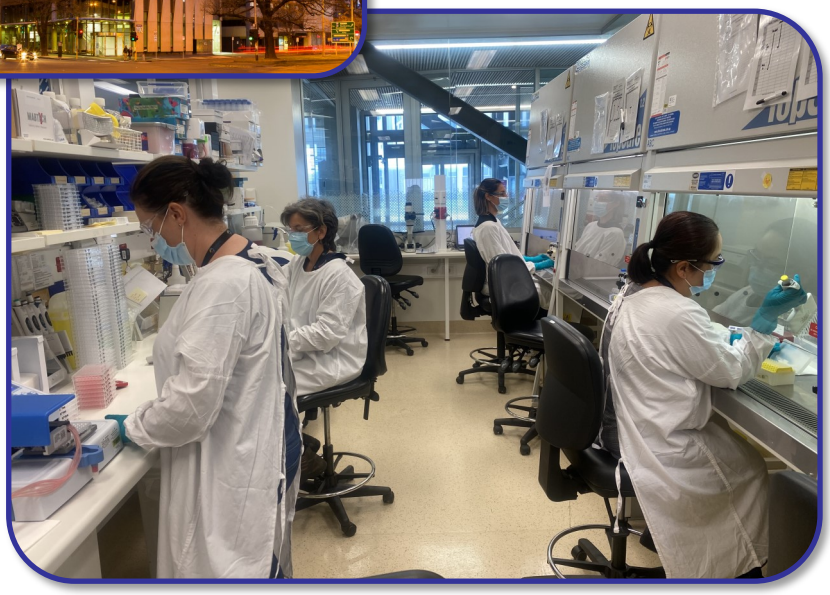

Annual Report 2020

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.

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Highlights of 2020

Surveillance

The Centre received and processed **2021 samples**, of which **99.6% were tested**. Of viruses tested, approximately **59.6%** were **A(H1N1)pdm09 viruses.**

Research, publications and grants

The Centre further developed its research program during 2020, with Centre staff involved as authors on **50 papers** in peer-reviewed journals. Centre staff were awarded several research grants, including **USD$629,251** from the **US National Institutes of Health (NIH).**

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.**

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 2020.

Director's report

I present the 2020 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.

In early January 2020, the World Health Organization was notified of a novel coronavirus causing severe respiratory illness that emerged in Wuhan, China in late 2019. In a few short weeks, the virus, named SARS-CoV-2 spread globally causing the Corona Virus Infectious Disease 2019 or COVID-19 pandemic. Although Australia was spared the scale of morbidity and mortality seen in many other countries, Melbourne suffered a large second wave of infections and a long shutdown.

Coincidentally 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 2021 influenza samples from 31 laboratories in Australia and 13 other countries during 2020. The largest proportion (nearly 60%) of the samples analysed were influenza A(H1N1)pdm09 viruses. The Centre continued to conduct antigenic and genetic characterisation of viruses and noted an increase in genetic diversification of the H1 HA gene. The Centre also continued routine testing of viruses for reduced susceptibility to neuraminidase inhibitors and the polymerase inhibitor baloxavir marboxyl.

During 2020 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 2020. 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 2020 because of the COVID-19 pandemic. However, Centre staff participated in remote training in several countries including the Pacific Islands, Cambodia, Mongolia and Indonesia. Centre staff presented remotely at several domestic and international conferences in 2020.

Centre staff contributed to a total of 50 original research papers, reviews and reports in 2020. 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, Director of VIDRL, and many other members of VIDRL staff, especially Jane Brewster, Anna Ayres and Dallas Wilson, for their support of the Centre's work at every level during 2020. 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 2020, 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 2021 and onwards.

Prof Kanta Subbarao
Centre Director

Surveillance

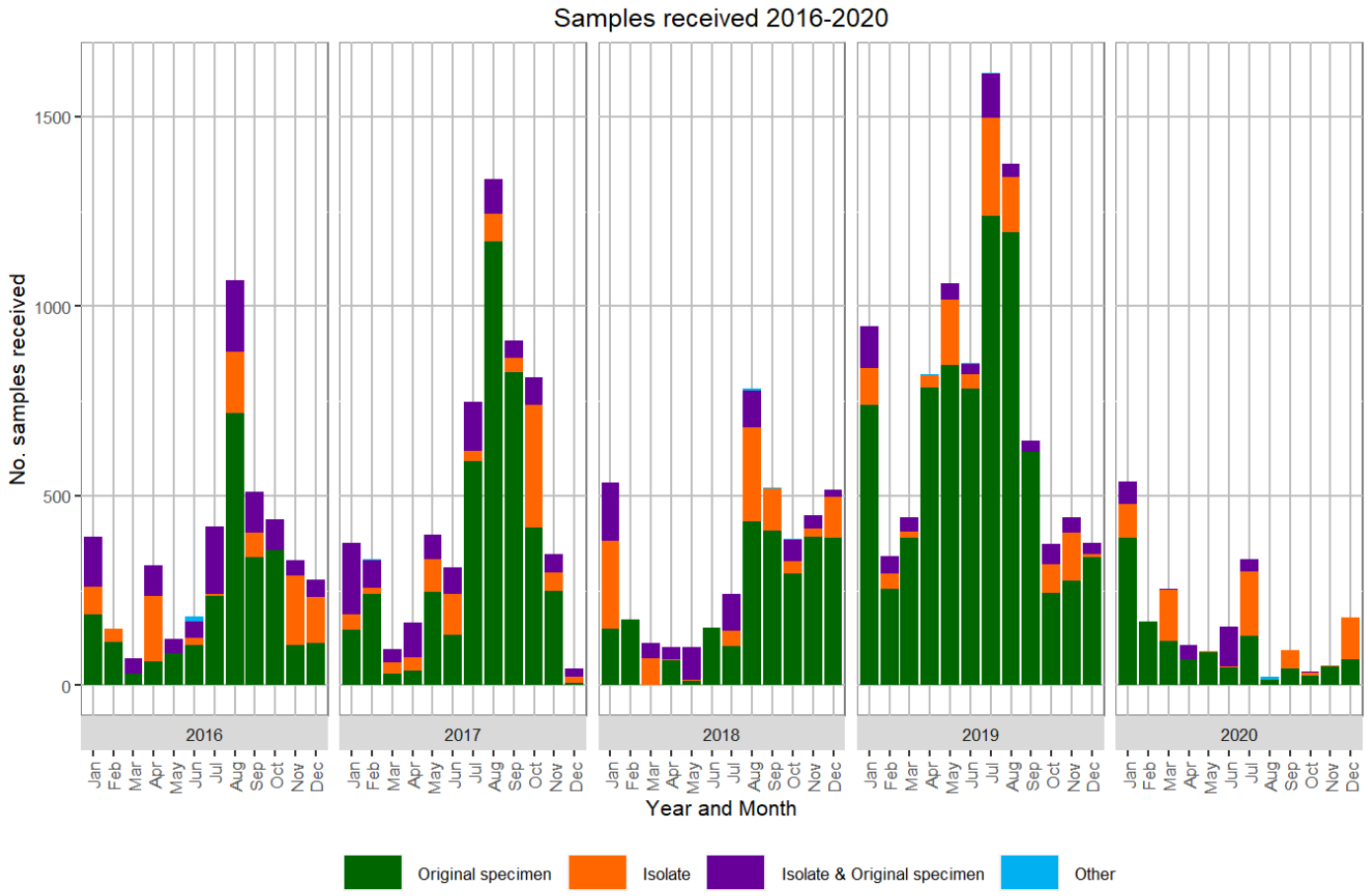
Introduction

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.

Two types of influenza virus, Type A and Type B, 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, 2016-2020



Receipt of Influenza Viruses

During 2020 the Centre received 2021 clinical specimens and/or virus isolates from 31 laboratories in 14 countries (Figures 1 and 2, Table 1). This is significantly lower than the number of samples received by the Centre during 2019, and is consistent with the low number of influenza infections during the 2020 Australian influenza season. This can be attributed to the restrictions in place during most of 2020 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). A total of 39 samples came from Australian general practictioner 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 2012 samples (99.6%) 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, 59.6% were A(H1N1)pdm09 viruses, 25.7% were identified as A(H3N2) viruses, 12.4% were B/Victoria and 0.3% were B/Yamagata viruses (Table 3).

Figure 2. Geographic spread of influenza laboratories sending viruses to the Centre during 2020.

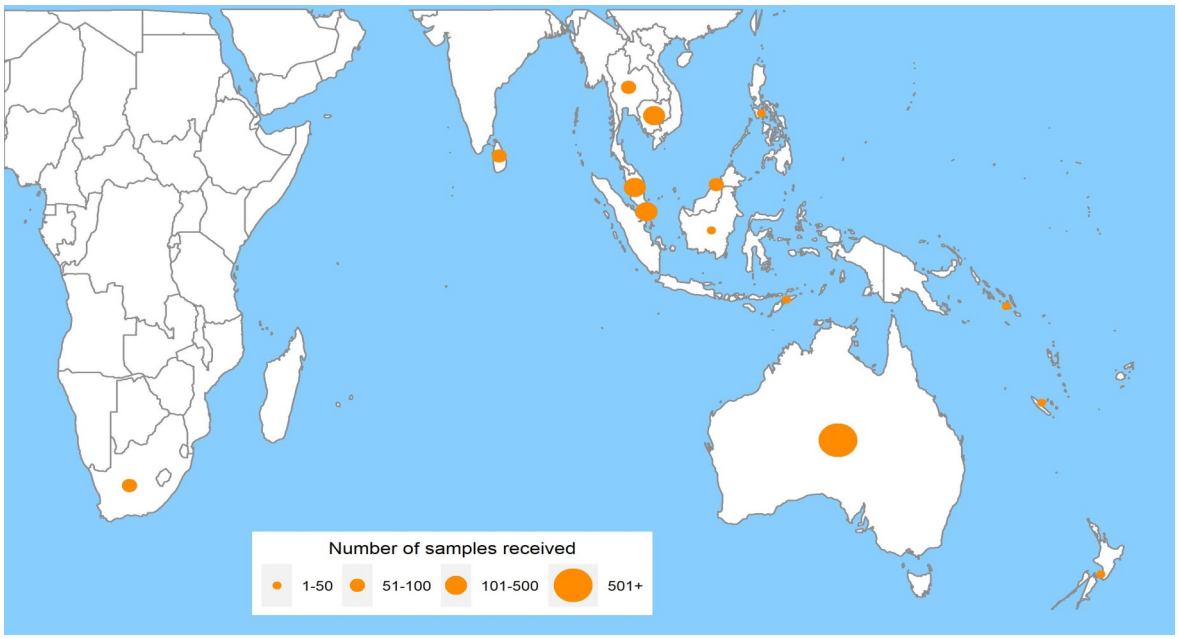


Figure 3. Age distribution of patients from whom samples were received at the Centre in 2020 and the age is known.

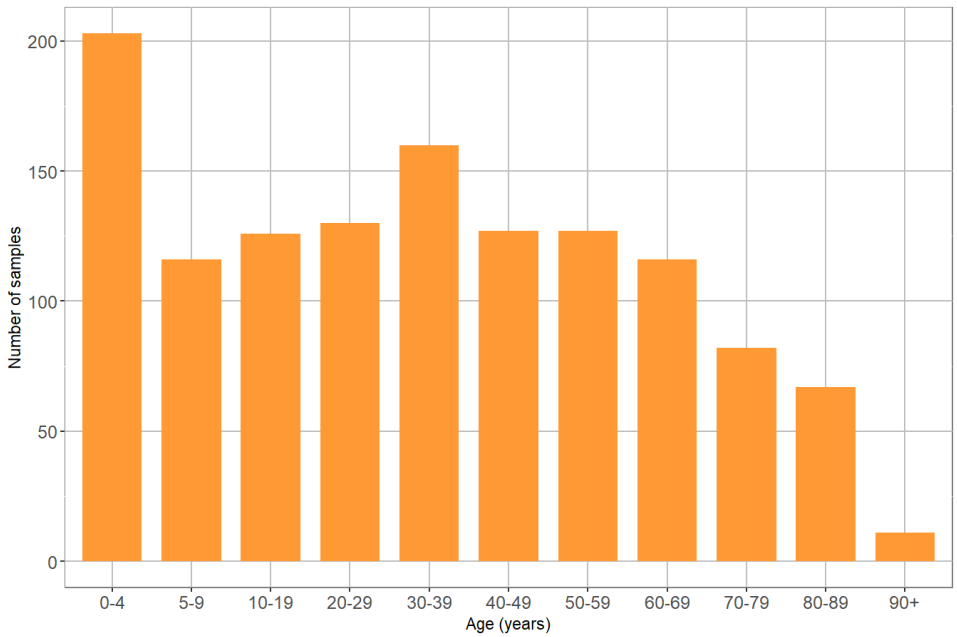


Table 1. Samples received by the Centre in 2020, by country.

