were not significantly reduced compared to the cell culture-propagated B/Phuket/3073/2013 vaccine virus

Table 13. Representative and vaccine candidate strains used for serological analyses during 2021.

FEBRUARY	SEPTEMBER
A(H1N1)pdm09	**A(H1N1)pdm09**
A/Arkansas/08/2020 (C)	A/Brisbane/02/2018 (C, E)
A/Guangdong-Maonan/SWL1536/2019 (C,E)	A/Victoria/74/2020 (C)
A/Hawaii/70/2019 (C)	A/Victoria/1/2020 (C,E)
A/Maryland/42/2019 (C)	A/Victoria/2570/2019*^ (E)
A/Wisconsin/588/2019 (C)	A/Perth/34/2020 (C)
A(H3N2) (microneutralisation assays)	**A(H3N2) (microneutralisation assays)**
A/Bangladesh/10006/2020 (C)	A/Brunei/40/2020 (C)
A/Cambodia/e0826360/2020 (C,E)	A/Cambodia/e0403374/2020 (C)
A/Darwin/726/2019 (C)	A/Kansas/14/2017 (C,E)
A/Hong Kong/2671/2019*^ (E)	A/Perth/20/2020 (C,E)
A/Tasmania/503/2020 (C,E)	A/South Australia/34/2019 (C,E)
	A/Tasmania/503/2020 (C)
	A/Victoria/31/2020 (C)
B/Victoria	**B/Victoria**
B/Rhode Island/01/2019 (C,E)	B/Brisbane/5/2020 (C)
B/Sichuan-Jingyang/12049/2019 (C,E)	B/South Africa/1921/2020 (C,E)
B/Victoria/2110/20119 (C,E)	B/Victoria/15/2020 (C,E)
B/Washington/02/2019*^ (C,E)	B/Victoria/28/2020 (C)
	B/Washington/02/2019*^ (C,E)
B/Yamagata	**B/Yamagata**
B/Phuket/3073/2013* (C,E)	B/Phuket/3073/2013* (C,E)
	B/Victoria/27/2020 (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 OIE/FAO Network of Expertise on Animal Influenza (OFFLU), the University of Cambridge, several WHO National Influenza Centres and other relevant organisations. In 2021 WHO made the recommendations reported below.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2021-2022, eConsultation, 26 February 2021

It is recommended that quadrivalent vaccines for use in the 2021-2022 influenza season (Northern Hemisphere winter) contain the following:

Egg-based vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus^;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus^.

Cell– or recombinant-based vaccines

- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus^;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus^.

It is recommended that trivalent vaccines for use in the 2021-2022 influenza season (Northern Hemisphere winter) contain the following:

Egg-based Vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus^; and
- a B/Washington/02/2019 (B/Victoria lineage)-like virus.

Cell– or recombinant-based vaccines

- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus^; and
- a B/Washington/02/2019 (B/Victoria lineage)-like virus.

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

WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2022, Geneva, Switzerland, 13-30 September 2021

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

Egg-based vaccines

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

Cell– or recombinant-based vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Darwin/6/2021 (H3N2)-like virus^;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus^.

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

Egg-based Vaccines

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

Cell– or recombinant-based vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Darwin/6/2021 (H3N2)-like virus^; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

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

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 2021 the following candidate vaccine viruses, which were originally isolated at the Centre in either eggs or cells, were listed by WHO as being suitable for vaccine use following the indicated meeting.

Type/Subtype/ Lineage	Egg-derived CVVs	Cell-derived CVVs
A(H1N1)pdm09	A/Victoria/2570/2019 A/Victoria/3/2020 A/Victoria/1/2020	
A(H3N2)	A/Cambodia/e0826360/2020* A/Tasmania/503/2020* A/Darwin/9/2021* A/Darwin/6/2021*	A/Cambodia/e0826360/2020* A/Tasmania/503/2020* A/Darwin/11/2021*
B/Victoria	B/Victoria/705/2018 B/Brisbane/35/2018	B/Darwin/7/2019 B/Singapore/WUH4618/2021*
B/Yamagata	B/Brisbane/9/2014 B/Phuket/3073/2013	B/Brisbane/9/2014 B/Singapore/INFKK-16-0569/2016 B/Singapore/INFKK-16-0610/2016

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

Australian Seasonal Influenza Vaccine Recommendation

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

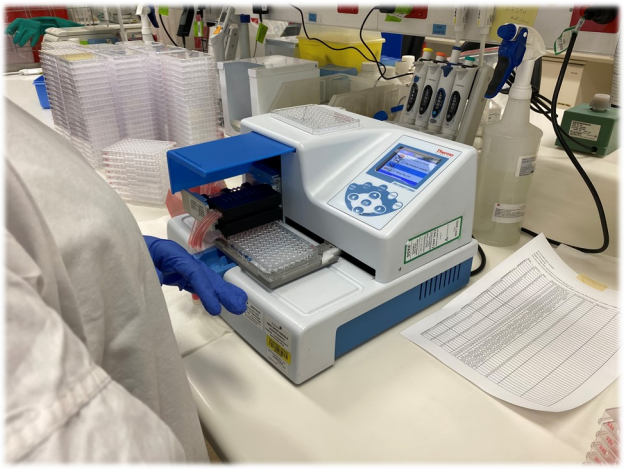
The AIVC met on 6 October 2021 and recommended that the following viruses be used for influenza vaccines in the 2022 Southern Hemisphere influenza season:

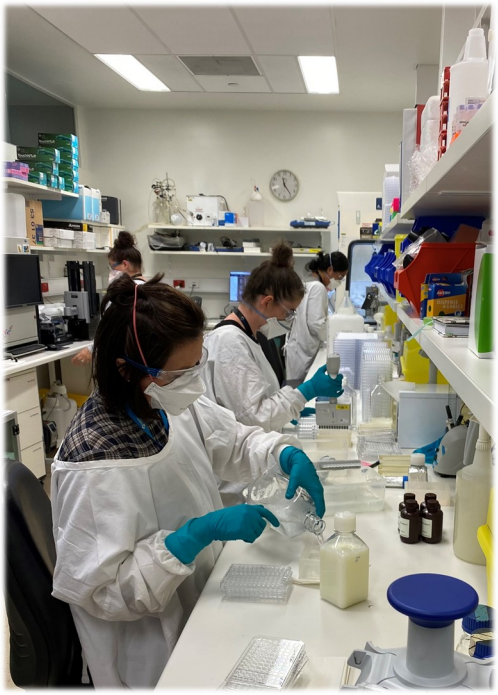
Egg-based quadrivalent vaccines:

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

Egg-based trivalent vaccines:

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

Due to ongoing travel restrictions imposed by the COVID-19 pandemic, many of our usual training programs were either postponed or moved to a virtual forum. Unfortunately the Centre was unable to host any visitors for on-site training, but we hope that we may be able to have more visitors in 2022.

Training Programs and Visits to Regional Laboratories

Patrick Reading, **Jean Moselen** and **Miku Kuba** have been working with the Secretariat of the Pacific Community (SPC) and the Department of Foreign Affairs and Trade (DFAT) Australia to advise on the implementation of PCR testing in Pacific Islands for molecular diagnosis of respiratory virus infections. This work has involved:

1. Guidance and advice on building new facilities or renovation of existing facilities,
2. Advice of all equipment and consumables to purchase for a functional PCR laboratory,
3. Regular online meetings for advice and planning to Pacific Island Countries,
4. Development of training materials for PCR, including training videos, lectures, SOPs and other guidance documents,
5. Advice and evaluation regarding the usefulness of automated platforms in the Pacific, and
6. Delivery of remote training to Pacific Island Countries that are setting up PCR for the first time.

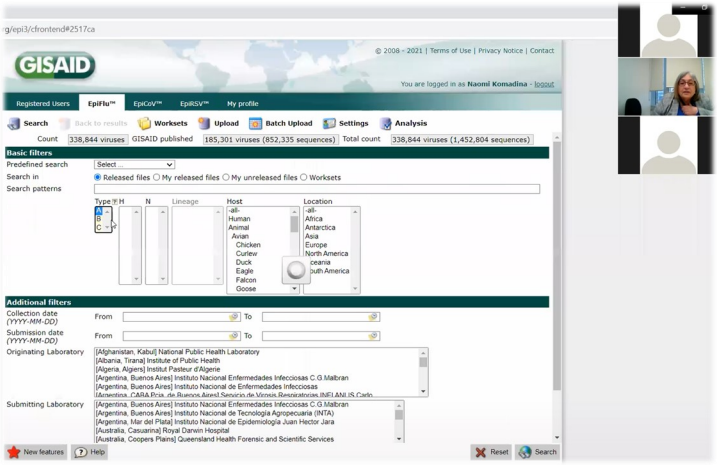
Countries receiving support, advice and training include Vanuatu, Cook Islands, Solomon Islands, Tonga, Tuvalu, Samoa and Kiribati. Since July 2021, our team have supported and completed training with Vanuatu and Kiribati and these countries have now commenced PCR testing for the first time. Arrangements are also in place with DFAT for an Australian scientist to be seconded to Tuvalu for 6 months (Feb – July 2022) with the aim of working with our team to enhance laboratory capacity in this island nation.

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

Training Programs and Visits to Regional Laboratories (continued)

Patrick Reading continues 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

Naomi Komadina, **Yi-Mo Deng**, and **Ammar Aziz** were trainers for a Bioinformatics workshop with research collaborators based in Mozambique. Training included accessing RSV and influenza data from GISAID, data processing, and analysis, as well as using Nextstrain and FluSurver. The workshop was attended by 12 participants and held across April-May 2021.



Ammar Aziz trained attendees for an Australia's Academic and Research Network (AARNET) Bioinformatics workshop on using ggtree to create publication quality phylogenetic trees. The workshop was held 7 June 2021.

Bonus Centre-based training

An internal training workshop on NGS sequencing using the Illumina iSeq™ 100, as well as subsequent data processing and analysis, was held 11-14 May 2021. The workshop was attended by up to 15 people from the Centre, and was taught by **Jean Moselen**, **Pina Iannello**, **Hilda Lau**, **Xiaomin Dong**, **Natalie Spirason**, **Ammar Aziz** and **Yi-Mo Deng**.

Research

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

Antivirals and Viral Fitness

Centre staff and students

Mariana Baz, Sook Kwan Leah Brown, Paulina Koszalka, Edin Mifsud (until July), Harry Stannard, Nikita Deshpande

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 which have emerged during in vitro passages, or clinical trials. Selected viruses are evaluated for their transmissibility capacity in ferrets. This information provides insights into the likelihood that such viruses could spread amongst the community.

Collaborators

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

Highlights and developments 2021

As an extension from the influenza antiviral routine surveillance work performed at the Centre, a study to investigate the phenotypic effect of 11 neuraminidase (NA) mutations linked to reduced inhibition (RI) or highly reduced inhibition (HRI) in influenza B viruses was performed using reverse genetics (RG) techniques. All 11 mutations were introduced into the NA gene of B/Yamanashi/166/98 (B Yamagata/16/88, (B Yamagata lineage)) or B/Brisbane/27/2016 (B/Victoria/2/87 (B Victoria lineage)) RG viruses and the phenotypic effects of these RG viruses were analysed by an in vitro NA inhibition (NAI) assay. Overall, this study confirmed that all 11 NA mutations caused a reduction in susceptibility of influenza B viruses to one or more NA inhibitors and also identified the potential impact of these selected mutations on the clinical performance of NA inhibitors when used to treat influenza B infection in humans. This work was submitted as a 'research article' to Antiviral Research and is under review.

The centre received clinical samples from two patients infected with influenza A(H1N1)pdm09 virus, that were enrolled in a clinical trial and given a combination of neuraminidase inhibitor (oseltamivir) and a polymerase inhibitor (baloxavir marboxil; BXM), developed clinical resistance to both drugs. These viruses developed dual-mutations in the NA gene (H275Y) and the PA gene (I38T), changes known to cause resistance to oseltamivir and BXM, respectively. In collaboration with F. Hoffmann-La Roche Ltd (Basel, Switzerland), we investigated the viral fitness of a purified clinical isolate with this dual-mutation and we compared it to antiviral sensitive isolate (WT) in an in vitro model. In addition, we studied the fitness of the mutant and WT viruses in a ferret challenge model available in our lab. A publication is currently under preparation.

The group has been involved with a cooperative research and development agreement (CRADA) with Romark Laboratories since 2016. This project aims to investigate the in vitro and in vivo aspects of the repurposed drug nitazoxanide for its effectiveness against human and potentially pandemic avian influenza viruses. Harry Stannard and Edin Mifsud were involved in a follow up study aiming to investigate if the combination of nitazoxanide and oseltamivir would reduce disease severity associated with high pathogenicity H5N1 influenza viruses. In collaboration with ACDP, CSIRO (Geelong) and Romark L.C. (Tampa, USA) we investigated the additional benefit of nitazoxanide and oseltamivir combination therapy compared to oseltamivir monotherapy and placebo treated ferrets at reducing clinical symptoms, viral shedding and dissemination to various tissues.

Antivirals and Viral Fitness (continued)

Paulina Koszalka continued her PhD project assessing influenza virus resistance against BXM. In addition to analysis of ferret experiments utilising antiviral treatment of influenza with BXM and oseltamivir, she established methods to assess in vitro drug synergy and optimised next generation sequencing techniques for influenza polymerase genes. She wrote and submitted a review article on combination therapies for influenza and is in the process of writing a research manuscript on BXM effectiveness of resistant influenza strains in the ferret model. As part of her thesis studies Paulina also collaborated with Professor James McCaw and Dr. Pengxing Cao to establish mathematical models to study the application of antiviral treatment with BXM and oseltamivir alone, and in combination as a strategy for pandemic influenza.