Country	Samples received				% Samples tested
	Specimens	Isolates	Specimen + Isolate	Other (eg. RNA/ DNA/tissue)	
AUSTRALASIA					
Australia	803	29	66	8	99.4%
New Zealand	26	9	1		88.9%
SOUTH PACIFIC					
New Caledonia	13				100%
Solomon Islands	26				100%
SOUTH EAST ASIA					
Brunei	54				100%
Cambodia	99	93			100%
Indonesia		46			100%
Malaysia		322			100%
Philippines	28		7		100%
Singapore	32	6	110		100%
Thailand	5	65			100%
Timor-Leste	22				100%
SOUTH ASIA					
Sri Lanka	96				100%
AFRICA					
South Africa		1	54		100%
TOTAL	**1204**	**571**	**238**	**8**	**99.6%**

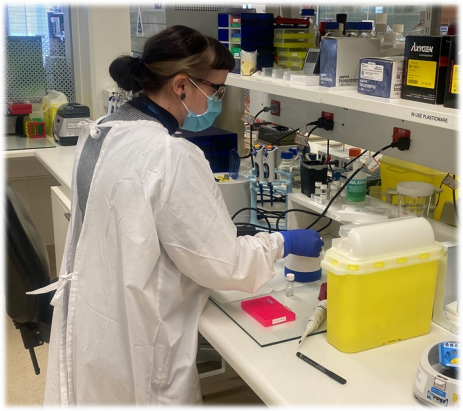


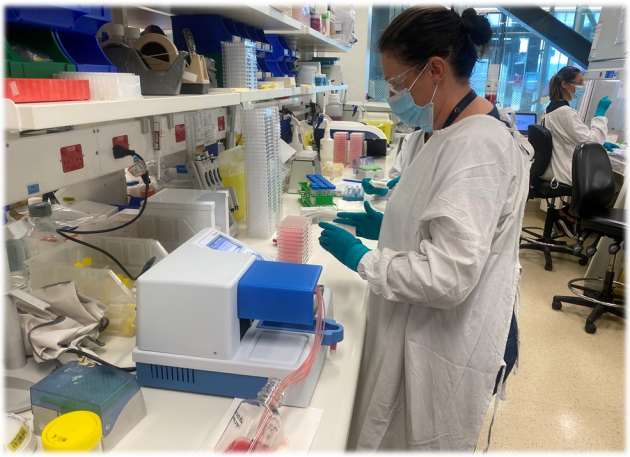
Table 2. Samples received from general practitioner based surveillance systems in Australia, 2020

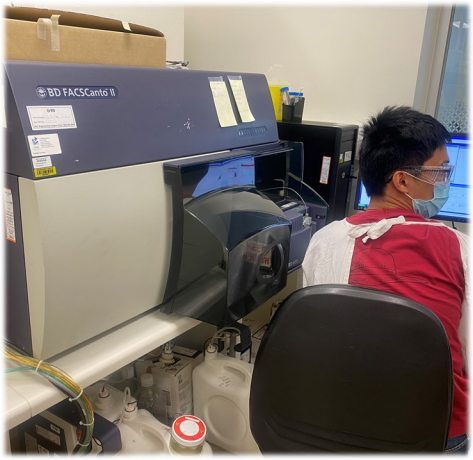
	No. samples received	No. isolates recovered*	Viruses analysed by HI assay
Australian Sentinel Practices Research Network *(ASPREN)*	21	5	5
Victorian Sentinel Practices Influenza Network *(VicSPIN)*	2	1	1
Influenza Complications Alert Network (*FluCAN*)	4		
TOTAL	**27**	**6**	**6**

** 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 2020, by country.

Country	Samples tested by cell culture and/or RT-PCR assay							
	A (H1N1)pdm09	A H3N2	A mixed subtype	A unsubtyped	B/Victoria	B /Yamagata	B lineage undetermined	Mixed type (A/B)
AUSTRALASIA								
Australia	349	104	3	16	65	1	1	1
New Zealand	21	3			3			
SOUTH PACIFIC								
New Caledonia	11				1			
Solomon Islands	1	1						
SOUTH EAST ASIA								
Brunei	29	4						
Cambodia	39	104			33			
Indonesia	14	18			12			
Malaysia	232	70			5			
Philippines	11	3			4			
Singapore	78	25			20	3		
Thailand	30	21			17			
Timor-Leste		11		6				
SOUTH ASIA								
Sri Lanka	9	14		1	16		2	
AFRICA								
South Africa	38	7			9			
TOTAL	**892**	**385**	**3**	**23**	**185**	**4**	**3**	**1**





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 2020

A total of 1962 isolates that were received at the Centre in 2020 were cultured and isolated in MDCK cells, of which 1383 (70.5%) produced a positive result. The largest proportion of viruses were A(H1N1)pdm09 viruses (63.1%), followed by A(H3N2) (24.4%) (Figure 4). The predominance of A(H1N1)pdm09 viruses for samples received and successfully isolated by cell culture at the was observed in some world regions (Africa, Australasia, South East Asia, and South Pacific) Centre (Figure 5). In the South Pacific Region, of viruses that were successfully cultured and isolated in cells, B/ Victoria viruses and A(H3N2) viruses predominated.

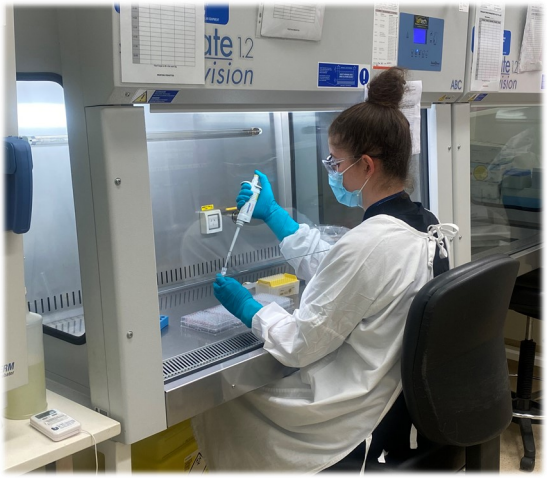


Figure 4. Influenza sub/types and lineages of samples received in 2020 and characterised by antigenic analysis.

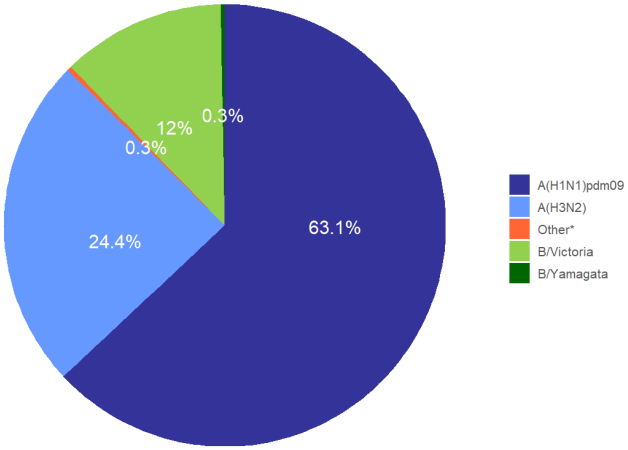
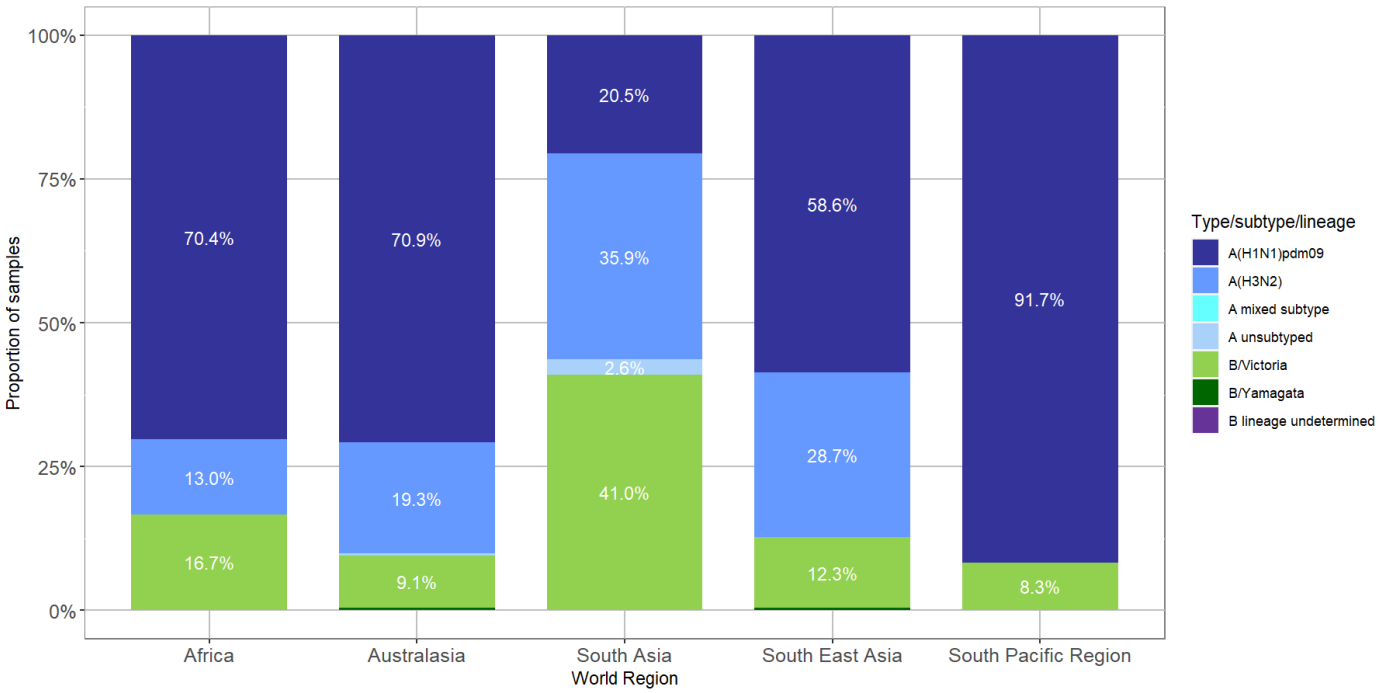


Figure 5. Influenza sub/types and lineages of isolates received from different world regions during 2020 as determined by antigenic analysis.



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 2020. Note that some viruses were analysed by both Sanger sequencing and NGS, and are therefore represented twice in this figure.

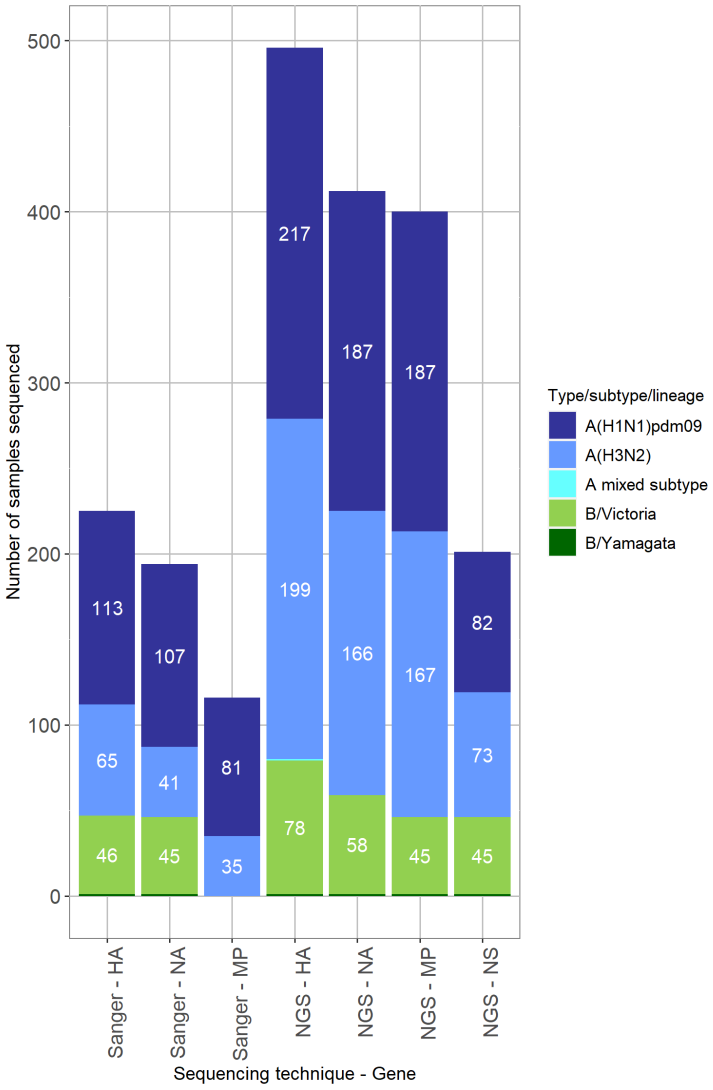
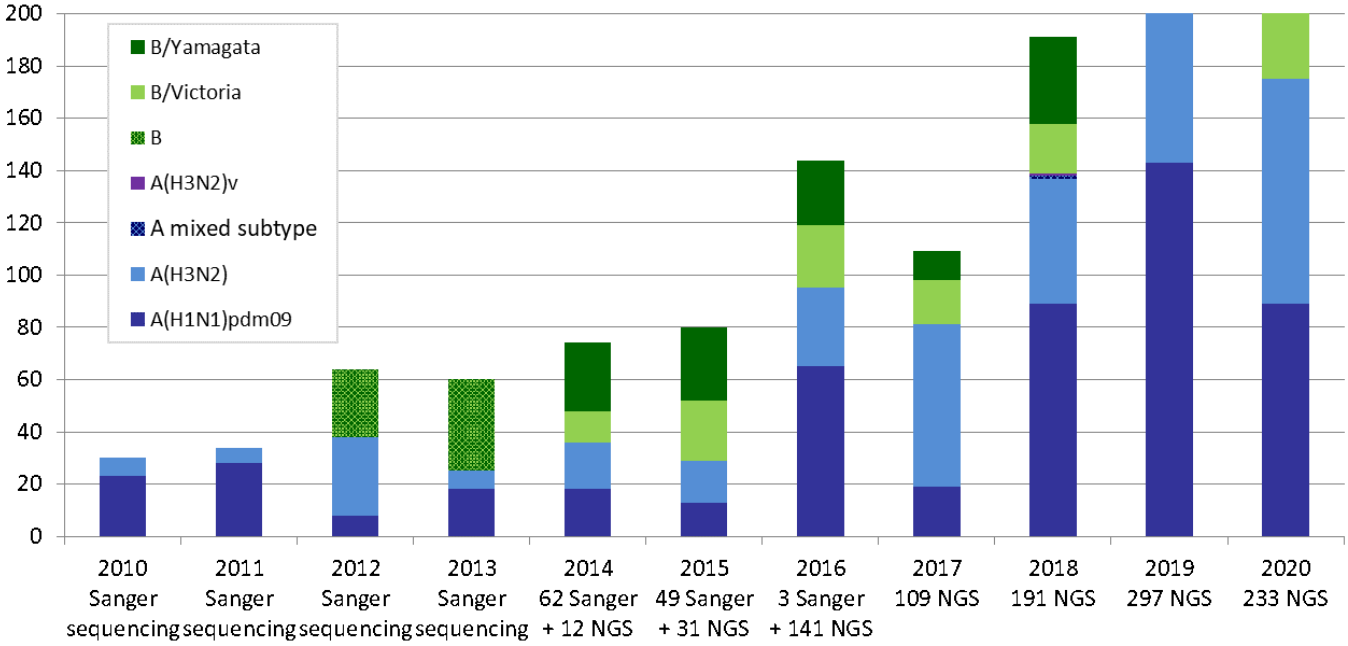


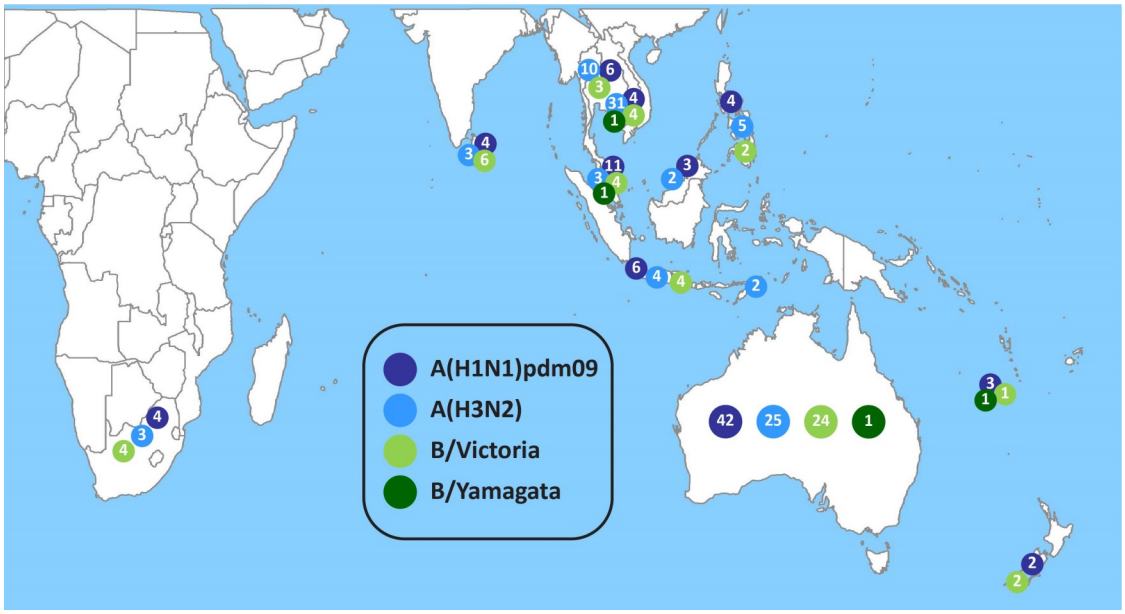
Figure 7. Number of viruses analysed by full genome sequencing 2010-2020 using Sanger sequencing and NGS techniques.



Sequencing 2020

In 2020, 706 HA, 590 NA, 508 MP and 201 NS genes from 709 human viruses received at the Centre were analysed by Sanger sequencing or NGS (Figure 6). Of these viruses, full genome sequencing was performed on 233 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 2020.



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 2020

A total of 169 gene sequences from 25 human influenza viruses were deposited with GISAID in 2020 (Table 4). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 19 influenza viruses (5 A(H1N1)pdm09 viruses and 14 A(H3N2) viruses) were also represented in the Centre's submissions (data not shown).

Table 4. Genetic sequences submitted to GISAID by the Centre in 2020.*

Gene / Type/ Subtype/Lineage	HA	NA	MP	NS	PB1	PB2	PA	NP	Total
A(H1N1)pdm09	9	9	6	6	6	6	5	6	**53**
A(H3N2)	14	14	14	14	14	14	14	14	**112**
B/Victoria	2	2							**4**
Total	**25**	**25**	**20**	**20**	**20**	**20**	**19**	**20**	**169**

** Counts include all sequences submitted to GISAID during 2020, 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 2020 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 799 A(H1N1)pdm09 isolates were analysed by HI assay in 2020. A large proportion of viruses (83.65%) displayed similar antigenic properties to the cell-grown vaccine reference strain A/Michigan/45/2015 (Figure 9A, Table 5). A little under two thirds of viruses displayed antigenic properties similar to the cell-grown vaccine reference strain A/Brisbane/02/2018 (Figure 9B, Table 5). With this in mind, the A(H1N1)pdm09 component was updated to the A/Victoria/2570/2019 virus for the 2021 Southern Hemisphere vaccine.

Haemagglutinin gene sequencing

Sequencing was performed on a total of 325 HA genes. Phylogenetic analysis showed that the majority of circulating A(H1N1)pdm09 viruses sent to the Centre during 2020 were in subclade 6B.1A 183P-5A 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/Michigan/45/2015 and A/Brisbane/02/2018 reference virus.

	A(H1N1)pdm09 reference strain: A/Michigan/45/2015		A(H1N1)pdm09 reference strain: A/Brisbane/02/2018	
Region	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**
Africa			21	17 (44.74%)
Australasia	30	8 (21.05%)	157	150 (48.86%)
South Asia			4	4 (50.00%)
South East Asia	50	6 (10.71%)	234	82 (25.95%)
Pacific			9	1 (10.00%)
TOTAL	**80**	**14 (14.89%)**	**425**	**254 (37.41%)**

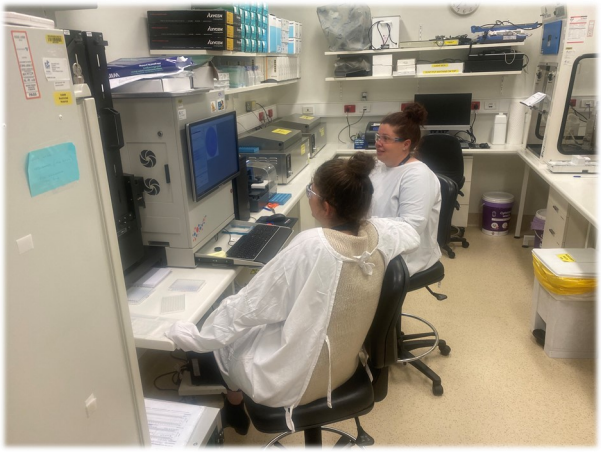


Figure 9. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/ Michigan/45/2015 reference virus.

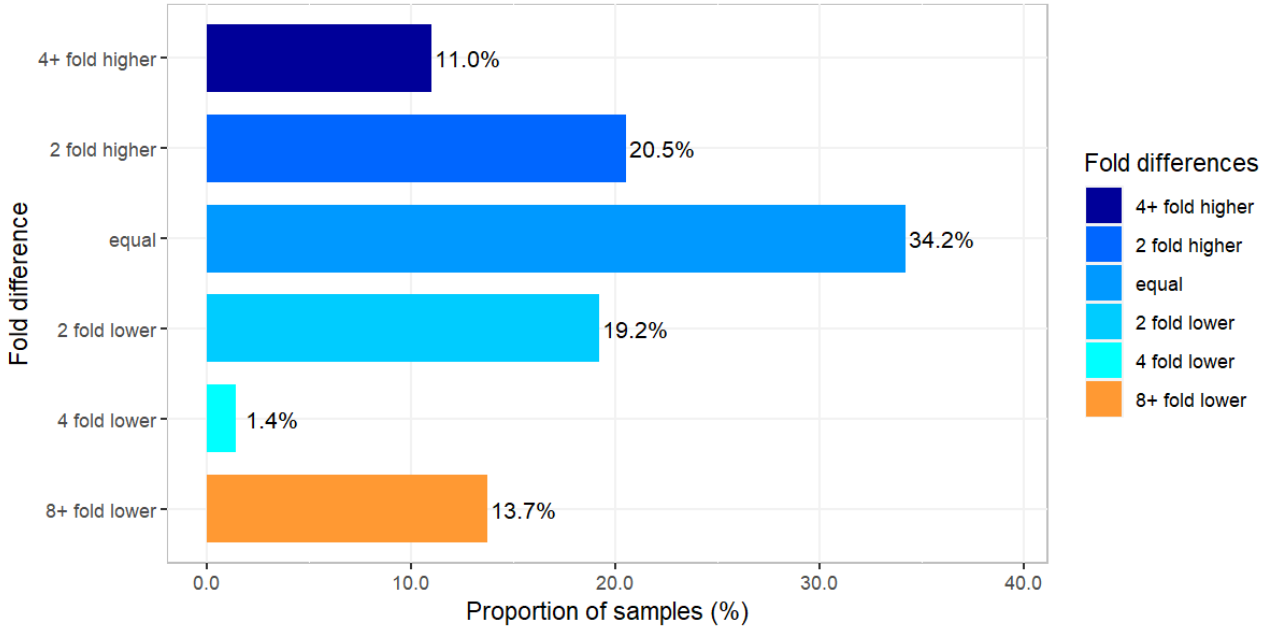
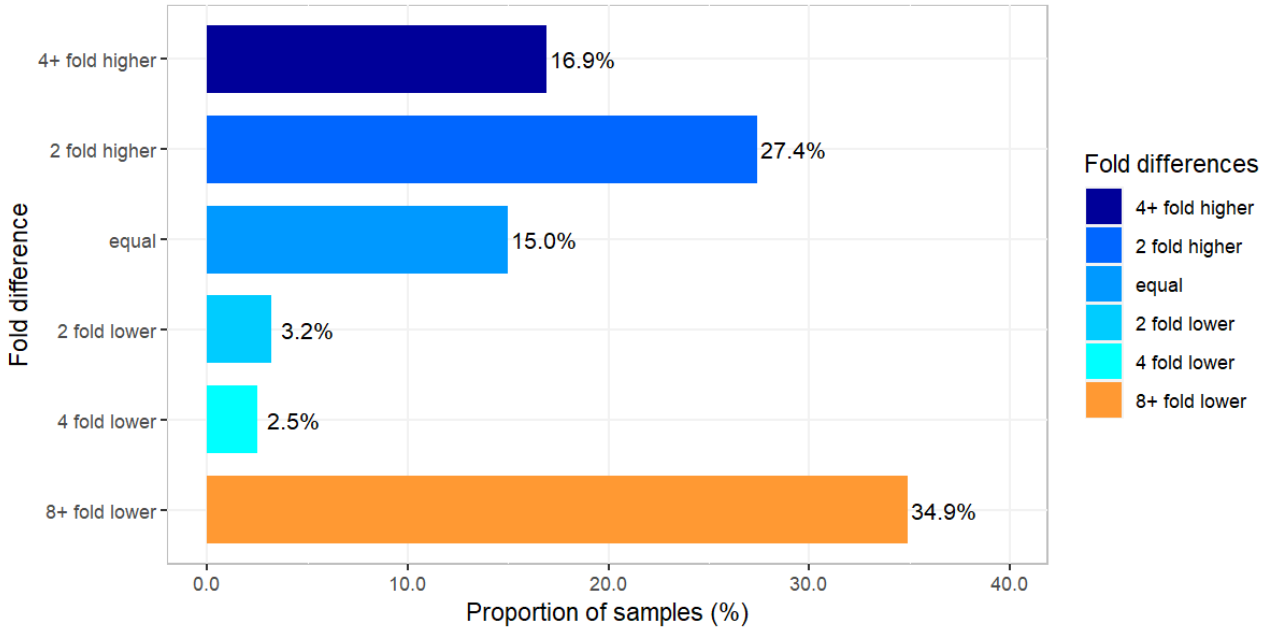
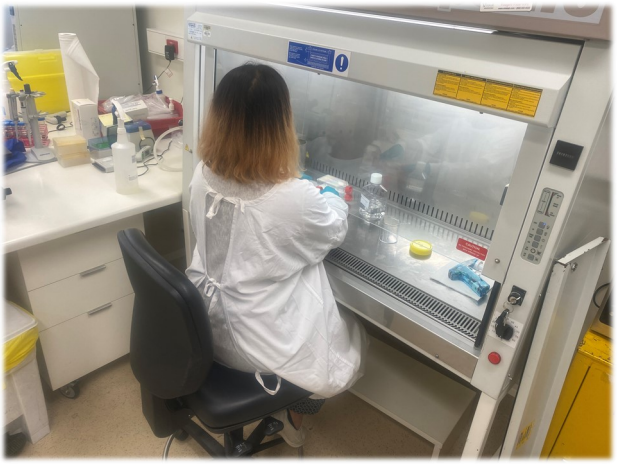


Figure 10. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/ Brisbane/02/2018 reference virus.