Nikita Deshpande has been involved in the generation of a RG system for B/Sydney/4/2020 (B/Victoria lineage), an Influenza B contemporary virus strain which can cause sporadic human infections. She has tested this system in rescue experiments and has successfully sequenced the rescued virus. Further studies will involve establishing a ferret model to study the wild type, and subsequently the reverse engineered virus' fitness. This system will allow easier manipulation of genes and testing of various antiviral drugs against new or existing mutations. Nikita has also been involved in 3 projects in collaboration with the University of Republic of Uruguay:

1. Immune response, endothelial biomarkers and severity of respiratory failure in COVID -19 patients;
2. Pre-vaccination seroprevalence of COVID-19 among healthcare personnel attending patients with respiratory failure in three institutions in Montevideo, Uruguay;
3. In vitro fitness of different SARS-CoV-2 isolated in Uruguay before the emergence of Delta variant. These studies are ongoing.

Avian influenza

Centre staff

Michelle Wille

Research overview

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

Collaborators

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

Highlights and developments 2021

In 2021, we collected and screened 392 swab samples from wild Anseriformes (ducks) and Charadriiformes (shorebirds and terns) in Victoria, Tasmania and Western Australia, with 8 influenza A virus detections. None of the viruses detected contained markers that would indicate they were highly pathogenic. Furthermore, to better understand influenza A infection burden we have collected and screened 392 paired serum samples for general anti-influenza A antibodies using a commercial NP-ELISA.

Starting at the end of 2019 we embarked on a large collaborative project with key collaborators at the ACDP, Deakin University, University of Sydney and state laboratories across Australia to sequence and analyse all AIV positive samples that have been collected since 2006. This project is critical understanding the ecology and evolution of avian influenza A in Australia and will bring more than 400 virus sequences into the public domain upon completion. This project is being funded by Wildlife Health Australia through funds provided by the Department of Agriculture and was completed in February 2021, with a preprint available on bioRxiv.

With the increased in intensity of HPAI outbreaks in Europe, we contributed to a technical report and risk assessment developed by the National Avian Influenza Wild Bird Program (Wildlife Health Australia) available at https://wildlifehealthaustralia.com.au/AboutUs/News.aspx#GlobalHPAI

Table R1. Samples collected from wild birds in 2021

Avian order	Serum samples		Swab samples	
	Samples collected	*Influenza-positive samples*	*Samples collected*	*Influenza-positive samples*
Anseriformes	128	4	128	9
Charadriiformes	264	4	264	11

Epidemiology

Centre staff

Sheena Sullivan, Vivian Leung, Genevieve O'Neill, Arseniy Khvorov (University of Melbourne, UoM), Leslie Dowson (UoM), Ellie Robinson, (UoM), Chris Bailie (Australian National University)

Research overview

We are interested in using surveillance data to examine fluctuations in influenza activity and vaccine effectiveness across populations and seasons. We have been working with influenza sentinel surveillance systems operating in Australia to estimate influenza vaccine effectiveness in the community, and conduct various simulation studies to understand the validity of vaccine effectiveness estimates for influenza vaccine strain selection.

We are particularly interested in understanding observations that vaccine effectiveness appears to be attenuated among people who are repeatedly vaccinated. To that end we are involved in several sero-epidemiology studies to understand the immunological mechanisms underlying these observations.

Collaborators

VE studies: Monique Chilver (University of Adelaide); James Fielding (VIDRL); Benjamin Cowling Huiying Chua (University of Hong Kong)

Burden of disease: Annette Regan (University of San Francisco), Onyebuchi Arah (University of California, Los Angeles)

Serological studies: Benjamin Teh (Peter Macallum Cancer Centre); James Fielding (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); Mark Thompson, Min Levine (US CDC); Scott Hensley (University of Pennsylvania).

Highlights and developments 2021

We continued to work with the Australian Sentinel Practices Research Network (ASPREN), the Victorian General Practice Sentinel Surveillance (VicSPIN) network, and the Influenza Complications Alert Network (FluCAN), but influenza activity was extremely low in 2021.

Drs 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. The study is managed by Leslie Dowson. A systematic review was conducted for this study (Ellie Robinson) and submitted for consideration by the SAGE Working Group on Influenza Vaccines for updating global influenza vaccination recommendations.

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).

Dr Sullivan continues working with colleagues in the US (Annette Regan and Onyebuchi Arah) to understand the burden of influenza and COVID-19 during pregnancy, with several manuscripts published as a result of this work (1,2).

The group continued its involvement in the COVID-19 response, providing epidemiological support at the Victorian Department of Health (Sheena Sullivan) and the Royal Melbourne Hospital (Vivian Leung, Chris Bailie). This work led to several published manuscripts (3,4,5,6). In addition, the group is working with the Victorian Department of Health to measure the impact of influenza vaccination on influenza-related emergency department presentations, hospitalisations and deaths in Victoria during 2016–2019 (Genevieve O'Neill).

1. Regan AK. et. al. 2022. *Paediatric and Perinatal Epidemiology*.
2. Regan AK. et. al. 2021. *J Infect Dis*.
3. Todd IMF. et. al. 2021. *Int J Epidemiol.*
4. Victorian Department of Health COVID-19 writing group. 2021. *Lancet Reg Health West Pac*.
5. Bailie CR. et. al. 2021. *Epidemiol Infect*.
6. Bailie CR. et. al. 2022. *Infect Dis Health*.

Immunity to Respiratory Viruses

Centre staff and student

Annette Fox, Louise Carolan, Ryan (Yeu-Yang) Tseng, Sheena Sullivan, Vivian Leung (until Dec), Maria Auladell Bernat (until March), Stephany Sanchez, Anastasia Jessica Hadiprodjo

Research overview

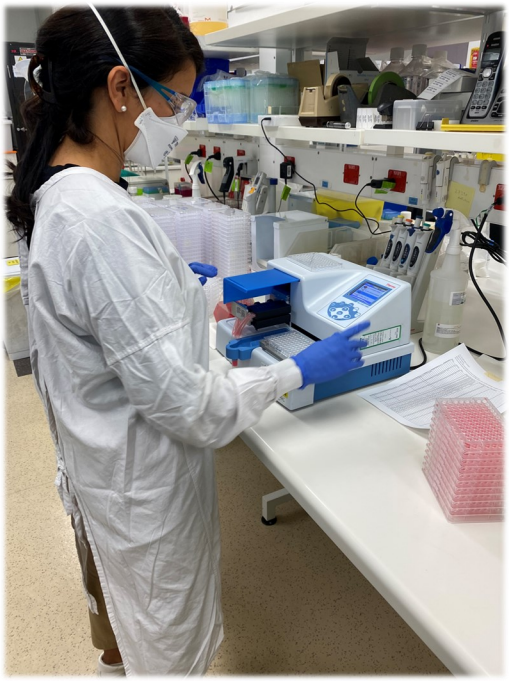
A key goal of our work is to identify strategies to improve the immunogenicity and, in turn, effectiveness of seasonal influenza vaccines. It is challenging to induce long-term immunity against highly mutable viruses such as influenza, not only due to immune escape, but also to a propensity for antibody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

Collaborators

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

Highlights and developments 2021

During 2021 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). Despite continued complications due to COVID-19 restrictions, 1119 of a target of 1500 participants were recruited from 6 hospitals across Australia. 3285 sera, including pre-vaccination, post-vaccination and post-season time-points were tested in HI against 8 viruses representing egg and cell-grown equivalents of the A(H1N1), A(H3N2), B/Yamagata and B/Victoria components of the vaccine administered in 2020. Preliminary analysis indicates that similar to 2020 only around 1/3 of participants seroconverted against the A(H3N2) component, and that the proportion converting was substantially higher among those with 1 or fewer prior vaccinations than among those vaccinated three or more times during the preceding 5 years.



Immunity to Respiratory Viruses (continued)

Sera spanning 2020 (n = 579) was also tested for antibodies against SARS-CoV-2 spike protein, with only one case of asymptomatic COVID-19 infection detected in this period. Blood was also collected from 469 participants to assess responses to COVID-19 vaccination during 2021, and is currently being collected to assess responses to breakthrough infections with the Omicron variant.

A series of assays have been developed to assess cellular and humoral responses to SARS-CoV-2 infection or vaccination. These include a 15 fluorochrome panel incorporating recombinant protein probes representing the spike proteins of a range of coronaviruses; ELISPOT to detect B cells making IgG or IgA reactive with a range of coronavirus proteins; and ELISA to detect serum IgG, IgA or IgM reactive with a range of coronavirus proteins (Figure R1a,c). Results of analysis via flow cytometry, ELISPOT and ELISA correlate well (Figure R1b).

Moreover, the assays detect increased frequencies of SARS-CoV-2 reactive B cells and antibodies among confirmed COVID-19 cases, from an exposed cruise ship cohort, compared to controls (Figure R1c). These methods will be used to determine the frequency, isotype and SARS-CoV-2 variant cross-reactivity of B cells and antibodies among cohort participants.

During 2021 we completed sample collection for an early life influenza imprinting study in collaboration with Centre Director Prof Kanta Subbarao. Blood samples were collected and processed to store peripheral blood mononuclear cells (PBMCs) and plasma. The study included 19 children aged 0.5 to 4.5 years, of whom two had no documented prior exposure to influenza, eight had prior influenza A infection, and eight had prior influenza vaccination. Sera has been titrated against a panel of 11 A(H3N2) viruses that are similar to circulating or vaccine strains that children may have had exposure to. Preliminary results suggest vaccine responses are greater among children who had prior exposure through infection compared to vaccination (Figure R2). Sera will also be titrated against A(H1N1) viruses.

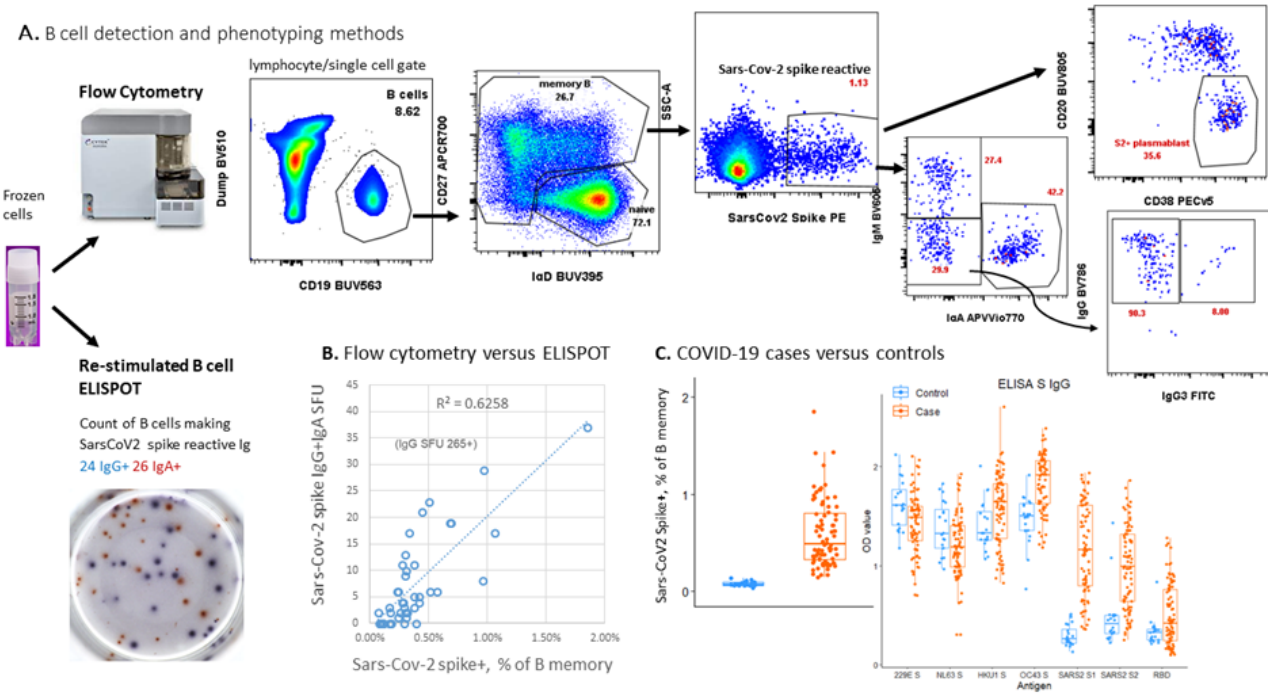


Figure R1. *Development and validation of methods to quantitate and characterize SARS-Cov-2 reactive B cells and antibodies.*

Immunity to Respiratory Viruses (continued)

Studies to dissect antibody responses to primary A(H3N2) virus infection in ferrets were also conducted in 2021. The WHOCCRRI uses primary infection ferret sera to quantitate antigenic difference between viruses as a key part of the process of selecting new vaccine candidate strains. Here, we investigated:

1) Why titres of sera raised against recent egg-grown A(H3N2) viruses are low against their cell-grown equivalents; and

2) Whether ferret antisera can detect change in antigenic sites other than immune-dominant site B

Much of the work was done by Jessica Hadiprodjo as part of her Honours project using reverse genetics viruses made by Ryan Tseng. The studies confirmed that antibody titres were higher against egg-grown compared to cell-grown A/Hong Kong/4801/2014 A(H3N2) virus, and that this was not due to infectious dose or virus growth in ferrets (data not shown).