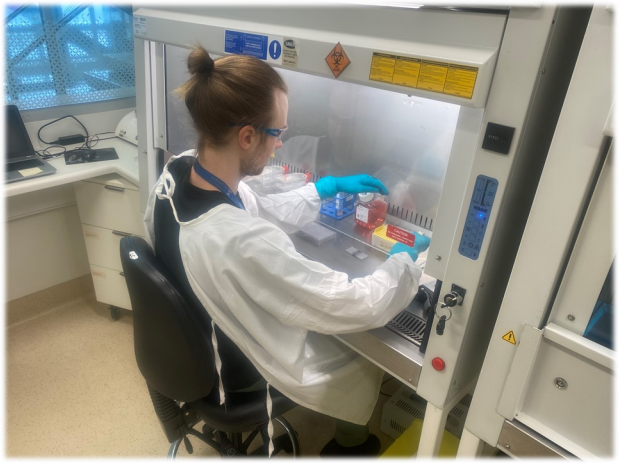
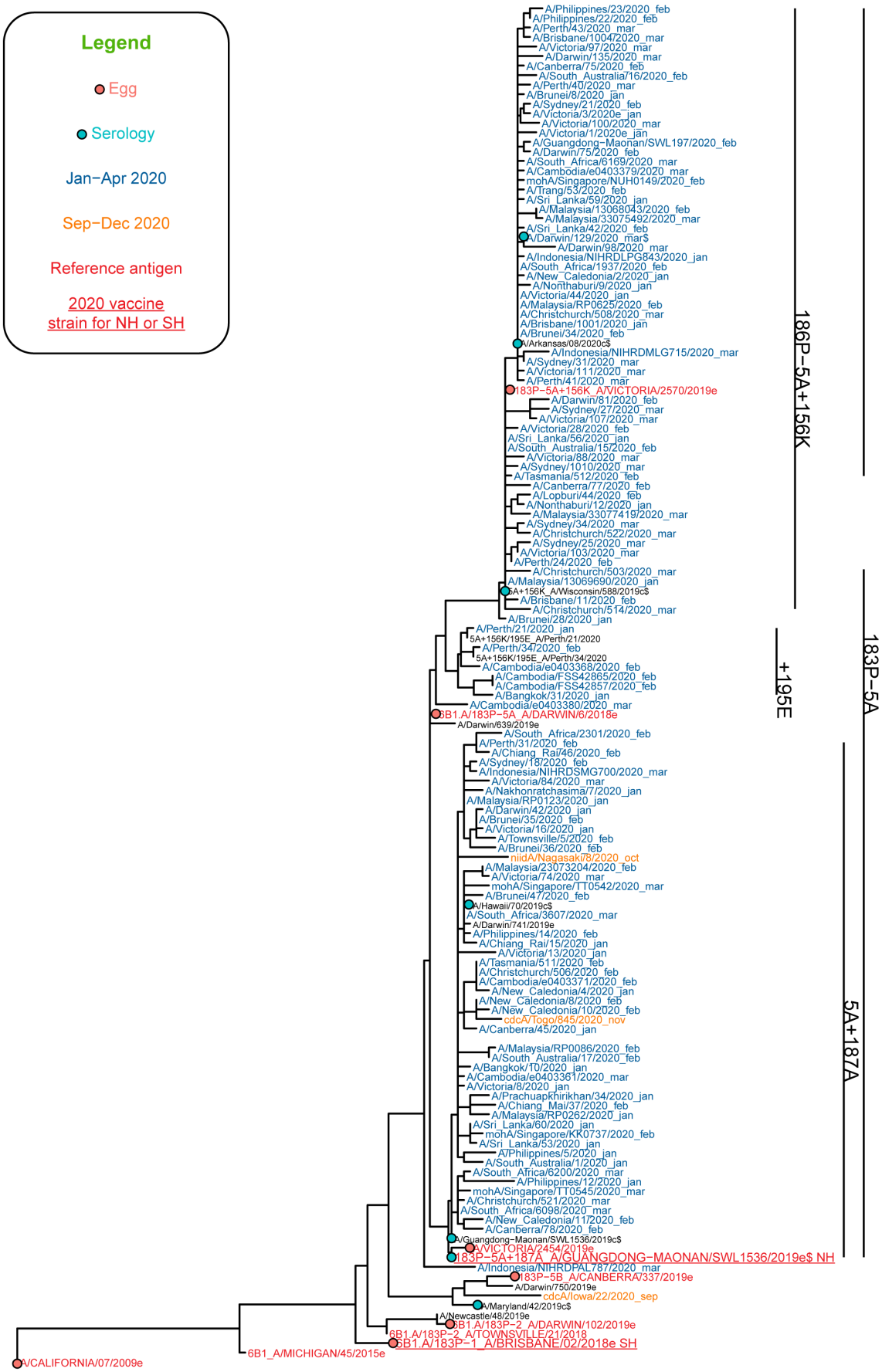


Figure 11. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2020.



Influenza A(H3N2)

Antigenic analysis

In recent years evolutionary changes in A(H3N2) viruses have made it difficult to detect antigenic change using conventional HI assays. To avoid binding of the neuraminidase protein to red blood cells, it has been necessary to add oseltamivir carboxylate to the assay. However, in the presence of oseltamivir, approximately 50% of current A(H3N2) isolates have insufficient haemagglutination titre to conduct the HI assay. Hence only a proportion of A(H3N2) virus isolates are successfully cultured and can be analysed by HI assay. Other assays, such as a focus reduction microneutralisation assay (FRA-MN) can be used to test the antigenic characteristics of these viruses. However, during 2020 no FRA-MNs were performed.

Of 314 A(H3N2) subtype isolates analysed by HI assay compared to the cell-propagated reference strain A/ Switzerland/8060/2017 (Figure 11, Table 6), the majority were low reactors. Additionally, isolates were analysed by HI assay against the A/South Australia/34/2019 cell-propagated reference strain (Table 6, Figure 12). A growing proportion were becoming low reactors. With this in mind, the A(H3N2) component was updated to the A/Hong Kong/2671/2019 virus for the 2021 Southern Hemisphere vaccine.

Haemagglutinin gene sequencing

A total of 253 HA genes from A(H3N2) viruses were sequenced. Phylogenetic analysis indicate that most circulating viruses fell into clade 3C2.a1b, represented by the new reference strain A/Hong Kong/2671/2019, which was recommended by WHO for inclusion in Southern Hemisphere vaccine in 2021 (Figure 14).

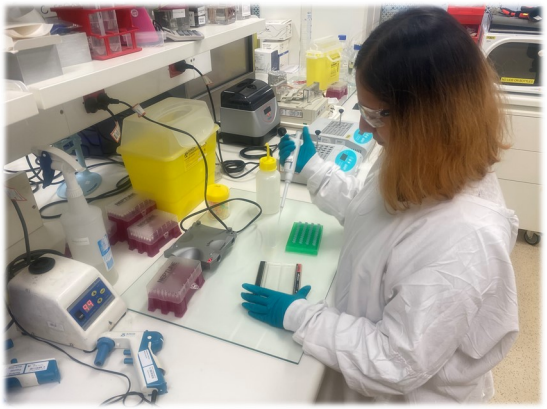


Table 6. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the cell-grown A/ Switzerland/8060/2017 reference virus.

	A(H3N2) reference strain: A/Switzerland/8060/2017		A(H3N2) reference strain: A/South Australia/34/2019	
Region	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**
Africa			4	2 (33.33%)
Australasia	38	22 (36.67%)	19	16 (45.71%)
South Asia	7	1 (12.50%)	5	
South East Asia	42	7 (14.29%)	115	36 (23.84%)
TOTAL	**87**	**30 (25.64%)**	**143**	**54 (27.41%)**

Figure 12. Summary of fold differences in titres of A(H3N2) viruses analysed at the Centre by HI assay compared to the A/ Switzerland/8060/2017 reference virus.

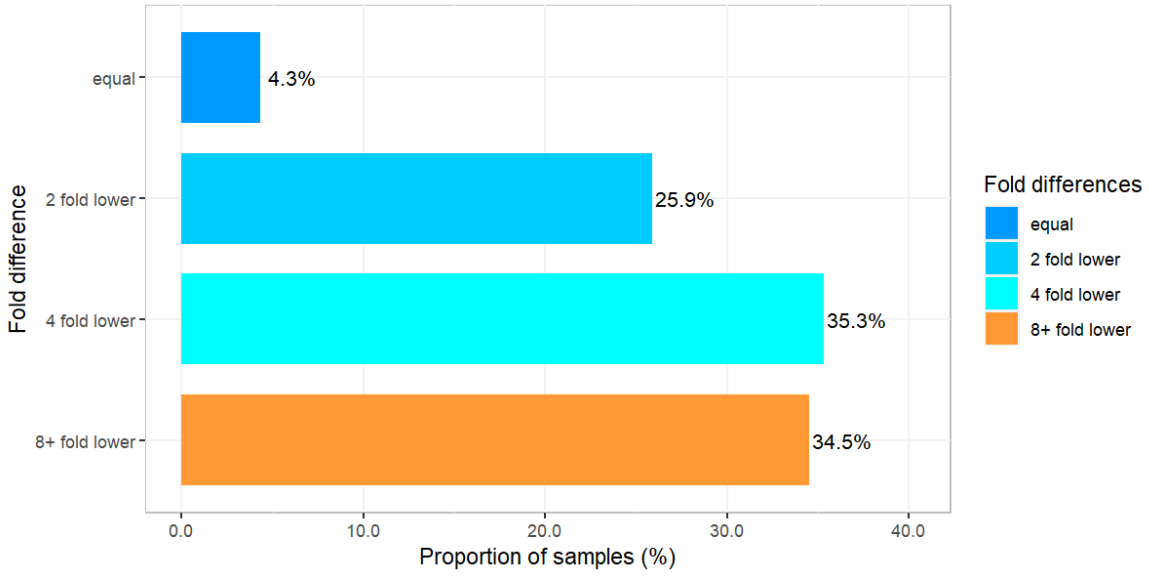
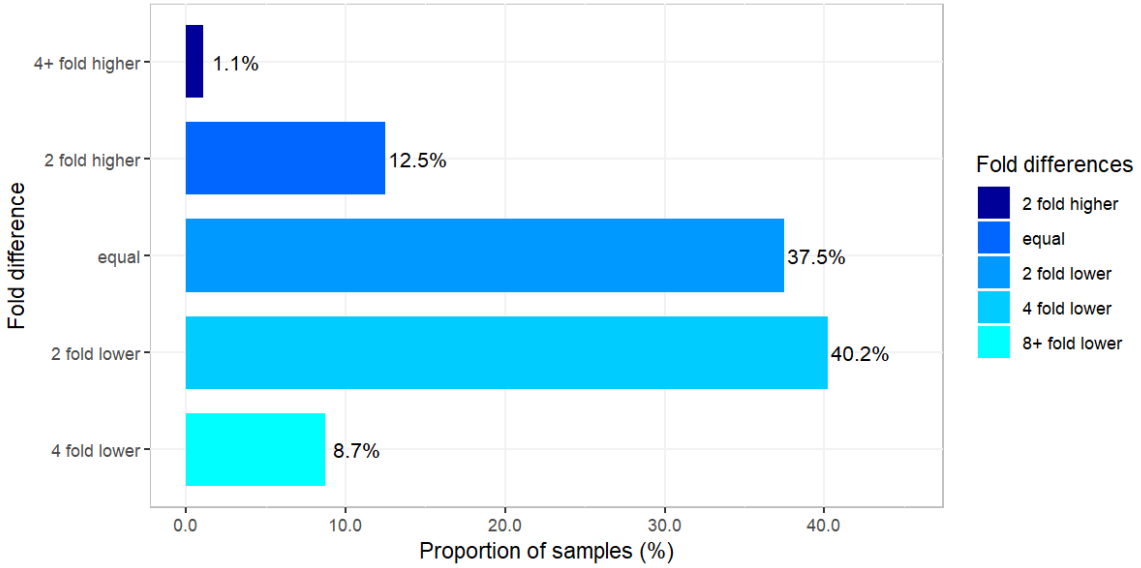


Figure 13. Summary of fold differences in HI titres of A(H3N2) viruses analysed at the Centre compared to the A/South Australia/34/2019 reference virus.



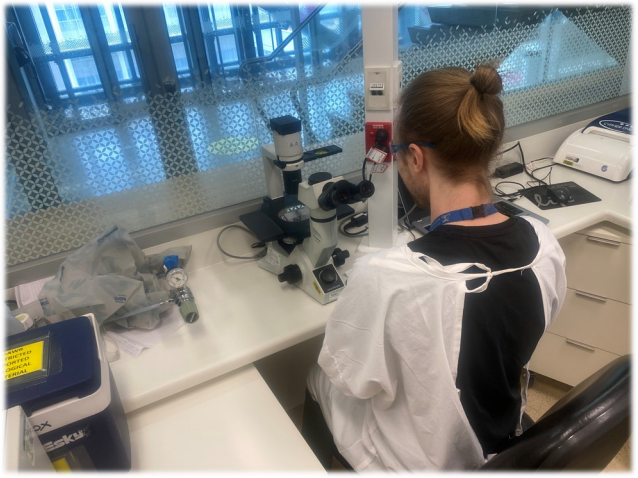
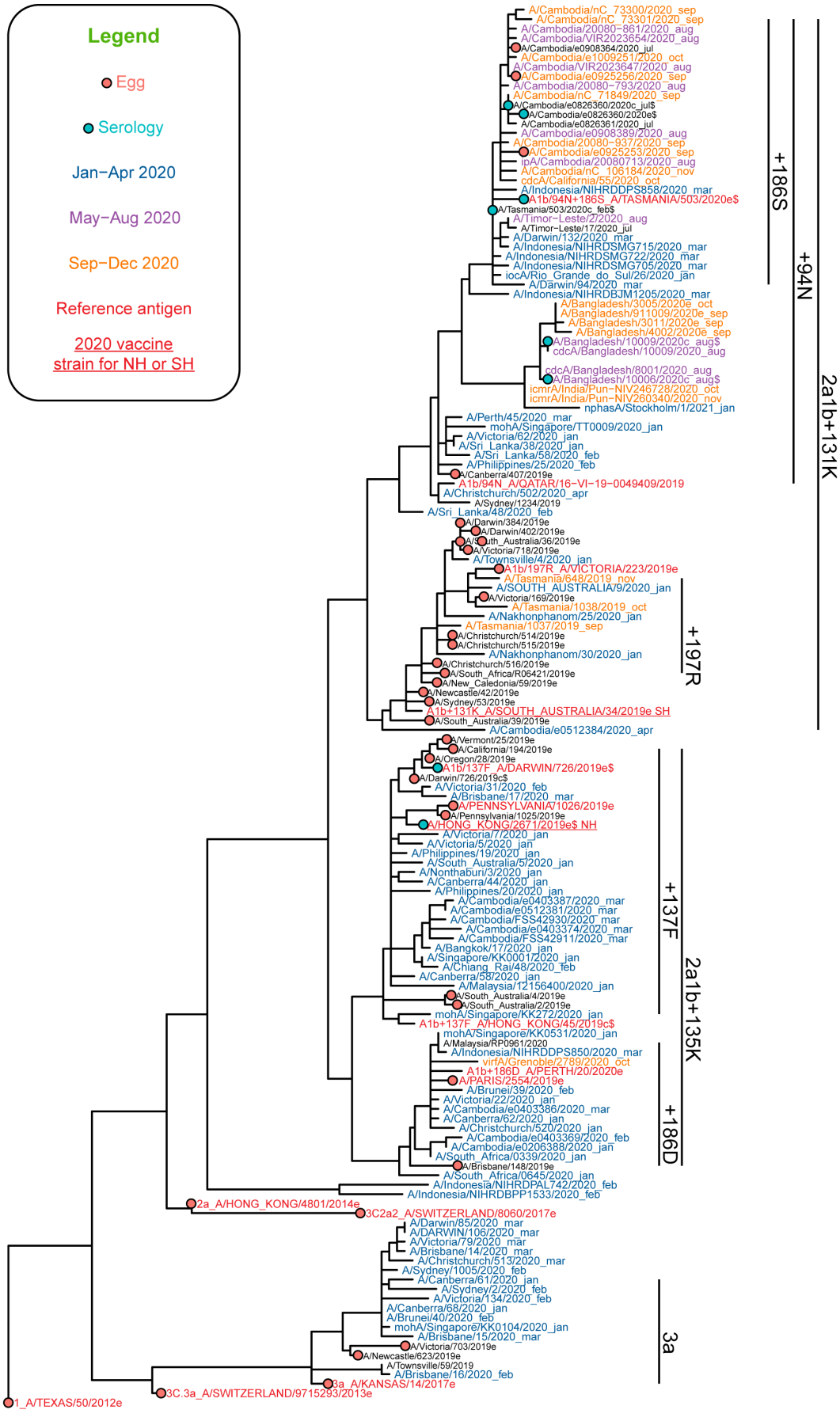


Figure 14. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2020.



Influenza B/Victoria

Introduction

There are currently two antigenically and genetically distinct lineages of influenza B virus in circulation—the B/Victoria/2/87 lineage (represented by the 2019 and 2020 vaccine strains, B/Colorado/6/2017 and B/Washington/02/2019, respectively), and the B/Yamagata/16/88 lineage (represented by the 2020 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 2020 the Centre received many more B/Victoria lineage viruses compared to B/Yamagata lineage viruses.

Antigenic Analysis

A total of 164 B/Victoria viruses were analysed by HI assay. All viruses were low reactors to the cell-grown reference virus B/Colorado/6/2017 (Table 7, Figure 15A). The vast majority of viruses were antigenically similar to the B/Washington/02/2019 reference virus (Table 7, Figure 15B).

Haemagglutinin gene sequencing

Phylogenetic analysis of 113 genes from B/Victoria lineage viruses showed the growth of the subclade V1A.3. This subclade contains the 2021 vaccine strain B/Washington/2/2019.

Table 7. Antigenic characterisation of B/Victoria viruses received at the Centre during 2020 compared to the B/Colorado/6/2017 and B/Washington/02/2019 reference viruses.

	B/Victoria lineage reference strain: B/Colorado/6/2017		B/Victoria lineage reference strain: B/Washington/02/2019	
Region	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**
Africa			9	
Australasia	8		37	2 (5.13%)
South Asia	11		5	
South East Asia	58	1 (1.69%)	32	
South Pacific			1	
TOTAL	**77**	**1 (1.28%)**	**84**	**2 (2.33%)**

Figure 15. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to B/Colorado/6/2017 reference virus.

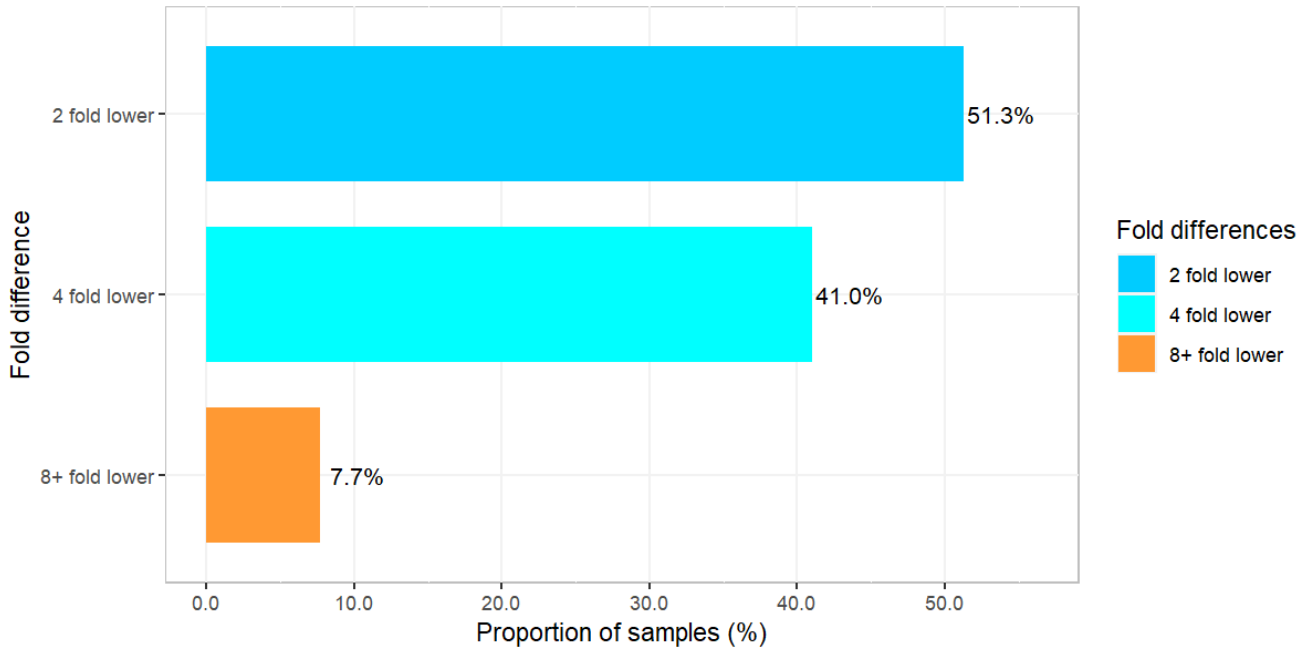
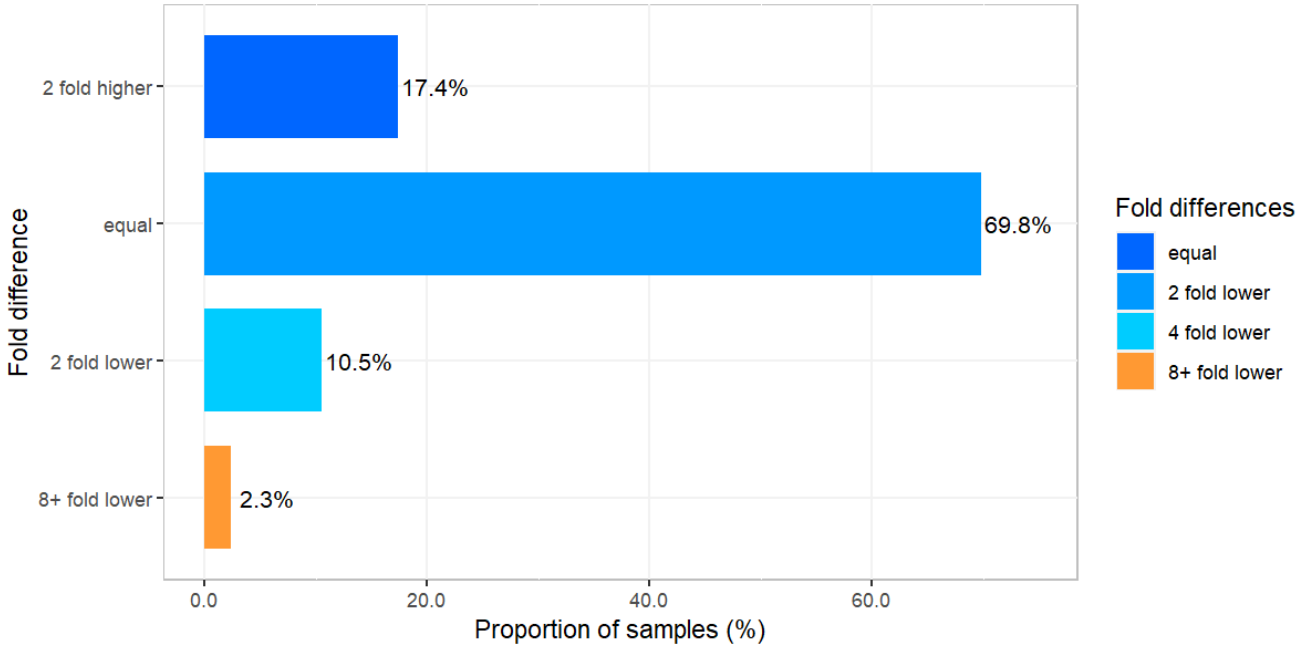


Figure 16. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to B/Washington/02/2019 reference virus.



Influenza B/Yamagata

Antigenic analysis

A total of 4 B/Yamagata viruses were analysed by HI assay, of which all were antigenically similar B/Phuket/3073/2013 virus grown in cells (Figure 17, Table 8).

Haemagglutinin gene sequencing

Sequencing was performed on 1 B/Yamagata virus (sample date 2019). Phylogenetic analysis was not performed for the B/Yamagata lineage in 2020, as there were no samples from this year available for analysis.

Table 8. Summary of fold differences in HI titres of B/Yamagata viruses analysed at the Centre compared to the B/Phuket/3073/2013 reference virus.

B/Yamagata lineage reference strain: B/Phuket/3073/2013		
Region	**Like**	**Low reactor (%)**
Australasia	1	0
South East Asia	3	0
TOTAL	**4**	**0**

Figure 17. Summary of fold differences in HI titres of B/Yamagata viruses analysed at the Centre compared to the B/Phuket/3073/2013 reference virus.