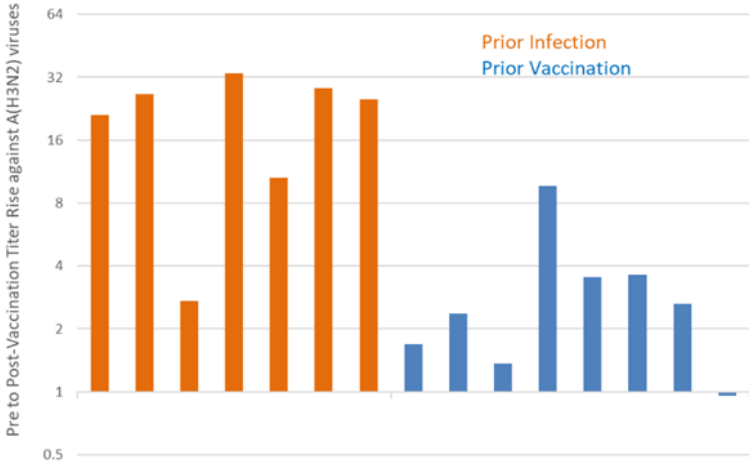
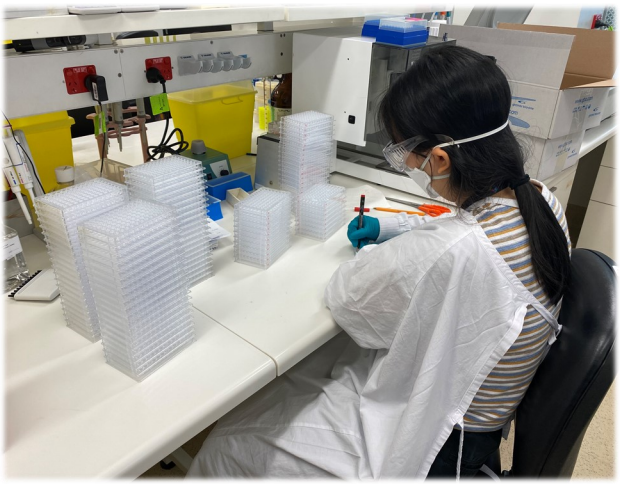


Figure R2. *Vaccine induced titre rise against A(H3N2) viruses among young children in the imprinting study who were first exposed to influenza A by infection versus vaccination.*



Published studies investigating A(H3N2) viruses circulating during 2011 or earlier indicate that a L194P substitution in HA, which arose when viruses were passaged in eggs, caused antigenic difference between egg and cell viruses, whereas an alternate G186V egg-adaptation had little effect. We generated reverse genetics (RG) viruses to examine the effect of these substitutions on A/Hong Kong/4801/2014 (HK14), which also adapts to eggs by substituting T160K (Figure R3a), removing an important glycosylation site near the sialic acid receptor binding pocket of HA (Figure R3b). Antisera raised against RG virus containing wild-type HA (RG-HK14e) had 6.5 fold lower titres against an virus containing cell-grown HA (RG-HK14c, Figure R3d). Virus that was engineered to adapt via G186V rather than L194P (RG-HK14e G186V P194L) had 21-fold lower titres against RG-HK14c. In contrast, virus engineered to adapt via L194P while retaining 160T had high titres against RG-HK14c.

These results indicate that the T160K substitution caused substantial antigenic difference between HK14 grown in eggs and cells, and that substitution of L194P was preferable to G186V, contrasting with earlier viruses. Viruses engineered to disrupt only antigenic site B or all but antigenic site B were used to confirm that antibodies in ferret sera are generally highly focused on antigenic site B.

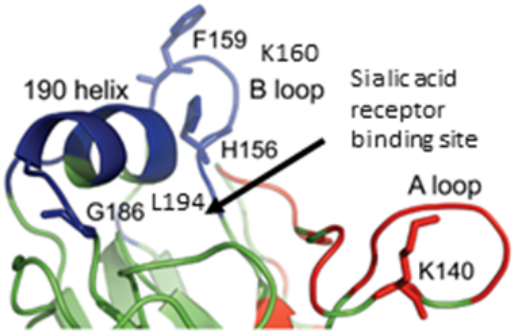
Immunity to Respiratory Viruses (continued)

A

Abbreviated Virus Name	Cell to egg substitution		
	186	194	160
RG-HK14e*	G-G	**L-P**	**T-K**
RG-HK14e G186V P194L	**G-V**	L-L	**T-K**
RG-HK14e K160T	G-G	**L-P**	T-T
RG-HK14e G186V P194L K160T	**G-V**	L-L	T-T

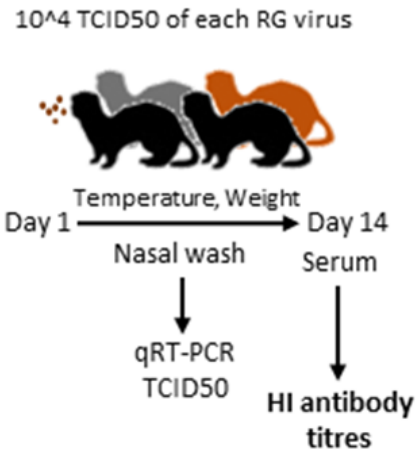
- *RG: reverse genetics virus containing HA of HK14e*
- *HK14e: A/Hong Hong/4801/2014egg*

B



Popova et al. 2012

C



D

Test Virus	Antisera Virus, titre (fold difference from homologous)			
	RG-HK14e	RG-HK14e G186V P194L	RG-HK14e K160T	RG-HK14e G186V P194L K160T
RG-HK14e	**3040**	331 (23)	1808 (0.9)	393 (4.0)
RG-HK14e G186V P194L	3616 (0.8)	**7499**	3609 (0.4)	3044 (0.5)
RG-HK14e K160T	796 (3.8)	90 (83)	**1612**	640 (2.5)
RG-HK14e G186V P194L K160T		*1029 (7.3)*	*1169 (1.4)*	**1586**
RG-HK14c	469 (6.5)	360 (21)	3350 (0.5)	1810 (0.9)
RG-HK14e P194L	5113 (0.6)	7231 (1.0)	5275 (0.3)	1810 (0.9)

Figure R3. *Experiments to determine which egg-adaptive substitutions in A/Hong Kong/4801/2014 (H3N2) account for antigenic difference between egg-grown and cell-grown virus. (A) Table listing the reverse genetics (RG) viruses containing wild-type or mutated HA of A/Hong Kong/4801/2014 egg and seven other gene segments of A/ Puerto Rico/8/34 (H1N1). Substitutions were introduced at three positions associated with adaption to egg-growth. (B) Molecular structure of the head a HA monomer showing the sialic acid receptor binding site and positions that were mutated. (C) Schematic of experiments to assess RG virus growth and antibodies induced in ferrets. (D) Geometric mean titres of antisera raised against each of the four RG viruses against the homologous/inoculating virus (bold), other RG viruses, or RG virus containing HA of cell-grown HK14 (red).*

Early Recognition and Response to Influenza Infection

Centre staff

Patrick Reading, James Barnes

Research overview

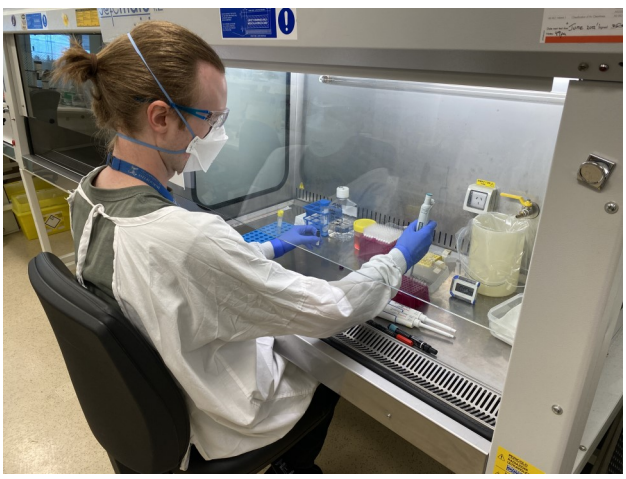
Our research, which is undertaken at the Centre and at the University of Melbourne, investigates how the body first recognises and responds to infections with influenza and other respiratory viruses. We employ in vitro studies using human proteins and cells, as wells as in vivo studies using mouse and 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

Paul Young (University of Queensland); Nathan Bartlett (University of Newcastle); Kirsten Spann (Queensland University of Technology); Lara Herrero (Griffith University); Daniel Steinfort (Royal Melbourne Hospital); Andrew Brooks, Justine Mintern, Stephen Kent, David Jackson, Georgia Deliyannis, Carol Hartley and Joanne Devlin (The University of Melbourne)



Highlights and developments 2021

During 2021, our research 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 are now using 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). In addition, we have been working on collaborative projects to investigate and assess the use of novel recombinant vaccines to provide broad spectrum protection against influenza and SARS-CoV-2. An important aspect of this has been to work towards establishing laboratory assays to measure antibody-dependent cell mediated cytotoxicity (ADCC) responses in human, mouse and ferret serum following vaccination and/or virus infection.

In 2021 our research group was funded by the NHMRC (via Project, Ideas and Development grants) and the Coalition of Epidemic Preparedness Innovations (CEPI) (2019-2021, 'Rapid response pipeline for stabilised subunit vaccines'). Overall, our research contributed to six peer-reviewed publications during 2021, in journals such as Clinical and Translational Immunology, mBio, The Journal of Virology and The Journal of Clinical Investigation. Additional publications relating to laboratory capacity building were published in Microbiology Australia and the Journal of Clinical Virology. Dr Reading led a research group at the University of Melbourne consisting of three post-doctoral scientists, four Ph.D. students and one Master of Biomedical Science student. Dr Reading also supervises James Barnes, a research assistant based at the Centre, who has been investigating ADCC responses to vaccination and infection, as well as assessing novel influenza vaccines in ferret models of infection.

Evolution, Modelling and Serological Responses to Influenza Viruses

Centre staff

Ian Barr, Malet Aban, Yi-Mo Deng, Sheena Sullivan, Annette Fox, Sam Wilks (honorary)

Research overview

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

The project titled, '*Advanced vaccination and immunity management strategies to protect from influenza virus infection*', funded by the US Department of Health and Human Services via the Biomedical Advanced Research and Development Authority (BARDA) and CEIRS (Centers of Excellence for Influenza Research and Surveillance) group based at the Mount Sinai Hospital (New York City NY, USA), was extended to September 2021. This project aims to identify future influenza viruses in advance of them becoming widespread. This would enable the generation of vaccine candidate viruses to provide enhanced protection, in contrast to the current system whereby vaccine viruses are chosen some 9-10 months in advance of the relevant influenza season. Work has continued using reverse engineered HA mutant influenza viruses with changes introduced by site directed mutagenesis and antibody escape mutants in order to produce viruses that may resemble future circulating influenza viruses. Extensive antigenic testing (using both HI and virus microneutralisation assays) of mutated viruses using a combination of ferret and human antisera has continued.

In 2018 the Centre, with Dan Layton and Andrew Bean at AAHL, CSIRO, obtained a 3-year post-doctoral position grant from the CSIRO ResearchPlus Program. The project investigates the differential responses in vitro between avian influenza viruses that cause severe disease and mild disease in humans. A molecular approach has been taken to allow a genome-wide scan of cellular genes to identify those that may account for these differences. The project was on hold for 2020 due to Dr Dai taking a year off for maternity leave and is being wrapped up in early 2022. We are awaiting genome sequencing data from the CRISPR/Cas9 screening of the avian fibroblast cell line DF-1 infected with high and low pathogenic avian influenza viruses.

We are working with Marios Koutsakos from the Department of Microbiology and Immunology, the University of Melbourne on his NHRMC Investigator grant project '*Antigenic evolution of influenza B viruses and antibody landscapes*'.

This project aims to understand the antigenic evolution of the influenza B HA protein across influenza B lineages (ancestral, B/Yamagata, B/Victoria) using antigenic cartography and virus sequencing. Antibody landscapes against IBV strains from 1940-2019 will be constructed from individuals aged 1-70 years and cross-sectionally sampled between 1992-2020.

The team has also been working with the infectious diseases team at the Peter MacCallum Cancer Centre (Ben Teh) on a randomised trial of influenza vaccination strategies for patients with haematological malignancy. The trial tested the use of high dose versus standard dose influenza vaccine for patients receiving autologous hematopoietic stem cell transplantation (autoHCT), who require revaccination after treatment. The trial found that patients responded well to vaccination as early as 2-months post-vaccination and responses were similar for high and standard dose regimens. A larger trial is planned for 2022.

Highlights and developments 2021

A manuscript from the BARDA supported project entitled, *'Role of influenza viral replicative fitness in the selection of antigenic escape variants that become dominant in human populations'* has been prepared and submitted for publication. Two other publications are being prepared currently.

A manuscript describing the result of the two-dose trial at PMCC was published in the journal Clinical Infectious Diseases (1).

1. Teh BW et. al. 2021. *Clin Infect Dis*.

Collaborators

Derek Smith and Sam Wilks (Cambridge University, UK); Yoshihiro Kawaoka (The University of Wisconsin, Madison WI, USA and The University of Tokyo, Japan); Ron Fouchier (Erasmus University, Rotterdam, The Netherlands); Edward Belongia (Marshfield Clinic Research Foundation, Marshfield WI, USA); Malik Peiris and Benjamin Cowling (University of Hong Kong, Hong Kong SAR), Dan Layton Andrew Bean and Meiling Dai (AAHL, CSIRO Geelong); Marios Koutsakos (The University of Melbourne); Ben The (Peter MacCallum Cancer Centre

Collaborative Agreements

The Centre is party to three 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) (2012-2021)

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 2021:

An egg isolate of A(H3N2) was obtained at the Centre (A/Darwin/9/2021) that formed the basis of the A(H3N2) egg-derived vaccine component recommended for the Southern Hemisphere influenza vaccine recommendation for 2022.