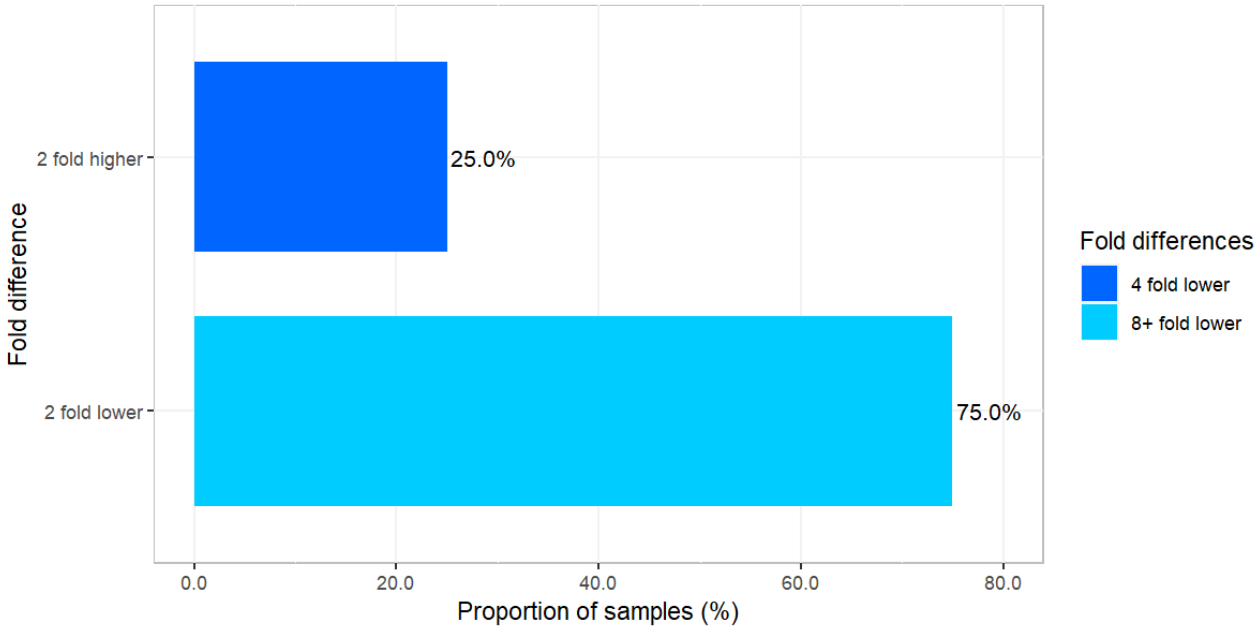
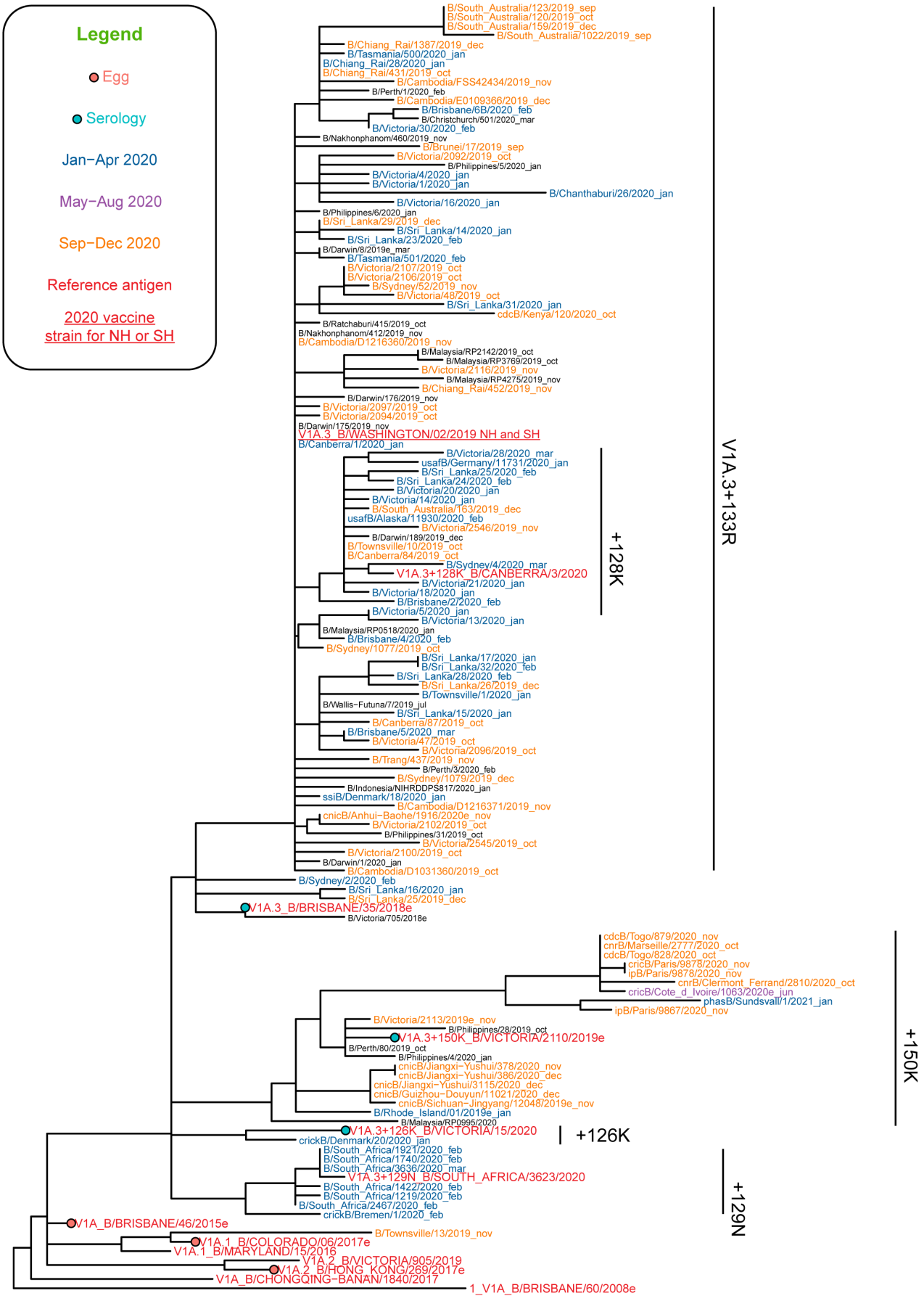


Figure 18. Phylogenetic tree of representative HA genes of B/Victoria viruses received by the Centre during 2020.



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 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 9. Viruses received by the Centre in 2020 and tested by NAI assay, by country.

Type/subtype/ lineage / Country	A(H1N1) pdm09	A(H3N2)	A mixed type	B/Victoria	B/Yamagata	Mixed type (A/B)	TOTAL
Australasia							
Australia	359	100	1	46	1	1	**508**
New Zealand	21	3		3			**27**
South Pacific							
New Caledonia	11			1			**12**
South East Asia							
Brunei	27	4					**31**
Cambodia	39	69		33			**141**
Indonesia	14	18		12			**44**
Malaysia	232	69		5			**306**
Philippines	11	3		4			**18**
Singapore	78	25		20	3		**126**
Thailand	30	21		17			**68**
Timor-Leste		2					**2**
South Asia							
Sri Lanka	8	13		16			**37**
Africa							
South Africa	38	7		9			**54**
TOTAL	**868**	**334**	**1**	**166**	**4**	**1**	**1374**

Antiviral resistance analyses 2020

NAI assays were used to analyse 1374 viruses for reduced inhibition by the NAIs (Tables 9 and 10). Viruses showing highly reduced inhibition to one or more NAIs underwent further analysis to determine the presence of amino acid substitutions in the NA protein associated with the reduction of inhibition by NAIs.

A total of 5 viruses (4 A(H1N1)pdm09 and 1 B/Victoria) had highly reduced inhibition by one or more of the NAIs. These viruses underwent further analysis to determine the presence of amino acid substitutions in the NA protein that associated with the reduction of inhibition by NAIs (Table 11), for example histidine to tyrosine at position 275 (H275Y) of the neuraminidase protein of A(H1N1)pdm09 viruses, which reduces inhibition by oseltamivir, or the equivalent H273Y mutation in B viruses.

Table 10. Neuraminidase inhibitor sensitivity of viruses received by the Centre in 2020.*

Type/Subtype/ Lineage	No. tested	Oseltamivir		Peramivir		Laninamivir		Zanamivir	
		RI	HRI	RI	HRI	RI	HRI	RI	HRI
A(H1N1)pdm09	868	1 (0.12%)	2 (0.23%)	2 (0.23%)	4 (0.46%)	1 (0.12%)		3 (0.35%)	1 (0.12%)
A(H3N2)	334								
A mixed subtype	1								
B/Victoria	166	1 (0.6%)		2 (1.2%)	1 (0.6%)	1 (0.6%)		2 (1.2%)	
B/Yamagata	4			1 (0.78%)					
Mixed type (A/B)	1								
TOTAL	**1374**	**2 (0.15%)**	**2 (0.15%)**	**4 (0.29%)**	**5 (0.36%)**	**2 (0.15%)**	**0**	**5 (0.36%)**	**1 (0.07%)**

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

Table 11. Characteristics of viruses received by the Centre during 2020 with highly reduced inhibition by NAIs.

Type/Subtype/ Lineage	Country/city of submitting laboratory	NAI(s) with highly reduced inhibition (marked with ∗)				Mutation(s) detected
		Oseltamivir	Peramivir	Laninamivir	Zanamivir	
A(H1N1)pdm09	Queensland		*			E119K, Q136K
	Western Australia	*	*			H275Y
	Western Australia	*	*			None
	Malaysia		*		*	Q136K
B Vic	Indonesia		*			None

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 baloxivir.

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 2020

In 2020, a total of 139 viruses were successfully analysed using the FRA-BX assay (Table 12), of which none showed reduced susceptibility to baloxavir. Genetic screening of 345 viruses (Table 12) by pyrosequencing or sequencing identified one A(H3N2) virus from Sydney that contained a valine at the position 38 of the PA endonuclease gene. This mutation is not known to have any impact on the susceptibility of influenza viruses to baloxavir, and analysis using the FRA-BX assay showed that this virus had no reduction in susceptibility to baloxavir.

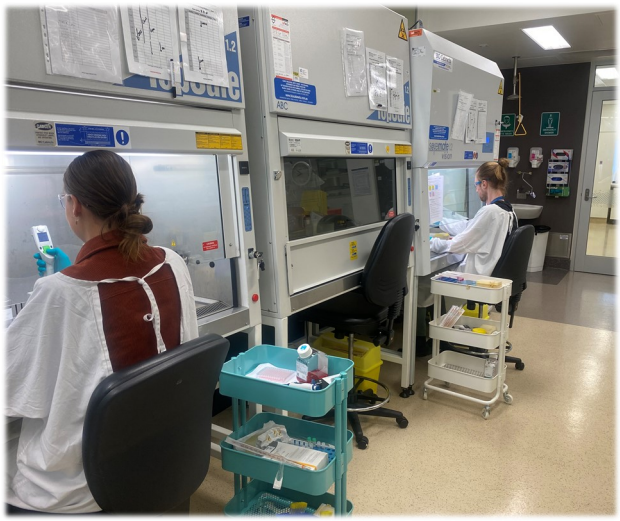
Resistance to Adamantanes

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 2020

Real-time PCR or sequencing was used to analyse 528 influenza A viruses, which were representative of those submitted to the Centre during 2020 (Figure 19). All but two A(H3N2) viruses out of the tested influenza A viruses carried the S31N mutation, indicating that they would be resistant to adamantanes.



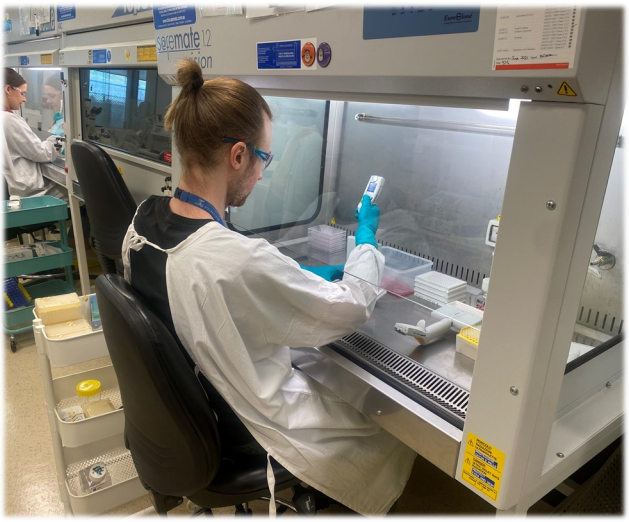
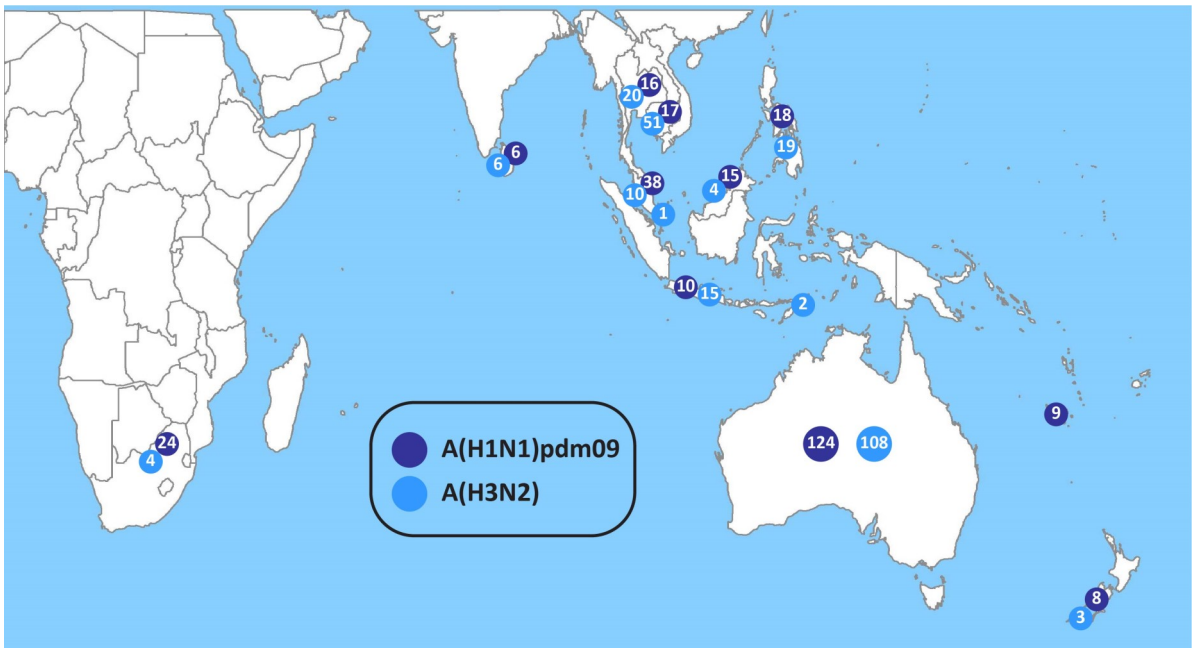


Table 12. Viruses screened for reduced susceptibility to baloxavir during 2020, by FRA=BX assay and pyrosequencing/ sequencing.

	FRA-BX assay						Pyrosequencing/sequencing				
Type/subtype/ lineage / Country	A(H1N1)pdm09	A(H3N2)	A mixed type	B/Victoria	B/Yamagata	TOTAL	A(H1N1)pdm09	A(H3N2)	B/Victoria	B/Yamagata	TOTAL
Australasia											
Australia	30	8	1	32	10	**81**	42	25	24	1	**92**
New Zealand							2		2		**4**
South Pacific											
New Caledonia							3		1	1	**4**
South East Asia											
Brunei					4	**4**	3	2			**5**
Cambodia	2	3		8		**13**	4	36	4	1	**45**
Indonesia							6	4	4		**14**
Malaysia				1		**1**	11	3	4	1	**19**
Philippines	2			1		**3**	4	5	3		**12**
Singapore	3	6		3	6	**18**					
Thailand	3	1		4		**8**	6	10	3		**19**
South Asia											
Sri Lanka				11		**11**	4	3	6		**13**
Africa											
South Africa							4	3	4		**11**
TOTAL	**40**	**18**	**1**	**60**	**20**	**139**	**89**	**91**	**55**	**4**	**239**

Figure 19. Geographic spread of viruses received at the Centre during 2020 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 2020

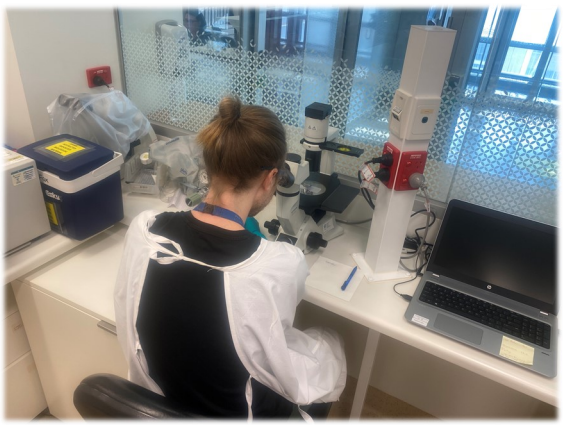
In 2020, a total of 27 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 51.9% (Tables 13 and 14).

Table 13. Virus isolation in eggs at the Centre in 2020.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	11	9	81.8%
A(H3N2)	36	13	36.1%
B/Victoria	5	5	100%
Total	**52**	**27**	**51.9%**

Table 14. Potential candidate vaccine strains isolated in eggs at the Centre in 2020.

A(H1N1)pdm09	A(H3N2)	B/Victoria
A/Darwin/741/2019	A/Darwin/726/2019	B/Victoria/2110/2019
A/Darwin/745/2019	A/Brisbane/148/2019	B/Victoria/2113/2019
A/Darwin/750/2019	A/Pennsylvania/1026/2019	B/Victoria/15/2020
A/Victoria/2570/2019	A/Pennsylvania/1025/2019	B/Victoria/28/2020
A/Singapore/GP2220/2019	A/California/194/2019	B/South Africa/1921/2020
A/Victoria/1/2020	A/Oregon/28/2019	
A/Victoria/3/2020	A/Vermont/25/2019	
A/Perth/21/2020	A/Canberra/407/2019	
A/Perth/34/2020	A/Perth/20/2020	
	A/Tasmania/503/2020	
	A/Singapore/KK0001/2020	
	A/Brunei/39/2020	
	A/Cambodia/e0826360/2020	



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 2020, 10 candidate vaccine viruses that had been received from other WHO Collaborating Centres and laboratories were passaged in eggs at the Centre (Table 15).

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).

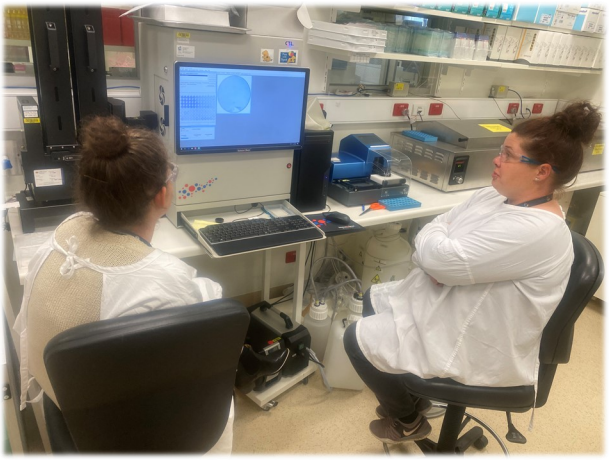
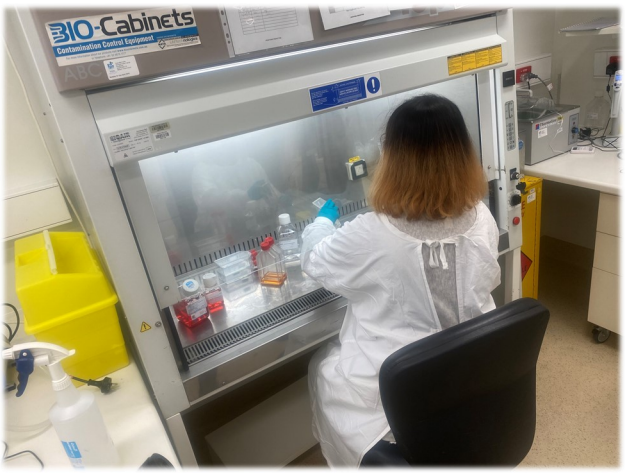


Table 15. Potential candidate vaccine viruses from other WHO Collaborating Centres isolated at the Centre during 2020.

A(H1N1)pdm09
CNIC-1909(A/Guangdong-Maonan/SWL1536/2019)
A/Okinawa/93/2019
A(H3N2)
A/South Africa/R06421/2019
A/Hong Kong/2671/2019
A/Paris/2554/2019
B/Victoria
B/Sichuan-Gaoxin/531/2018
NYMC BX-85C (hy B/Washington/2/2019)
B/Sichuan-Jingyang/12048/2019
B/Rhode Island/01/2019
B/Yamagata
B/Norway/2134/2019



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 16).

Serum panel analyses in February 2020

In February the Centre analysed serum panels from children (7 months to 17 years), adults (18-64 years) and elderly adults (>65 years) who had received the seasonal quadrivalent inactivated egg- or cell-based vaccine, or the recombinant HA 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 6B.1A subclades, including those in 5A with the additional substitutions D187A and Q189E, were reduced compared to GMTs against the cell-grown vaccine strain A/Brisbane02/2018. Moreover, these reductions were greater when measured against egg-propagated vaccine virus.

A(H3N2): In HI assays, GMTs of antibodies against representative recent A(H3N2) viruses from genetic group 3C.2a1b were reduced compared to HI titres against egg-and cell-propagated A/Kansas/14/2017-like vaccine viruses. In virus neutralisation tests, geometric mean neutralisation titres (GMNT) against recently representative A(H3N2) viruses from group 3C.2a1b were also reduced when compared to egg-and cell-propagated A/Kansas/14/2017-like vaccine viruses; notably titres were significantly reduced in vaccinated children. Circulating 3C.3a viruses were recognised well in both HI and MN assays.

B/Victoria: Serum panel analyses showed that the GMT of antibodies against recent B/Victoria/2/87 lineage viruses representing the three amino acid deletions in the HA protein were reduced were reduced when compared to egg-and cell-propagated B/Colorado/06/2017 vaccine virus.

B/Yamagata: GMTs against representative recent B/Yamagata/16/88 lineage viruses were only slightly reduced compared to HI titres to cell-propagated B/Phuket/3073/2013 vaccine virus.

Serum panel analyses in September 2020

In September, the Centre analysed serum panels from adults (18-64 years) who had received the seasonal quadrivalent inactivated egg-based vaccine in Australia, and the recombinant HA 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 6B.1 viruses in the 5A-187A, 5A-156K and 5B subclades were significantly reduced compared to GMTs against the egg-grown and cell-grown vaccine strain A/Brisbane/02/2018.

A(H3N2): Serology studies using both HI assays and virus neutralization assays showed that GMTs and GMNTs of antibodies against recent A(H3N2) viruses in genetic groups 3C.3a and 3c.2a1b were significantly reduced compared to the titres against egg- and cell-propagated A/South Australia/34/2019 vaccine virus.

B/Victoria: Serum panel analyses showed that GMT of antibodies against recent B/Victoria/2/87 lineage viruses representing the dominant HA1 triple deletion group, were not significantly reduced compared to the egg-and cell- propagated B/Washington/02/2019 vaccine virus.

B/Yamagata: GMTs against representative recent B/Yamagata/16/88 lineage viruses were only slightly reduced compared to HI titres to the cell-propagated B/Phuket/3073/2013 vaccine virus.

Table 16. Representative and vaccine candidate strains used for serological analyses during 2020.

FEBRUARY	SEPTEMBER
A(H1N1)pdm09	**A(H1N1)pdm09**
A/Brisbane/02/2018*^ (C, E)	A/Brisbane/02/2018*^ (C, E)
A/Canberra/337/2019 (C,E)	A/Victoria/74/2020 (C)
A/Okinawa/93/2019 (E)	A/Victoria/1/2020 (C,E)
A/Victoria/2454/2019 (C,E)	A/Victoria/2570/2019 (E)
A/Victoria/2570/2019 (C)	A/Perth/34/2020 (C)
A(H3N2) (microneutralisation assays)	**A(H3N2) (microneutralisation assays)**
A/Kansas/14/2017 (C,E)	A/Brunei/40/2020 (C)
A/Hong Kong/2671/2019 (E)	A/Cambodia/e0403374/2020 (C)
A/South Africa/R06421/2019 (E)	A/Kansas/14/2017 (C,E)
A/Sydney/1234/2019 (E)	A/Perth/20/2020 (C,E)
A/Hong Kong/45/2019 (C)	A/South Australia/34/2019*^ (C,E)
A/Shanghai-Jiading/1977/2019 (C)	A/Tasmania/503/2020 (C)
	A/Victoria/31/2020 (C)
B/Victoria	**B/Victoria**
B/Colorado/6/2017*^ (C,E)	B/Washington/2/2019 (C,E)
B/Darwin/8/2019 (C,E)	B/Brisbane/5/2020 (C)
B/Victoria/2113/2019 (C)	B/South Africa/1921/2020 (C,E)
	B/Victoria/15/2020 (C,E)
	B/Victoria/28/2020 (C)
B/Yamagata	**B/Yamagata**
B/Phuket/3073/2013* (C,E)	B/Phuket/3073/2013* (C,E)
B/Darwin/58/2019 (C,E)	B/Victoria/27/2020 (C)
B/South Australia/6/2019 (E)	
B/Darwin/26/2018	

**Trivalent vaccine strain ^Quadrivalent vaccine strain*

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

Note: HI assays for A(H3N2) viruses were performed in the presence of oseltamivir

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 2020 WHO made the recommendations reported below.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2020-2021, Geneva, Switzerland, 24-27 February 2020

It is recommended that quadrivalent vaccines for use in the 2020-2021 influenza season (Northern Hemisphere winter) contain the following:

Egg-based vaccines

- an A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/2671/2019 (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/Hawaii/70/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/45/2019 (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 2020-2021 influenza season (Northern Hemisphere winter) contain the following:

Egg-based Vaccines

- an A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/2671/2019 (H3N2)-like virus; and
- a B/Washington/02/2019 (B/Victoria lineage)-like virus.

Cell– or recombinant-based vaccines

- an A/Hawaii/70/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/45/2019 (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 2021, WHO e-Consultation, 23–26 September 2020

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

Egg-based vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Hong Kong/2671/2019 (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/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Hong Kong/2671/2019 (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 influenza season (Southern Hemisphere winter) contain the following:

Egg-based Vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus^;
- an A/Hong Kong/2671/2019 (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/Hong Kong/2671/2019 (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.*

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 2020 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/2454/2019 (Feb) A/Victoria/3/2020 (Sept) A/Victoria/1/2020 (Sept)	
A(H3N2)	A/Hong Kong/2671/2019# (Feb) A/Christchurch/516/2019# (Sept)	A/Newcastle/82/2018 (Sept)
B/Victoria	B/Brisbane/35/2018#(Sept) B/Victoria/705/2018# (Sept)	B/Darwin/7/2019# (Sept)
B/Yamagata	B/Brisbane/9/2014 (Feb, Sept) B/Phuket/3073/2013 (Feb, Sept)	B/Brisbane/9/2014 (Feb, Sept) B/Singapore/INFKK-16-0569/2016 (Feb, Sept) B/Singapore/INFTT-16-0610/2016# (Feb, Sept)

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 7 October 2020 and recommended that the following viruses be used for influenza vaccines in the 2021 southern hemisphere influenza season:

Egg-based quadrivalent vaccines:

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus
- an A/Hong Kong/2671/2019 (H3N2)-like virus;
- a B/Washington/02/2019-like (B/Victoria lineage) virus; and
- a B/Phuket/3073/2013-like (B/Yamagata lineage) virus.