For the full recommendation, click here.

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

Centre staff: Several staff are involved in this CRADA

Overview: The Centre is evaluating the suitability of a proprietary Seqirus cell line (MDCK 33016PF) for influenza virus isolation and growth as a basis for cell-based vaccine manufacture.

Highlights and developments 2021:

A qualified cell isolate of A(H3N2) was obtained at the Centre (A/Darwin/6/2021) that formed the basis of the A(H3N2) cell-derived vaccine component recommended for the Southern Hemisphere influenza vaccine recommendation for 2022.

For the full recommendation, click here.

Collaborative Research and Development Agreement with Roche (2020-2021)

Centre staff: Harry Stannard, Edin Mifsud, Ian Barr

Overview: A project entitled 'Assessing the fitness and transmissibility of variant human influenza viruses in vitro and in the ferret', was commenced to look at an influenza virus isolated from a patient under treatment with baloxavir and oseltamivir that developed dual mutations, one in the NA gene (H275Y) and the other in the PA gene (I38T), reducing the susceptibility of the virus to both of these drugs. The ability for this double mutant will be compared in cell culture and in transmission studies in ferrets.

Highlights and developments 2021:

The study has been successfully completed and a manuscript is in preparation.

Research Funding and Awards

Centre staff members are Chief Investigators in grants administered across 2021 (includes those awarded outside of 2021):

Center of Excellence for Influenza Research and Surveillance (CEIRS) Grant: ***Investigate and model initial pandemic influenza vaccination target groups***

USD $1,224,502 was awarded to **Ian Barr** (Co-Investigator) for the period 2016-2021. The grant was administered by the University of Cambridge.

US CDC contract: ***Breadth of antibodies induced by alternative licensed influenza vaccines***

USD $200,000 was awarded to **Annette Fox** (Lead Investigator) and **Sheena Sullivan** (Co-Investigator) for 2021. The grant was administered by the University of Melbourne and work was undertaken at the Centre.

Doherty Collaborative Seed Grant: ***Characterising CD4+ T cell memory generated by seasonal flu vaccination***

$20,000 was awarded to **Annette Fox** (Co-Investigator) for 2020-2021. The grant was administered by the Doherty Institute and work was undertaken at the Department of Microbiology and Immunology (University of Melbourne) and at the Centre.

Victorian Medical Research Acceleration Fund: ***Host cell kinome as a target for the treatment of SARS-CoV-2 infection***

$100,000 was awarded to **Kanta Subbarao** (Co-Investigator) for the period 2020-2021. The grant was administered by the Royal Melbourne Institute of Technology.

Victorian DHHS COVID-19 Victorian Consortium Antiviral Pillar: ***Establishment of an in vitro antiviral testing platform***

$480,000 was awarded to **Kanta Subbarao** (Lead Investigator) for the period 2020-2021. The grant was administered by the University of Melbourne.

CEIRS Sub-Grant: ***Natural history of SARS-CoV-2 in comparison to influenza A virus: a multi-site study focused in the Southern hemisphere and equatorial regions***

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

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

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

NHMRC Project Grant: ***Identification of molecular factors that influenza reassortment and pandemic potential of highly pathogenic avian influenza H5 viruses***

$784,418 was awarded to **Kanta Subbarao** (Chief Investigator) for the period 2019-2021. The grant was administered by the University of Melbourne.

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

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

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

$500,000 was awarded to **Kanta Subbarao** (Chief Investigator) for the period 2020-2021. The grant was administered by the University of Melbourne.

NHMRC Medical Research Future Fund Coronavirus Research Response 2020: ***Stem cell-derived human tissue models for the identification of drugs to treat COVID-19***

$610,000 was awarded to **Kanta Subbarao** (Chief Investigator) for the period 2020-2021. The grant is administered by the University of Melbourne.

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

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

NHMRC Development Grant: *Clamp stabilised vaccines to provide broad spectrum protection against influenza*

$949,516 was awarded to **Patrick Reading** (Chief Investigator) for the period 2019-2021. The grant was administered by the University of Queensland.

Department of Foreign Affairs and Travel (DFAT) Sino-Australia COVID-19 Partnership Seed Funding 2020: *Insights about SARS-CoV-2 Transmission from Hotel Quarantine in Australia and Hong Kong*

$50,000 awarded to **Sheena Sullivan** (Chief Investigator), alongside Prof Ben Cowling and Bing Yi at the University of Hong Kong for the period 2020-2021. The project aims to compare hotel quarantine approaches in Australia and Hong Kong.

Department of Foreign Affairs and Travel (DFAT) Sino-Australia COVID-19 Partnership Seed Funding 2020: *Haplotype Analysis of the SARS-CoV-2 genome*

$50,000 was awarded to **Sheena Sullivan** (Co-Investigator) for the period 2020-2021. The grant was administered by the National Foundation for Australia-China Relations DFAT.

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

$40,000 was awarded to **Sheena Sullivan** (Co-Investigator) for the period 2020-2021. The grant was administered by the Peter Doherty Institute for Infection and Immunity.

Australian Government Department of Agriculture National Avian Influenza Wild Bird Surveillance Special Project Proposal: *Placing Australia in the global avian influenza phylogeography*

$69,132 was awarded to **Michelle Wille** (Lead Investigator) and Frank Wong (Australian Centre for Disease Preparedness, ACDP) for the period 2019-2021. The grant was administered by the Royal Melbourne Hospital and ACDP.

CEIRS Sub-Grant: *Assessing transmission of COVID-19 in occupationally exposed health care workers*

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

Coalition for epidemic preparedness innovations (CEPI) Project Grant: *Rapid response pipeline for stabilised subunit vaccines*

USD $10,600,000 was awarded to **Patrick Reading** (Chief Investigator) for the period 2018-2021. The grant was administered by the University of Queensland.

Australian Research Council (ARC) Discovery Project Grant: *Harnessing innate immunity to mitigate bovine respiratory disease*

$553,019 was awarded to **Patrick Reading** (Partner Investigator) for the period 2020-2022. The grant is administered by the University of Melbourne.

Royal Melbourne Hospital Grant in Aid: *Can rapid point of care testing improve influenza infection outcomes for residents in aged care?*

$25,000 was awarded to **Sheena Sullivan** (Principal Investigator) for the period 2020-2021. The grant was administered by the Royal Melbourne Hospital.

Australian Partnership for Preparedness Research on Infectious Disease Emergencies Centre of Research Excellence (APPRISE CRE): *COVID-19 impacts on residents of aged-care homes*

$30,000 top-up funding was awarded to **Sheena Sullivan** for the period 2020-2021. This project augments the '*Can rapid point of care testing improve influenza infection outcomes for residents in aged care?*' project with the Royal Melbourne Hospital, looking at the feasibility of point-of-care testing for influenza to include outcomes relevant to COVID-19.

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

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

Research Students

PhD Candidates

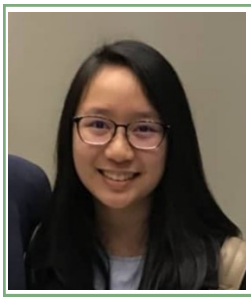
Ms Paulina Koszalka, a PhD candidate from Monash University, continued her PhD project titled "Efficacy, resistance and drug interactions for influenza antivirals in clinical development", under the supervision of **Kanta Subbarao**, Vijaykrishna Dhanasekaran (Monash University), Stephen Turner (Monash University), and Aeron Hurt (Roche).

Paulina after her Oration in November

Masters students

Dr Chris Bailie, an MAE candidate from the Australian National University, completed his placement at the Centre in November 2021 under the supervision of **Sheena Sullivan**.

Honours students

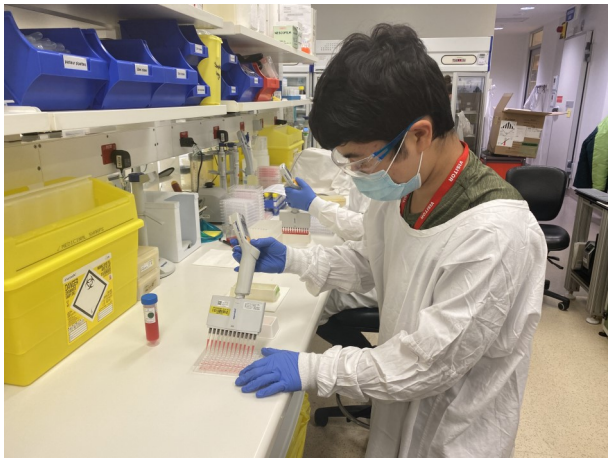


Ms Anastasia Jessica Hadiprodjo, an Honours student from the University of Melbourne, completed her project titled, 'Optimising antigenic characterisation of influenza viruses for vaccine strain selection' in 2021, under the supervision of **Annette Fox** and **Sheena Sullivan**.

A socially-distanced farewell to Chris

Work experience students

Mr Daniel Stavretis from Balwyn High School completed a work experience placement between 6-10 December 2021.



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 65 original research papers, reviews and reports in 2021.

Centre Publications 2021

1. **Bailie CR**, Franklin L, Nicholson S, Mordant F, Alpren C, Stewart T, Barnes C, **Fox A**, Druce J, **Subbarao K**, Catton M, van Diemen A, **Sullivan SG**. 2021. Symptoms and laboratory manifestations of mild COVID-19 in a repatriated cruise ship cohort. Epidemiol Infect 149:e44.
2. Bond KA, Williams E, Nicholson S, Lim S, Johnson D, Cox B, Putland M, Gardiner E, Tippett E, Graham M, Mordant F, Catton M, Lewin SR, **Subbarao K**, Howden BP, Williamson DA. 2021. Longitudinal evaluation of laboratory-based serological assays for SARS-CoV-2 antibody detection. Pathology 53:773-779.
3. Calisher CH, Carroll D, Colwell R, Corley RB, Daszak P, Drosten C, Enjuanes L, Farrar J, Field H, Golding J, Gorbalenya AE, Haagmans B, Hughes JM, Keusch GT, Lam SK, Lubroth J, Mackenzie JS, Madoff L, Mazet JK, Perlman SM, Poon L, Saif L, **Subbarao K**, Turner M. 2021. Science, not speculation, is essential to determine how SARS-CoV-2 reached humans. Lancet 398:209-211.
4. Chang JJ, Rawlinson D, Pitt ME, Taiaroa G, Gleeson J, Zhou C, Mordant FL, De Paoli-Iseppi R, Caly L, Purcell DFJ, Stinear TP, Londrigan SL, Clark MB, Williamson DA, **Subbarao K**, Coin LJM. 2021. Transcriptional and epi-transcriptional dynamics of SARS-CoV-2 during cellular infection. Cell Rep 35:109108.
5. Chappell KJ, Mordant FL, Li Z, Wijesundara DK, Ellenberg P, Lackenby JA, Cheung STM, Modhiran N, Avumegah MS, Henderson CL, Hoger K, Griffin P, Bennet J, Hensen L, Zhang W, Nguyen THO, Marrero-Hernandez S, Selva KJ, Chung AW, Tran MH, Tapley P, **Barnes J**, **Reading PC**, Nicholson S, Corby S, Holgate T, Wines BD, Hogarth PM, Kedzierska K, Purcell DFJ, Ranasinghe C, **Subbarao K**, Watterson D, Young PR, Munro TP. 2021. Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Infect Dis 21:1383-1394.
6. Clarke M, Goodchild LM, Evans S, Giles LC, **Sullivan SG**, **Barr IG**, Lambert S, Marshall H. 2021. Body mass index and vaccine responses following influenza vaccination during pregnancy. Vaccine 39:4864-4870.
7. Cunningham AL, McIntyre P, **Subbarao K**, Booy R, Levin MJ. 2021. Vaccines for older adults. Bmj 372:n188.
8. Darmaa O, Burmaa A, Gantsooj B, Darmaa B, Nymadawa P, **Sullivan SG**, Fielding JE. 2021 Influenza epidemiology and burden of disease in Mongolia, 2013-2014 to 2017-2018. 12(2).
9. Deliyannis G, Wong CY, McQuilten HA, Bachem A, Clarke M, Jia X, Horrocks K, Zeng W, Girkin J, Scott NE, Londrigan SL, **Reading PC**, Bartlett NW, Kedzierska K, Brown LE, Mercuri F, Demaison C, Jackson DC, Chua BY. 2021. TLR2-mediated activation of innate responses in the upper airways confers antiviral protection of the lungs. JCI Insight 6.
10. Feng S, **Sullivan SG**, Tchetgen Tchetgen EJ, Cowling BJ. 2021. The Causal Interpretation of "Overall Vaccine Effectiveness" in Test-Negative Studies. Am J Epidemiol 190:1993-1999.
11. Fielding J, **Sullivan SG**, Beard F, Macartney K, Williams J, Dawson A, Gilbert GL, Massey P, Crooks K, Moss R, McCaw JM, McVernon J. 2021. Constructing an ethical framework for priority allocation of pandemic vaccines. Vaccine 39:797-804.
12. Fulford TS, Van H, Gherardin NA, Zheng S, Ciula M, Drummer HE, Redmond S, Tan HX, Boo I, Center RJ, Li F, Grimley SL, Wines BD, Nguyen THO, Mordant FL, Ellenberg P, Rowntree LC, Kedzierski L, Cheng AC, Doolan DL, Matthews G, Bond K, Hogarth PM, McQuilten Z, Subbarao K, Kedzierska K, Juno JA, Wheatley AK, Kent SJ, Williamson DA, Purcell DFJ, Anderson DA, Godfrey DI. 2021. A point-of-care lateral flow assay for neutralising antibodies against SARS-CoV-2. EBioMedicine 74:103729.

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14. Geoghegan JL, Di Giallonardo F, **Wille M**, Ortiz-Baez AS, Costa VA, Ghaly T, Mifsud JCO, Turnbull OMH, Bellwood DR, Williamson JE, Holmes EC. 2021. Virome composition in marine fish revealed by meta-transcriptomics. Virus Evol 7:veab005.

15. Han AX, Felix Garza ZC, Welkers MR, Vigeveno RM, Tran ND, Le TQM, Pham Quang T, Dang DT, Tran TNA, Ha MT, Nguyen TH, Le QT, Le TH, Hoang TBN, Chokephaibulkit K, Puthavathana P, Nguyen VVC, Nghiem MN, Nguyen VK, Dao TT, Tran TH, Wertheim HF, Horby PW, **Fox A**, van Doorn HR, Eggink D, de Jong MD, Russell CA. 2021. Within-host evolutionary dynamics of seasonal and pandemic human influenza A viruses in young children. Elife 10.

16. Hensen L, Nguyen THO, Rowntree LC, Damelang T, Koutsakos M, **Aban M**, **Hurt A**, Harland KL, Auladell M, van de Sandt CE, Everitt A, Blacker C, Oyong DA, Loughland JR, Webb JR, Wines BD, Hogarth PM, Flanagan KL, Plebanski M, Wheatley A, Chung AW, Kent SJ, Miller A, Clemens EB, Doherty PC, Nelson J, Davies J, Tong SYC, Kedzierska K. 2021. Robust and prototypical immune responses toward influenza vaccines in the high-risk group of Indigenous Australians. Proc Natl Acad Sci U S A 118.

17. Hoye BJ, Donato CM, Lisovski S, **Deng YM**, Warner S, **Hurt AC**, Klaassen M, Vijaykrishna D. 2021. Reassortment and Persistence of Influenza A Viruses from Diverse Geographic Origins within Australian Wild Birds: Evidence from a Small, Isolated Population of Ruddy Turnstones. J Virol 95.

18. Hughes A, **Sullivan SG**, Marshall C. 2021. Factors associated with vanA VRE acquisition in Cardiothoracic Surgery patients during an acute outbreak. Infect Dis Health 26:258-264.

19. Jiang W, Wong J, Tan HX, Kelly HG, **Whitney PG**, **Barr I**, Layton DS, Kent SJ, Wheatley AK, Juno JA. 2021. Screening and development of monoclonal antibodies for identification of ferret T follicular helper cells. Sci Rep 11:1864.

20. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, **Subbarao K**, Kent SJ, Triccas JA, Davenport MP. 2021. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nature Medicine doi:10.1038/s41591-021-01377-8.

21. Koutsakos M, Rowntree LC, Hensen L, Chua BY, van de Sandt CE, Habel JR, Zhang W, Jia X, Kedzierski L, Ashhurst TM, Putri GH, Marsh-Wakefield F, Read MN, Edwards DN, Clemens EB, Wong CY, Mordant FL, Juno JA, Amanat F, Audsley J, Holmes NE, Gordon CL, Smibert OC, Trubiano JA, Hughes CM, Catton M, Denholm JT, Tong SYC, Doolan DL, Kotsimbos TC, Jackson DC, Krammer F, Godfrey DI, Chung AW, King NJC, Lewin SR, Wheatley AK, Kent SJ, **Subbarao K**, McMahon J, Thevarajan I, Nguyen THO, Cheng AC, Kedzierska K. 2021. Integrated immune dynamics define correlates of COVID-19 severity and antibody responses. Cell Rep Med 2:100208.

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25. **Leung VKY**, **Deng YM**, **Todd A**, **Peck H**, **Buettner I**, **Zakis T**, **Subbarao K**, **Barr IG**, Nahapetyan K, Inbanathan FY, Samaan M, Reading PC. 2021. A second external quality assessment of isolation and identification of influenza viruses in cell culture in the Asia Pacific region highlights improved performance by participating laboratories. J Clin Virol 142:104907.

26. **Leung VKY**, **Fox A**, **Carolan LA**, **Aban M**, **Laurie KL**, Druce J, **Deng YM**, Slavin MA, Marshall C, **Sullivan SG**. 2021. Impact of prior vaccination on antibody response and influenza-like illness among Australian healthcare workers after influenza vaccination in 2016. Vaccine 39:3270-3278.

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32. Lynch SA, **Subbarao K**, Mahanty S, Barber BE, Roulis EV, van der Hoek L, McCarthy JS, Spann KM. 2021. Prevalence of Neutralising Antibodies to HCoV-NL63 in Healthy Adults in Australia. Viruses 13.

33. McMillan CLD, Cheung STM, Modhiran N, **Barnes J**, Amarilla AA, Bielefeldt-Ohmann H, Lee LYY, Guilfoyle K, van Amerongen G, Stittelaar K, Jakon V, Lebas C, **Reading P**, Short KR, Young PR, Watterson D, Chappell KJ. 2021. Development of molecular clamp stabilized hemagglutinin vaccines for Influenza A viruses. NPJ Vaccines 6:135.

34. McNab S, Ha Do LA, Clifford V, Crawford NW, Daley A, Mulholland K, Cheng D, South M, Waller G, **Barr I**, Wurzel D. 2021. Changing Epidemiology of Respiratory Syncytial Virus in Australia-Delayed Re-Emergence in Victoria Compared to Western Australia/New South Wales (WA/NSW) After Prolonged Lock-Down for Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 73:2365-2366.

35. Meischel T, Fritzlar S, Villalon-Letelier F, Tessema MB, Brooks AG, **Reading PC**, Londrigan SL. 2021. IFITM Proteins That Restrict the Early Stages of Respiratory Virus Infection Do Not Influence Late-Stage Replication. J Virol 95:e0083721.

36. **Mifsud EJ**, **Kuba M**, **Barr IG**. 2021. Innate Immune Responses to Influenza Virus Infections in the Upper Respiratory Tract. Viruses 13.

37. Mills RJ, Humphrey SJ, Fortuna PRJ, Lor M, Foster SR, Quaife-Ryan GA, Johnston RL, Dumenil T, Bishop C, Rudraraju R, Rawle DJ, Le T, Zhao W, Lee L, Mackenzie-Kludas C, Mehdiabadi NR, Halliday C, Gilham D, Fu L, Nicholls SJ, Johansson J, Sweeney M, Wong NCW, Kulikowski E, Sokolowski KA, Tse BWC, Devilée L, Voges HK, Reynolds LT, Krumeich S, Mathieson E, Abu-Bonsrah D, Karavendzas K, Griffen B, Titmarsh D, Elliott DA, McMahon J, Suhrbier A, **Subbarao K**, Porrello ER, Smyth MJ, Engwerda CR, MacDonald KPA, Bald T, James DE, Hudson JE. 2021. BET inhibition blocks inflammation-induced cardiac dysfunction and SARS-CoV-2 infection. Cell 184:2167-2182.e22. Nguyen TH, McAuley JL, Kim Y, Zheng MZ, Gherardin NA, Godfrey DI, Purcell DF, Sullivan LC, Westall GP, **Reading PC**, Kedzierska K, Wakim LM. 2021. Influenza, but not SARS-CoV-2, infection induces a rapid interferon response that wanes with age and diminished tissue-resident memory CD8(+) T cells. Clin Transl Immunology 10:e1242.

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39. Nguyen THO, Koutsakos M, van de Sandt CE, Crawford JC, Loh L, Sant S, Grzelak L, Allen EK, Brahm T, Clemens EB, Auladell M, Hensen L, Wang Z, Nüssing S, Jia X, Günther P, Wheatley AK, Kent SJ, **Aban M**, **Deng YM**, **Laurie KL**, **Hurt AC**, Gras S, Rossjohn J, Crowe J, Xu J, Jackson D, Brown LE, La Gruta N, Chen W, Doherty PC, Turner SJ, Kotsimbos TC, Thomas PG, Cheng AC, Kedzierska K. 2021. Immune cellular networks underlying recovery from influenza virus infection in acute hospitalized patients. Nat Commun 12:2691.

Centre Publications (continued)

40. Nicholson S, Karapanagiotidis T, **Khvorov A**, Douros C, Mordant F, Bond K, Druce J, Williamson DA, Purcell D, Lewin SR, **Sullivan S**, **Subbarao K**, Catton M. 2021. Evaluation of 6 Commercial SARS-CoV-2 Serology Assays Detecting Different Antibodies for Clinical Testing and Serosurveillance. Open Forum Infect Dis 8:ofab239.

41. **Peck H**, Laurie KL, Rockman S, **Leung V**, **Lau H**, **Soppe S**, **Rynehart C**, Baas C, Trusheim H, **Barr IG**. 2021. Enhanced isolation of influenza viruses in qualified cells improves the probability of well-matched vaccines. NPJ Vaccines 6:149.

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43. Price O, Dietze P, **Sullivan SG**, Salom C, Peacock A. 2021. Uptake, barriers and correlates of influenza vaccination among people who inject drugs in Australia. Drug Alcohol Depend 226:108882.

44. Pymm P, Adair A, Chan LJ, Cooney JP, Mordant FL, Allison CC, Lopez E, Haycroft ER, O'Neill MT, Tan LL, Dietrich MH, Drew D, Doerflinger M, Dengler MA, Scott NE, Wheatley AK, Gherardin NA, Venugopal H, Cromer D, Davenport MP, Pickering R, Godfrey DI, Purcell DFJ, Kent SJ, Chung AW, **Subbarao K**, Pellegrini M, Glukhova A, Tham WH. 2021. Nanobody cocktails potently neutralize SARS-CoV-2 D614G N501Y variant and protect mice. Proc Natl Acad Sci U S A 118.

45. **Reading PC**, Strugnell RA. 2021. COVID-19 in Fiji. Microbiology Australia 42:192-195.

46. Rowntree LC, Chua BY, Nicholson S, Koutsakos M, Hensen L, Douros C, Selva K, Mordant FL, Wong CY, Habel JR, Zhang W, Jia X, Allen L, Doolan DL, Jackson DC, Wheatley AK, Kent SJ, Amanat F, Krammer F, **Subbarao K**, Cheng AC, Chung AW, Catton M, Nguyen THO, van de Sandt CE, Kedzierska K. 2021. Robust correlations across six SARS-CoV-2 serology assays detecting distinct antibody features. Clinical & Translational Immunology 10:e1258.

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49. **Subbarao K**. 2021. The success of SARS-CoV-2 vaccines and challenges ahead. Cell Host Microbe 29:1111-1123.

50. **Subbarao K**. 2021. Live Attenuated Cold-Adapted Influenza Vaccines. Cold Spring Harb Perspect Med 11.

51. Tan HX, Juno JA, Lee WS, Barber-Axthelm I, Kelly HG, Wragg KM, Esterbauer R, Amarasena T, Mordant FL, **Subbarao K**, Kent SJ, Wheatley AK. 2021. Immunogenicity of prime-boost protein subunit vaccine strategies against SARS-CoV-2 in mice and macaques. Nat Commun 12:1403.

52. Tang JW, Bialasiewicz S, Dwyer DE, Dilcher M, Tellier R, Taylor J, Hua H, Jennings L, Kok J, Levy A, Smith D, **Barr IG**, **Sullivan SG**. 2021. Where have all the viruses gone? Disappearance of seasonal respiratory viruses during the COVID-19 pandemic. J Med Virol 93:4099-4101.

53. **Todd AK**, Costa AM, Waller G, Daley AJ, **Barr IG**, **Deng YM**. 2021. Rapid detection of human respiratory syncytial virus A and B by duplex real-time RT-PCR. J Virol Methods 294:114171.

54. Todd IMF, Miller JE, Rowe SL, Burgner DP, **Sullivan SG**. 2021. Changes in infection-related hospitalizations in children following pandemic restrictions: an interrupted time-series analysis of total population data. Int J Epidemiol 50:1435-1443.

55. Toh ZQ, Higgins RA, Do LAH, Rautenbacher K, Mordant FL, **Subbarao K**, Dohle K, Nguyen J, Steer AC, Tosif S, Crawford NW, Mulholland K, Licciardi PV. 2021. Persistence of SARS-CoV-2-Specific IgG in Children 6 Months After Infection, Australia. Emerg Infect Dis 27.

56. **Tseng YY**, Kuan CY, Mibayashi M, Chen CJ, Palese P, Albrecht RA, Hsu WL. 2021. Interaction between NS1 and Cellular MAVS Contributes to NS1 Mitochondria Targeting. Viruses 13.

57. **Tseng YY**, Liao GR, Lien A, Hsu WL. 2021. Current concepts in the development of therapeutics against human and animal coronavirus diseases by targeting NP. Comput Struct Biotechnol J 19:1072-1080.

Centre Publications (continued)

58. Victorian Department of Health COVID-19 writing group (includes **Sullivan SG**). 2021. Population -based analysis of the epidemiological features of COVID-19 epidemics in Victoria, Australia, January 2020 - March 2021, and their suppression through comprehensive control strategies. Lancet Reg Health West Pac 17:100297.

59. Villalón-Letelier F, Brooks AG, Londrigan SL, **Reading PC**. 2021. MARCH8 Restricts Influenza A Virus Infectivity but Does Not Downregulate Viral Glycoprotein Expression at the Surface of Infected Cells. mBio 12:e0148421.

60. Watterson D, Wijesundara DK, Modhiran N, Mordant FL, Li Z, Avumegah MS, McMillan CL, Lackenby J, Guilfoyle K, van Amerongen G, Stittelaar K, Cheung ST, Bibby S, Daleris M, Hoger K, Gillard M, Radunz E, Jones ML, Hughes K, Hughes B, Goh J, Edwards D, Scoble J, Pearce L, Kowalczyk L, Phan T, La M, Lu L, Pham T, Zhou Q, Brockman DA, Morgan SJ, Lau C, Tran MH, Tapley P, Villalón-Letelier F, **Barnes J**, Young A, Jaberolansar N, Scott CA, Isaacs A, Amarilla AA, Khromykh AA, van den Brand JM, **Reading PC**, Ranasinghe C, **Subbarao K**, Munro TP, Young PR, Chappell KJ. 2021. Preclinical development of a molecular clamp-stabilised subunit vaccine for severe acute respiratory syndrome coronavirus 2. Clin Transl Immunology 10:e1269.

61. Wheatley AK, **Fox A**, Tan HX, Juno JA, Davenport MP, **Subbarao K**, Kent SJ. 2021. Immune imprinting and SARS-CoV-2 vaccine design. Trends Immunol 42:956-959.

62. Wheatley AK, Juno JA, Wang JJ, Selva KJ, Reynaldi A, Tan HX, Lee WS, Wragg KM, Kelly HG, Esterbauer R, Davis SK, Kent HE, Mordant FL, Schlub TE, Gordon DL, Khoury DS, **Subbarao K**, Cromer D, Gordon TP, Chung AW, Davenport MP, Kent SJ. 2021. Evolution of immune responses to SARS-CoV-2 in mild-moderate COVID-19. Nat Commun 12:1162.

63. Wheatley AK, Pymm P, Esterbauer R, Dietrich MH, Lee WS, Drew D, Kelly HG, Chan LJ, Mordant FL, Black KA, Adair A, Tan HX, Juno JA, Wragg KM, Amarasena T, Lopez E, Selva KJ, Haycroft ER, Cooney JP, Venugopal H, Tan LL, MT ON, Allison CC, Cromer D, Davenport MP, Bowen RA, Chung AW, Pellegrini M, Liddament MT, Glukhova A, **Subbarao K**, Kent SJ, Tham WH. 2021. Landscape of human antibody recognition of the SARS-CoV-2 receptor binding domain. Cell Rep 37:109822.

64. Williams TC, Sinha I, **Barr IG**, Zambon M. 2021. Transmission of paediatric respiratory syncytial virus and influenza in the wake of the COVID-19 pandemic. Euro Surveill 26.

65. Yang B, Tsang TK, Wong JY, He Y, Gao H, Ho F, Lau EHY, Wu P, **Sullivan SG**, Cowling BJ. 2021. The differential importation risks of COVID-19 from inbound travellers and the feasibility of targeted travel controls: A case study in Hong Kong. Lancet Reg Health West Pac 13:100184.

Presentations

Centre staff members presented talks and posters at numerous events during 2020, including national and international conferences, WHO meetings, educational lectures and research seminars.

ORAL PRESENTATIONS

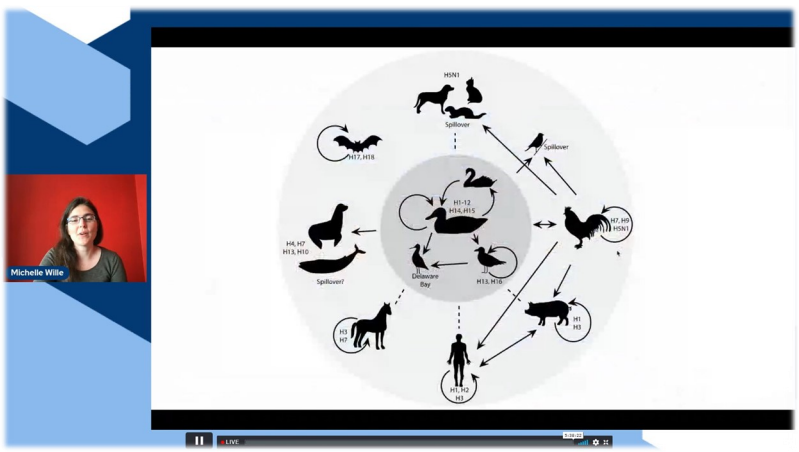
Event/Institute; Location, date	SPEAKER, Title(s)
13th Annual Centres of Excellence for Influenza Research and Surveillance (CEIRS) Network Meeting, Virtual Forum, 11-15 January 2021	ANNETTE FOX: Vaccine Assessment Using Antibody Landscapes and B Cell Probes Shows That Infection History Dictates Influenza Vaccine Immunogenicity
Global Vaccine and Immunization Research Forum, Virtual Forum, 22 February 2021	KANTA SUBBARAO: Universal Influenza Vaccines
RCPA National Microbiology webinar, March 2021	KANTA SUBBARAO: What's new about influenza in 2021
AOA Visiting Professorship lecture, SUNY Upstate Medical University, Virtual Forum, March 2021	KANTA SUBBARAO: The Scientific and Public Health Response to the Emergence of a New Pathogen
RCPA update, Virtual Forum, March 2021	KANTA SUBBARAO: SARS-CoV-2 Vaccine Science

ORAL PRESENTATIONS (continued)

Event/Institute; Location, date	SPEAKER, Title(s)
COVID Affair meeting, Virtual Forum, 17 March 2021	IAN BARR: Was the flu season in the northern hemisphere impacted by COVID?
COVID Affair meeting, Virtual Forum, 17 March 2021	SHEENA SULLIVAN: Was the flu season in the northern hemisphere impacted by COVID?
National Academy of Sciences Open Session on Vaccine Research and Development for Advancing Pandemic and Seasonal Influenza Preparedness and Response, Virtual Forum, 30 March 2021	ANNETTE FOX: Vaccinating against influenza viruses: can new memory be induced when old memory is recalled?
Communicable Diseases Network of Australia, Virtual Forum, April 2021	KANTA SUBBARAO: SARS-CoV-2 Variants of Concern
COVID-19 vaccine forum, Department of Health, Australian Technical Advisory Group on Immunisation (ATAGI) and the National COVID-19 Health and Research Advisory Committee (NCHRAC), Virtual Forum, April 2021	KANTA SUBBARAO: SARS-CoV-2 variants of concern
GSK Virtual Vaccine Days, Attributes of current and new vaccine technologies symposium, 28 April 2021	KANTA SUBBARAO: Overview of the technology platforms for vaccine development: established vaccines & new technologies
APPRISE COVID-19 research meeting update, Virtual Forum, 6 May 2021	SHEENA SULLIVAN: Challenges of responding to COVID-19 outbreaks in aged care
Genomics Gone Viral Symposium, Peter Doherty Institute, Melbourne, 18 May 2021	IAN BARR: Genomics for influenza
Organoids are US, Virtual Forum, 1 June 2021	KANTA SUBBARAO: SARS-CoV-2 infection in stem cell derived human tissues
ASM Virology Special Interest Group Online Meeting, monthly Zoom Virology seminar; Virtual Forum, 15 June 2021	SHEENA SULLIVAN: Long-term SARS-CoV-2 antibody responses in a cohort of returned cruise ship passengers
Doherty Seminar Series; Virtual Forum, 15 July 2021	PATRICK READING: Regional laboratory capacity building before and during COVID-19
XXV Latin American Congress of Microbiology (ALAM) 2021, 25-28 August 2021	MARIANA BAZ: Antiviral therapy against influenza viruses
2021 Asia Pacific Alliance for the Control of Influenza (APACI) Respiratory Diseases Workshop, India; Virtual Forum, 29 August 2021	KANTA SUBBARAO: Universal flu vaccines
9th Advanced Vaccinology Course in India (INDVAC); Virtual Forum, 25 September 2021	KANTA SUBARAO: Influenza Vaccines
10th Anniversary ID Week Virtual Conference; Virtual Forum, 3 October 2021	KANTA SUBBARAO: Where Did Influenza Go?
37th Annual Workshop on Infectious Disease NRL Workshop; Virtual Meeting, 11-13 October 2021	IAN BARR: The Effect of Changing Behaviours on Human Respiratory Diseases

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
ISIRV-WHO virtual conference, COVID-19, Influenza and RSV: Surveillance-informed prevention and treatment; Virtual Forum, 19 October 2021	KANTA SUBBARAO: SARS-CoV-2 Evolution: Implications for Vaccine Strain Selection
8th FIMSA Congress, Hybrid meeting (Busan, Korea), 3 November 2021	KANTA SUBBARAO: Strategies to Improve Seasonal and Pandemic Influenza Vaccines
14th Australian Influenza Symposium; Virtual Forum, 11-12 November 2021	HEIDI PECK: Detection of influenza infection through supervised hotel quarantine in Australia
Australian Influenza Symposium; Virtual Forum, 11 November 2021	IAN BARR: WHO RSV global surveillance program – Phase 2 – An update
14th Australian Influenza Symposium; Virtual Forum, 11-12 November 2021	KANTA SUBBARAO: SARS-CoV-2 Vaccines and Antivirals
14th Australian Influenza Symposium; Virtual Forum, 11-12 November 2021	SHEENA SULLIVAN: The 2020/2021 influenza seasons in Australia and what to expect in 2022
18th Asia Pacific Congress of Clinical Microbiology and Infection (APCCMI); Singapore/Virtual Forum, 11-13 November 2021	KANTA SUBBARAO: Novel Influenza Viruses
8th ESWI Influenza Conference; Virtual Forum, 5 December 2021	KANTA SUBBARAO: Influenza in the time of COVID-19

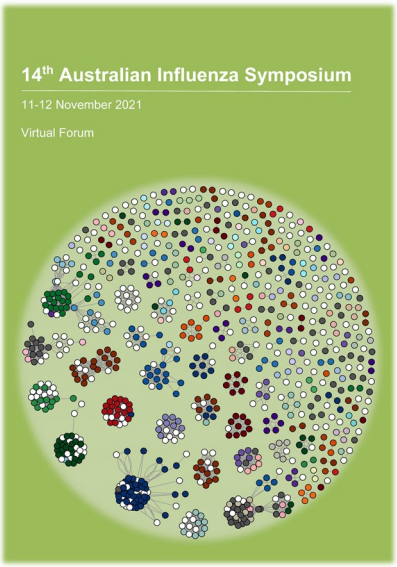
Unfortunately there were no Poster presentations during 2021.



Australian Influenza Symposium

The 14th Australian Influenza Symposium was held as a virtual forum by ASN Events on 11-12 November 2021. This Symposium also included multiple sessions on COVID-19, as well as influenza and RSV.

The Symposium was attended by 355 people, including representatives from the biomedical, clinical, research, public health, government, and industry sectors. The Symposium also welcomed a range of international speakers, including:



Eddie Holmes, Marie Bashir Institute for Infectious Diseases & Biosecurity, University of Sydney

Stanley Perlman, Department of Microbiology and Immunology, University of Iowa

Jenifer Juno, Department of Microbiology and Immunology, University of Melbourne, Doherty Institute

Peter McIntyre, Department of Women's and Children's Health, University of Otago, Dunedin, NZ

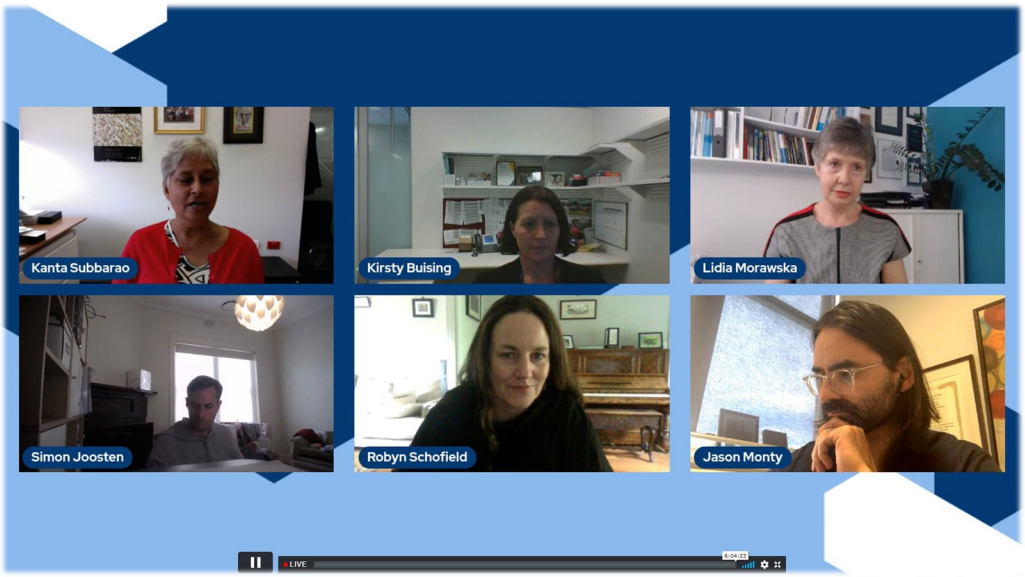
Bev Menner, COVID Vaccine Lead, CSL Limited

Keith Chappell, School of Chemistry and Molecular Biosciences, University of Queensland

The full program booklet can be accessed via our website here.

Delegates were able to enjoy talks from a diverse range of perspectives during the live sessions, with additional proffered talks provided as pre-recorded videos on the online platform. These videos are still available to delegates for viewing. The Symposium was also reported on Twitter using the tag, #AIS2021Virtual

The organizing committee for the Symposium was **Ian Barr** and **Miku Kuba**. The majority of staff members from the Centre attended the symposium, and in addition, **Kanta Subbarao**, **Ian Barr**, **Sheena Sullivan**, **Michelle Wille**, and **Heidi Peck** presented talks. **Kanta Subbarao** also chaired a plenary session and roundtable discussion.

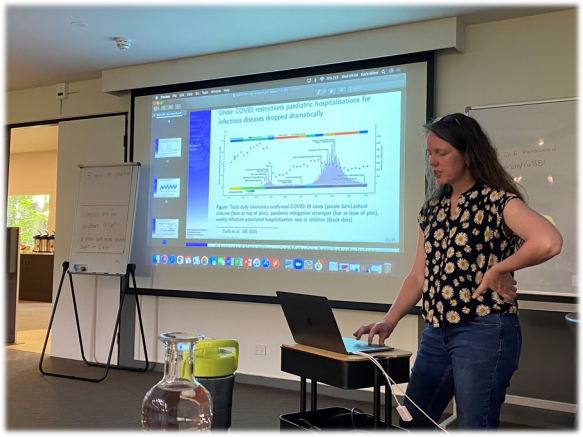


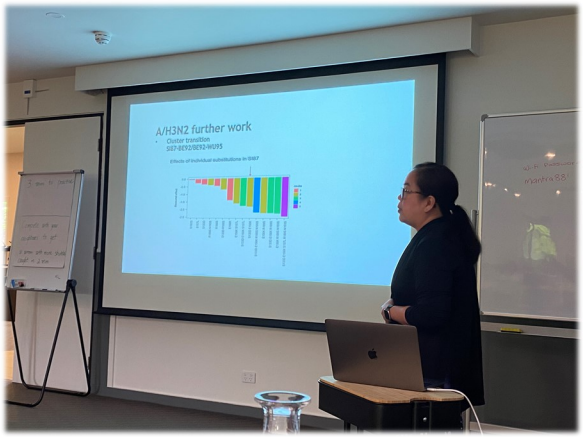
Centre Staff Retreat

The Centre retreat was held 30 November 2021 - 1 December 2021 at Peppers Mineral Springs in Hepburn Springs.

Staff from each section were able to reflect and discuss the impact of the COVID-19 pandemic on their workload and strategise for the upcoming year.

These discussions also included planning for the next influenza pandemic and how the Centre may approach this, given what we have learnt from the current pandemic.





The research groups also presented data from their various, ongoing research projects, which covered a range of topics including COVID-19 and RSV in addition to influenza. These presentations highlighted the diversity in expertise and techniques available at the Centre.

Numerous team building exercises from the retreat, in conjunction with the above presentations, also brought a more light-hearted side to the two day event, bringing a much needed social aspect since the beginning of the COVID-19 pandemic.

Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2021.

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

Mariana Baz:
WHO Expert Working Group for GISRS Surveillance of Antiviral Susceptibility, *Member*
World Society for Virology Membership Review Committee, *Deputy*
World Society for Virology, *Organising Committee*
Microorganisms, *Guest Editor*

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

Annette Fox

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

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

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

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

Kanta Subbarao
ACT Accelerator COVAX Pillar Independent Product Group, *Member*
Advisory Group for CDC funded grant 'A Prospective Household cohort study of Influenza, Respiratory Syncytial virus and other respiratory pathogens community burden and Transmission dynamics in South Africa – COVID version (PHIRST-C) to the National Institute for Communicable Diseases, South Africa, *Member*
Committee on Vaccine Research and Development Recommendations for Advancing Pandemic and Seasonal Influenza Preparedness and Response, US National Academy of Medicine, *Co-Chair*
Data Safety and Monitoring Board, Booster Study of COVID-19 vaccines in Thailand, Clinixir, *Member*
Department of Biotechnology, Government of India COVID-19 Vaccine Expert Committee, *Member*
Australian Influenza Vaccine Committee (Therapeutic Goods Administration), *Member*
Australian Technical Advisory Group on Immunisation (ATAGI) COVID-19 Working Group, *Member*

Committees and Advisory Groups

Kanta Subbarao (continued)

Doherty Institute Leadership Group, *Member*
Doherty Institute Operational Management Committee, *Member*
Doherty Institute, *Discipline leader, Global Health*
External Advisory Board, FLUCOP consortium, *Member*
External Advisory Group, NIAID Collaborative Influenza Vaccine Innovation Centers (CIVICs), NIAID, Influenza Vaccines Research and Development (R&D) Roadmap, *Member*
International Committee on Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response. US National Academy of Medicine. 2020-2021, *Member*
National Influenza Surveillance Committee (Department of Health) NIH, Bethesda, MD, USA, *Chair*
Scientific Advisory Board for the Gates Center for Structure Guided Design of Next Generation Vaccine Immunogens at The Scripps Research Institute, La Jolla, CA, USA. *Member*
Scientific Advisory Board for the Universal Influenza Vaccine Project at Mount Sinai School of Medicine, New York City NY, USA, *Member*
Scientific Advisory Committee for Maddie Riewoldt's Vision, Australia, *Member*
Scientific Advisory Working Group for the Vaccine Research Center, NIAID, NIH, Bethesda, MD, USA
Steering Committee for BCG vaccination to reduce the impact of COVID-19 in healthcare workers (BRACE) trial, Melbourne, *Member*
Technical Expert Mechanism (PCITEM) 2017-present, *Member*
Vaccine Advisory Group, Vaccine Alliance Aotearoa New Zealand, *Member*
WHO Advisory Group on Human Challenge Studies for COVID-19 Vaccines, *Member*
WHO Working group on Influenza Preparedness and Response, *Member*
WHO Pandemic Influenza Preparedness (PIP) Framework Partnership Contribution Independent Technical Expert Mechanism (PCITEM), *Member*
WHO Technical Advisory Group on COVID-19 Vaccine Composition 2021-2022, *Chair*
WHO Technical Advisory Group on Emergency Use Listing, *Member*
Cell Host and Microbe, *Editorial board*
Journal of Virology, *Editorial board*
mBio, *Editorial board*
Med, *Editorial board*
PLoS Pathogens, *Section Editor*

Sheena Sullivan

Australasian Epidemiology Association, *Victorian Convenor*
Doherty Institute, *Equity and Diversity in Science Committee*
International Society for Influenza and Other Respiratory Viruses, *Council Member*
International Journal of Epidemiology, *Associated Editor*
Influenza and Other Respiratory Viruses, *Associated Editor*
National Influenza Surveillance Committee (Department of Health), *Observer*
WHO SAGE Working Group on Influenza Vaccines, *Member*

Michelle Wille

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

Visitors to the Centre

There were no visitors to the Centre during 2021 due to ongoing COVID-19 restrictions.

Engagement in WHO activities

Event; Location, Date	Centre staff involved
Global consultation on 2021 Research Priorities for COVID-19 Vaccine Development, Virtual Forum, January 15 2021	Kanta Subbarao was an invited panellist
WHO GISRS meeting, COVID Vaccines: Methodological approaches to assess variants effect on efficacy, effectiveness and impact, Virtual Forum, 11 February 2021	Kanta Subbarao was an invited speaker Sheena Sullivan was an invited panellist
WHO Consultation on the Composition of Influenza Vaccines for the northern hemisphere 2021-2022 (e-Consultation), 17 February – 4 March 2021	Kanta Subbarao, Ian Barr, Heidi Peck, Yi-Mo Deng, and Sheena Sullivan attended
Integrated Surveillance of Influenza and SARS-CoV-2: Unpacking the US CDC Influenza A, Influenza B, SARS-CoV-2 Multiplex RT-PCR (Flu SC2) Assay; Virtual Forum, 26 May 2021	Pina Ianello attended
14th Bi-Regional Meeting of National Influenza Centres and Influenza Surveillance in the WHO's Western Pacific and South-East Asia Regions; Virtual Forum, 17-19 August 2021	Ian Barr and Sheena Sullivan attended
COVID-19 vaccines: will emerging data allow increased reliance on vaccine immune responses for public health and regulatory decision-making?; Virtual Forum, 9 September 2021	Kanta Subbarao attended
WHO Consultation on the Composition of Influenza Vaccines for the southern hemisphere 2021, 13-30 September 2021	Kanta Subbarao, Ian Barr, Yi-Mo Deng, Heidi Peck, and Ammar Aziz attended
WHO Pandemic Foresight Expert Workshop, October 2021	Kanta Subbarao attended
WHO SAGE meeting (including the joint SAGE/MPAG session on the Malaria vaccine), 4-7 October 2021	Sheena Sullivan attended
2nd WHO Global e-Consultation on the Integrated Sentinel Surveillance of Influenza and SARS-CoV-2 and the Development of GISRS Plus; Virtual Forum, 12-14 October 2021	Ian Barr and Sheena Sullivan attended
10th Meeting of the WHO Expert Working Group of the GISRS for Surveillance of Antiviral Susceptibility, 2 -4 November and 6 December 2021	Mariana Baz attended
WHO consultation on COVID-19 vaccines research: How can vaccine research further contribute to achieve the control of the pandemic everywhere?, 6 December 2021	Kanta Subbarao was an invited panellist

Other Conference Participation and Professional Engagement

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

Event; Location, date	Centre staff involvement
Keystone Symposium eSymposia 'COVID-19:One Year Later'; Virtual Forum, 8-9 February 2021	Kanta Subbarao, Nikita Deshpande, Paulina Koszalka, and James Barnes attended
Epigenetics 2021; Virtual Forum, 17-19 February	Nikita Deshpande attended
34th International Conference on Antiviral Research (ICAR); Virtual Forum, 22-26 March 2021	Nikita Deshpande and Sook Kwan Brown attended
GASK Virtual Vaccine Days Attributes of current and new vaccine technologies symposium, 28 April 2021	Kanta Subbarao was session moderator
Pint of Science Festival, May 2021	Michelle Wille was a volunteer
COVID-19 Lessons to Inform Pandemic Influenza Response workshop; Virtual Forum, 18-25 May	Annette Fox attended
Organoids are US; Virtual Forum, 1 June 2021	Nikita Deshpande attended
World Society for Virology: Tracking Global Viral Epidemics; Virtual Forum, 16-18 June 2021	Nikita Deshpande attended
APQO/Qualcon 2021; Virtual Forum, October 2021	Katie Milne attended
Global Health Webinar - COVID-19: balancing priority groups and vaccine equity; Virtual forum, 8 October 2021	Kanta Subbarao was an invited panellist
Victorian Infection & Immunity Network Young Investigator Symposium Series; Virtual Forum, 15-17 November 2021	Ryan Tseng was part of the Symposium Organising Committee, Session 2 and 3 Co-Chair

Community Engagement

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

Chris Bailie

- Contributed to an article on The Conversation titled, 'Flu vaccines are updated every year. We can learn from this process as we respond to COVID variants', published 18 March 2021; https://theconversation.com/flu-vaccines-are-updated-every-year-we-can-learn-from-this-process-as-we-respond-to-covid-variants-156580

Ian Barr

- Participated in an interview for Channel 7 News titled, 'Experts push for high vaccination rates despite lower flu virus cases', published 24 February 2021; https://www.youtube.com/watch?v=G90nVN_6uwI&feature=youtu.be

Community Engagement (continued)

Ian Barr (continued)

- Featured in an article on Medscape titled, 'No Flu Season Will Affect Next Year's Vaccine Prep', published 3 March 2021; https://www.medscape.com/viewarticle/946779
- Authored an article on The Conversation titled, 'Yes, COVID vaccines are front and centre. But don't forget about your flu shot', published 24 March 2021; https://theconversation.com/yes-covid-vaccines-are-front-and-centre-but-dont-forget-about-your-flu-shot-157051
- Featured in an article with the New Daily titled, 'Flu season to hit harder, later in 2021 with doctors 'scrambling' to administer shots', published 5 April 2021; https://thenewdaily.com.au/news/2021/04/05/flu-season-late-2021/
- Participated in an interview with Radio National Breakfast titled, 'Could a more deadly influenza virus emerge after COVID-19?', published 9 April 2021; https://www.abc.net.au/radionational/programs/breakfast/deadly-influenza-virus-could-emerge-after-covid-19/13295106
- Participated in an interview with The Australian Science Media Centre titled, 'COVID-19 Briefing: What is 'gain of function' research?', published 13July 2021; https://www.scimex.org/newsfeed/covid-19-briefing-alertwhatis-gain-of-function-research
- Participated in an interview with The Financial Times titled, 'US and Europe brace for winter flu outbreaks as social distancing ends', published 6 August 2021; https://www.ft.com/content/3a9ff5fd-e49a-49e5-803e-13bc382349db
- Participated in an interview with newsGP titled, 'Flu-zero: More than a year since Australia's last flu death', published 16 August 2021; https://www1.racgp.org.au/newsgp/clinical/australia-records-zero-flu-deaths-over-past-12-mon?utm_source=twitter&utm_medium=newsgpau&utm_campaign=348fdaf8-5556-40c2-836d-a67f3ea231f9
- Participated in an interview with The New Daily titled, 'The surprising health upside to Australia's COVID lockdowns, and why a flu shot still matters', published 19 August 2021; https://thenewdaily.com.au/life/wellbeing/2021/08/19/covid-influenza-australia-lockdown/
- Participated in an interview with ABC News titled, 'Influenza cases hit an all-time low in Australia in 2021 — that could be a problem when it returns', published 16 September 2021; https://www.abc.net.au/news/2021-09-16/queensland-what-happened-to-the-flu-in-2021/100456616
- Participated in an interview with WebMD titled, 'Flu Shot Highly Recommended This Year', published 29 September 2021; https://www.webmd.com/cold-and-flu/news/20210929/flu-shot-highly-recommended-this-year
- Participated in an interview with Chemical & Engineering News titled, 'Flu shots or COVID-19 boosters: which should you get first?', published 30 September 2021; https://cen.acs.org/pharmaceuticals/vaccines/Flu-shots-COVID-19-boosters-which-should-you-get-first/99/web/2021/09
- Quoted in an interview with CNN titled, 'Experts warn the flu could make a comeback this winter', published 13 October 2021; https://wsvn.com/news/us-world/experts-warn-the-flu-could-make-a-comeback-this-winter/
- Participated in an interview with ABC News titled, 'COVID-19 pandemic drove flu to historic lows, and may have eliminated one virus type completely', published 21 October 2021; https://www.abc.net.au/news/science/2021-10-21/influenza-virus-yamagata-eradication-vaccine-covid-pandemic/100546836
- Participated in an interview with Richard Glover on ABC Drive Sydney, published 22 October 2021; https://www.abc.net.au/radio/sydney/programs/drive/drive/13589140

Community Engagement (continued)

Ian Barr (continued)

- Participated in an interview with Guardian Australia titled, 'Flu deaths drop dramatically in Australia due to Covid measures with one type possibly eliminated', published 4 November 2021; https://www.theguardian.com/society/2021/nov/04/flu-deaths-drop-dramatically-in-australia-due-to-covid-measures-with-one-type-possibly-eliminated
- Participated in an interview with The Age titled, 'After two years of low cases, big influenza season is coming', published 22 November 2021; https://www.theage.com.au/politics/federal/after-two-years-of-low-cases-big-influenza-season-is-coming-20211117-p599u0.html
- Participated in an interview with The Wall Street Journal titled, 'Did Covid-19 Cause Flu Strain to Go Extinct?', published 9 December 2021; https://www.wsj.com/articles/did-covid-19-cause-flu-strain-to-go-extinct-11639054801?st=dbz3dgvyv3i5n22&reflink=desktopwebshare_permalink
- Featured in an article by the Peter Doherty Institute titled, 'Growing influenza viruses in specialised cells could lead to more effective seasonal flu vaccines', which discussed the NPJ Vaccines article, published 23 December 2021; https://www.doherty.edu.au/news-events/news/growing-influenza-viruses-in-specialised-cells-could-lead-to-more-effective-seasonal-flu-vaccines

Mariana Baz

- Participated in an interview with 'TV Ciudad' ('City TV') about COVID-19 vaccine platforms, variants, and booster strategies, published 5 August 2021; https://sobreciencia.uy/la-estrategia-de-mezclar-plataformas-de-vacunas-no-es-nueva-y-ha-demostrado-ser-eficaz/

Heidi Peck

- Featured in an article by the Peter Doherty Institute titled, 'Growing influenza viruses in specialised cells could lead to more effective seasonal flu vaccines', which discussed the NPJ Vaccines article, published 23 December 2021; https://www.doherty.edu.au/news-events/news/growing-influenza-viruses-in-specialised-cells-could-lead-to-more-effective-seasonal-flu-vaccines

Patrick Reading

- Featured in a promotional video from the Pacific Community on 'Real time Covid-19 testing facility for Cook Islands', published 20 October 2021; https://www.youtube.com/watch?v=KM-rPCVE6YU

Kanta Subbarao

- Participated in an interview with ABC News 24 to mark the one year anniversary of the first COVID-19 case in Australia, published 25 January 2021; https://thedohertyinstitute.cmail20.com/t/i-l-mijudkd-jucihtuku-e/
- Featured in an article on Nature Online titled, 'How to redesign COVID vaccines so they protect against variants', published 29 January 2021; https://www.nature.com/articles/d41586-021-00241-6
- Participated in an interview with Virginia Trioli for ABC Melbourne Radio titled, 'Flu vaccine on track to be rolled out at usual time', published 25 February 2021; https://www.abc.net.au/radio/melbourne/programs/mornings/flu-vaccine-rollout-on-track/13191048
- Participated in an interview for NPR Radio titled, 'Why Scientists Are Infecting Healthy Volunteers With The Coronavirus', published 8 March 2021; https://www.npr.org/sections/health-shots/2021/03/08/974903666/why-scientists-are-infecting-healthy-volunteers-with-the-coronavirus

Community Engagement (continued)

Kanta Subbarao (continued)

- Co-authored an article on The Conversation titled, 'Flu vaccines are updated every year. We can learn from this process as we respond to COVID variants', published 18 March 2021; https://theconversation.com/flu-vaccines-are-updated-every-year-we-can-learn-from-this-process-as-we-respond-to-covid-variants-156580
- Participated in an interview for the ABC program, 'Invisible Wars', published 5 April 2021; https://iview.abc.net.au/show/invisible-wars
- Participated in a panel discussion for Melbourne Knowledge Week titled, 'Pandemic-proofing the future', published 26 April 2021; https://mkw.melbourne.vic.gov.au/event/pandemic-proofing-the-future/
- Participated in an interview with Virginia Trioli for ABC Melbourne Radio titled, 'Epidemiologists and engineers form group to study airborne COVID transmission, but struggle to get funding', published 27 April 2021; https://www.abc.net.au/radio/melbourne/programs/mornings/kanta-subbarao-aerosols-group/13319390
- Featured in an article on the 'Where I Work' series by Nature, titled, 'Global virus tracker', published 3 May 2021; https://www.nature.com/articles/d41586-021-01175-9
- Participated in an interview with Norman Swan on Health Report titled, 'Antibody tests for suitability of vaccines', published 31 May 2021; https://www.abc.net.au/radionational/programs/healthreport/antibody-tests-for-suitabiltiy-of-vaccines/13364082
- Featured in press release article from the Doherty Institute, titled 'Victorian collaboration boosts coronavirus research', published 28 June 2021; https://www.doherty.edu.au/news-events/news/victorian-collaboration-boosts-coronavirus-research
- Participated in an interview with Nature titled, 'COVID vaccine boosters: the most important questions', published 5 August 2021; https://www.nature.com/articles/d41586-021-02158-6
- Participated in an interview with ABC news titled, 'COVID vaccine booster shots 'will happen' in Australia, with experts weighing up Delta risk and breakthrough infections', published 25 August 2021; https://www.abc.net.au/news/2021-08-25/pfizer-moderna-covid-vaccine-booster-shots-for-australia/100393856
- Participated in an interview with Daily News titled, 'Here's what the next 6 months of the pandemic will bring', published 14 September 2021; https://www.nydailynews.com/health-fitness/sns-bb-next-six-months-pandemic-20210914-xgbp264eg5dyvmdfwvcnz6mrim-story.html
- Participated in an interview with 1st News titled, 'Will Covid-19 ‘end’ in the next 6-8 months? Here’s what experts say', published 14 September 2021; https://1stnews.com/will-covid-19-end-in-the-next-6-8-months-heres-what-experts-say/
- Featured in numerous articles on her Australian Academy of Health and Medical Sciences (AAHMS) fellowship, published 26 October 2021; https://www.doherty.edu.au/news-events/news/new-fellows-elected-to-the-australian-academy-of-health-and-medical-sciences-aahms
- Was featured in a Sabin Vaccine Institute The Influenzer Inititative episode titled 'Reshaping Vaccine R&D for Pandemic Prevention', published 17 November 2021; https://www.youtube.com/watch?v=LOZSIZKE3BQ
- Featured in a Good Weekend article by The Sydney Morning Herald titled, 'Who Mattered 2021', published 27 November 2021; https://www.smh.com.au/interactive/2021/gw-australians-who-mattered/
- Featured in a short video interview by The Royal Melbourne Hospital on the Omicron variant, as well as other COVID-19 variants, published 1 December 2021; https://twitter.com/TheRMH/status/1465787724477046787?s=20

Community Engagement (continued)

Kanta Subbarao (continued)

- Featured in an article by The Age titled, ‘Gremlin or Grinch? In a Melbourne lab, Omicron grows in a test tube’, published 21 December 2021; https://www.theage.com.au/national/victoria/gremlin-or-grinch-in-a-melbourne-lab-omicron-grows-in-a-test-tube-20211216-p59i9p.html

Sheena Sullivan

- Co-authored an article on The Conversation titled, 'Flu vaccines are updated every year. We can learn from this process as we respond to COVID variants', published 18 March 2021; https://theconversation.com/flu-vaccines-are-updated-every-year-we-can-learn-from-this-process-as-we-respond-to-covid-variants-156580
- Participated in an interview with The Wire 2SER 107.3 regarding the COVID-19 vaccine rollout, published 29 June 2021; https://app.mediaportal.com/isentia/#/playnow?u=155554&p=-2284130214&key=196183111323912721019837772396322177246
- Participated in an interview with Cosmos Magazine titled, 'Now that Australia is re-opening, what are the numbers that count?', published 12 November 2021; https://cosmosmagazine.com/health/covid/covid-numbers-that-count-now/
- Participated in an interview with MJA Podcasts (Episode 48) titled, 'Impact of opening international borders on influenza cases, with Associate Professor Sheena Sullivan', published 22 November 2021; https://www.mja.com.au/podcast/215/11/mja-podcasts-2021-episode-48-impact-opening-international-borders-influenza-cases
- Participated in an interview with ABC News, Xinhua print, Financial times print, and Sydney ABC radio to discuss the recent MJA publication titled, 'Preparing for out-of-season influenza epidemics when international travel resumes', published 22 November 2021;
- Participated in an interview with The Age titled, 'After two years of low cases, big influenza season is coming', published 22 November 2021; https://www.theage.com.au/politics/federal/after-two-years-of-low-cases-big-influenza-season-is-coming-20211117-p599u0.html
- Featured in an interview with Cosmos Magazine titled, 'COVID Booster: pandemic pluses, summer flu and long-lasting vaccine passes its first test', published 27 November 2021; https://cosmosmagazine.com/health/covid/long-lasting-immunity-from-covid-19/?utm_content=buffer1b01d&utm_medium=social&utm_source=twitter.com&utm_campaign=buffer

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 2021, the website was viewed by 8,590 unique users from 151 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 2021. The Centre’s Twitter profile gained 146 followers during the year, with a total of 816 followers by 31 December 2021.

New and departing staff members

New staff

- Presa Chanthalavanh (April)
- Xiaomin Dong (February)
- Anastasia Jessica Hadiprojo (December)
- Shaeley Henderson (April)
- Genevieve O'Neill (June)
- Stephany Sanchez (May)
- Harry Stannard (April)

Departing staff

Ms Jayde Simpson had been a part of the Centre as Administration Officer for the past nine years. She has now returned to her native New Zealand to enjoy a slower life on the beach.

Mr Anthony Leggieri had been a medical scientist with the surveillance group for the last one and a half years. He has now taken on a new role with Sonic Healthcare and Melbourne Pathology.

Ms Ankita George had been a research assistant within the research division for the last two years. She has now taken on a new role as a research assistant in a Neuro-Oncology lab at the Murdoch Children's Research Institute.

Dr Edin Mifsud had been a post-doctoral researcher with the Centre for the past four years. She has now taken on a position with Seqirus as a Medical Science Liaison.

Ms Shaeley Henderson had been an admin officer with the Centre for the past six months.

Ms Vivian Leung had been an epidemiologist at the Centre for the past seven years. She has now taken on a position with the Royal Melbourne Hospital.

Dr Chris Bailie had been a MAE student under the supervision of A/Prof Sheena Sullivan at the Centre for the past year and a half. Congratulations on finishing your degree, Chris.

Management and staff

Director
Prof Kanta Subbarao

Deputy Director
Prof Ian Barr

Administrative officer
Jayde Simpson (until Mar)
Shaeley Henderson* (until Sep)

Quality & Regulatory Officer
Katie Milne

Educator/Research scientist
Prof Patrick Reading

Laboratory Manager/ Senior Medical Scientist
Dr Paul Whitney

Communications officer
Dr Miku Kuba

Surveillance

ANTIGENIC ANALYSIS
Head: Heidi Peck
Medical scientists:
Monica Bobbitt
Presa Chanthalavanh*
Joelle Dharmakumara
Leah Gillespie
Anthony Leggieri (until Feb)
Lani Metuisela
Megan Triantafilou
Tasoula Zakis
Laboratory Assistant:
Violeta Stojceva

GENETIC ANALYSIS
Head: Dr Yi-Mo Deng
Medical scientists:
Dr Xiaomin Dong*
Pina Iannello
Hilda Lau
Jean Moselen
Natalie Spirason

ANTIVIRAL DRUG SENSITIVITY
Head: Dr Mariana Baz
Medical scientist: Sook Kwan Brown

BIOINFORMATICS
Manager: Naomi Komadina
Bioinformatician: Dr Ammar Aziz

Vaccine development

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

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

Research

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

ANTIVIRALS AND ANIMAL INFLUENZAS
Senior research scientist:
Dr Mariana Baz
Post-Doctoral researchers
Dr Edin Mifsud (until Sep)
Dr Nikita Deshpande
Dr Michelle Wille (Honorary)
Research assistants:
Malet Aban
Ankita George (until Feb)
Harry Stannard*
Ph. D Students:
Paulina Koszalka

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

Epidemiology

Head:
A/Prof Sheena Sullivan
Epidemiologists:
Vivian Leung (until Nov)
Genevieve O'Neill*
Research assistant:
Arseniy Khvorov
MAE Candidate:
Dr Chris Bailie (until Nov)

**New staff members in 2021*