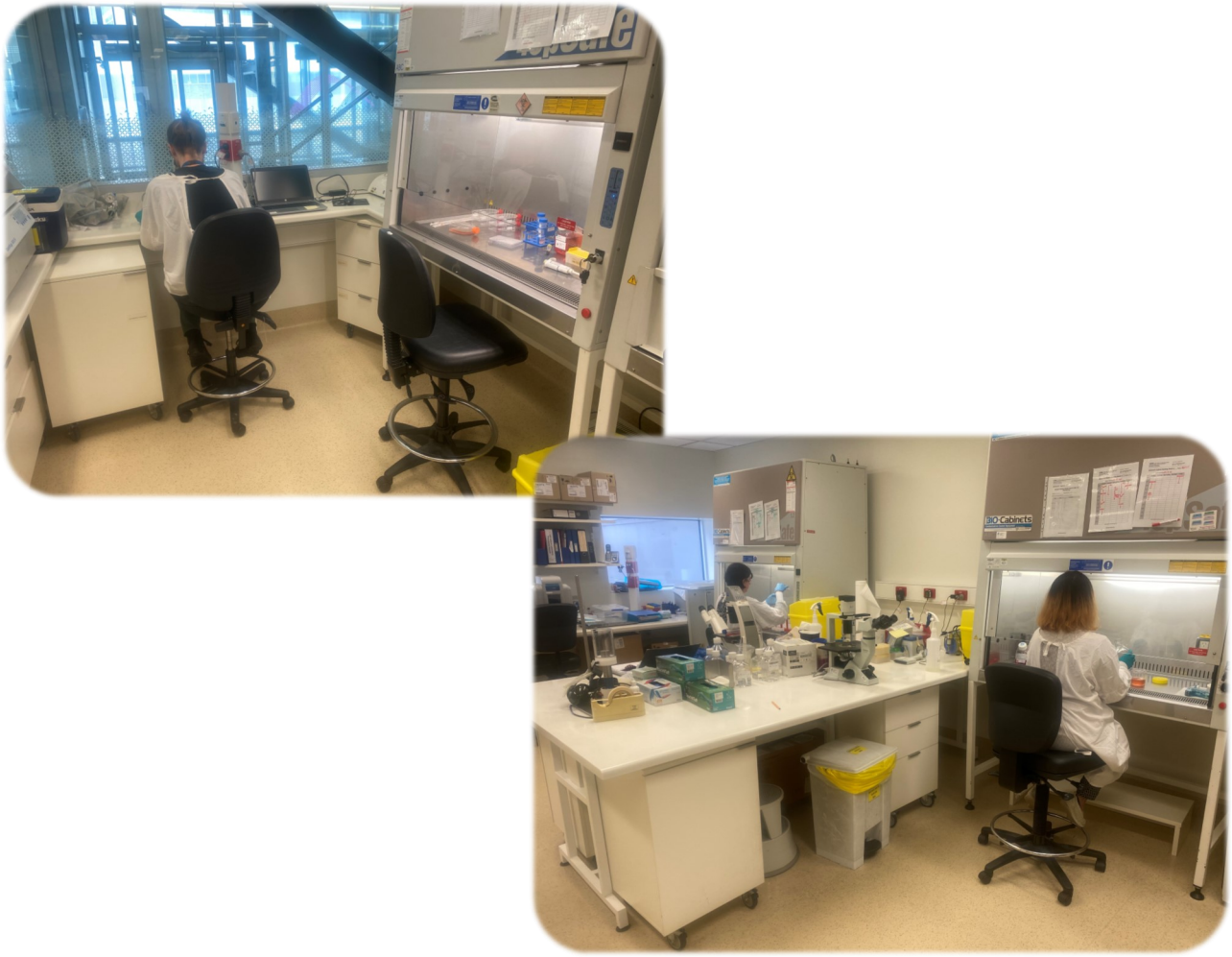
Egg-based trivalent vaccines:

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus
- an A/Hong Kong/2671/2019 (H3N2)-like virus; and
- a B/Washington/02/2019-like (B/Victoria lineage) virus.

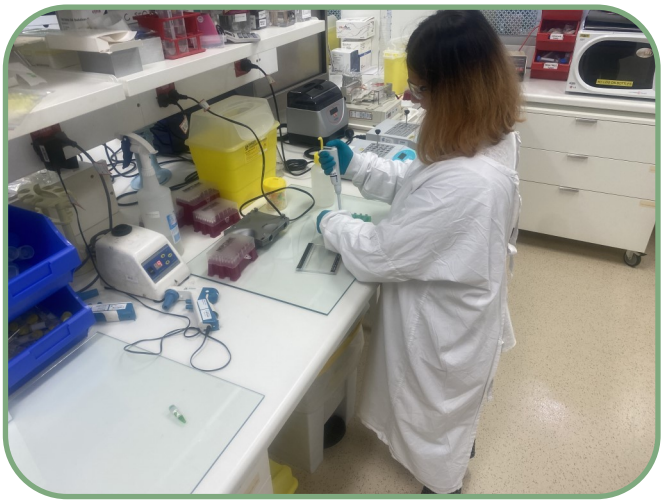
Preparation and Distribution of Diagnostic Reagents

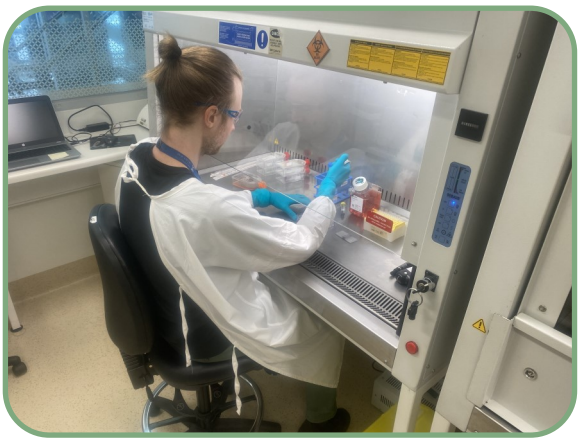
Reagents for Antigenic Typing of Influenza Viruses

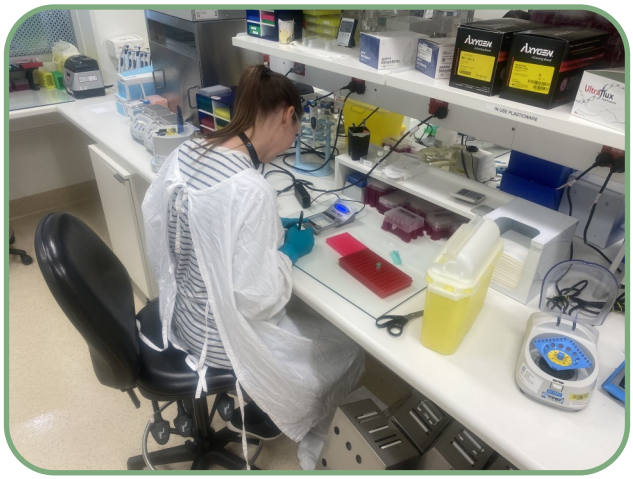
In the past, the Centre prepared and made available a kit of influenza reagents for laboratories in the Asia-Pacific region to conduct their own initial identification test on virus isolates. Due to the lack of demand for the Centre's kits, this activity ceased after 2019 and no kits were sent out during 2020. Laboratories requesting kits will be referred to the International Reagent Resource website who supply a similar kit provided by the Centers for Disease Control and Prevention, Atlanta, GA, USA.

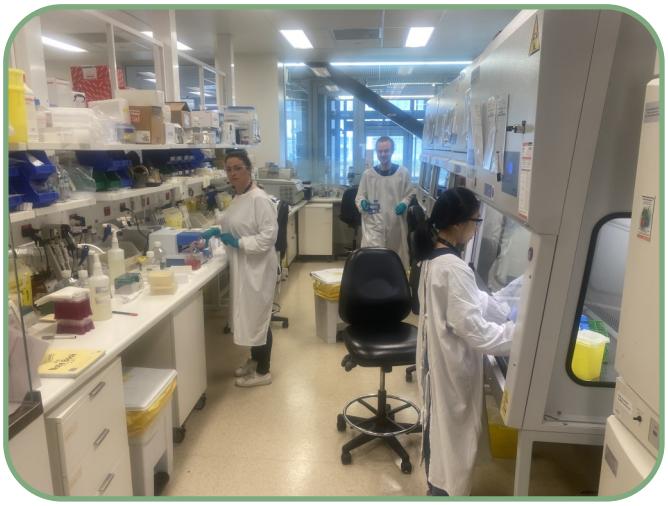


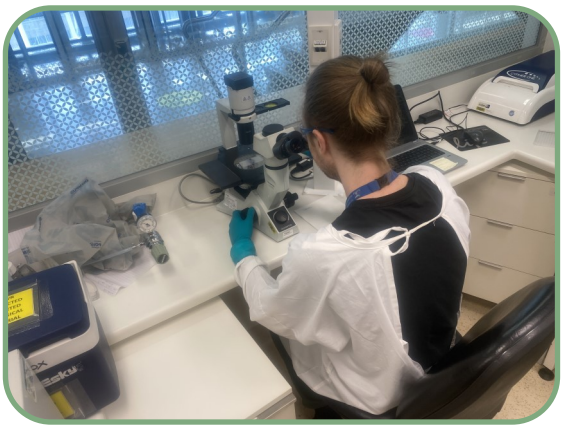
Around the lab...











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 2021.

Training Programs and Visits to Regional Laboratories

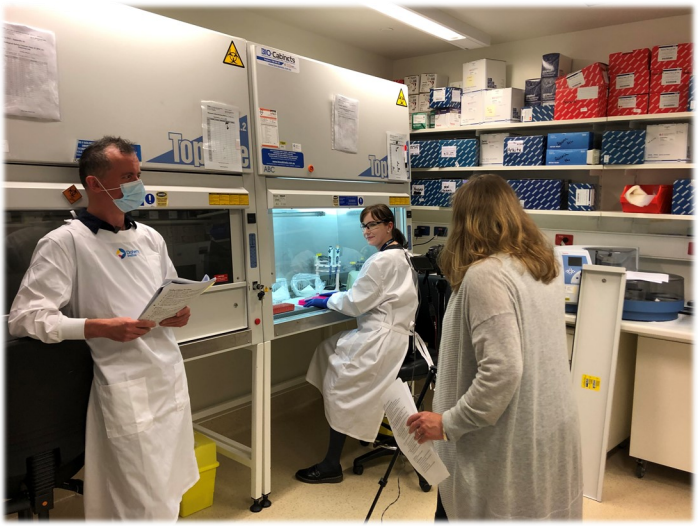
Vivian Leung and **Arseniy Khvorov** gave presentations on 'Introduction to R' and 'Introduction to machine learning', respectively, as part of the 'Intro to Power BI' workshop organised by the Performance Unit at Western Health on 12 March 2020

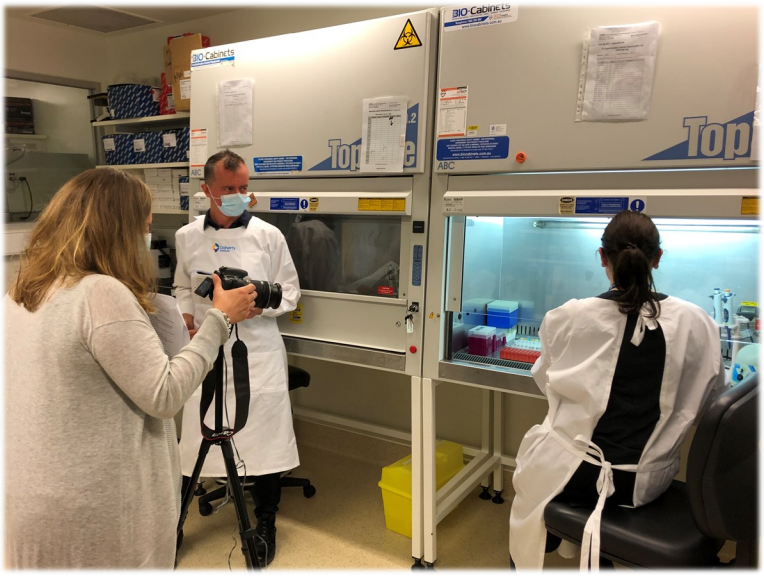
Kanta Subbarao was a presenter at the India Vaccinology Course (INDVAC) on 9 October. This event was held as a virtual forum due to ongoing COVID-19 travel restrictions.

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 (i) guidance and advice on building new facilities or renovation of existing facilities, (ii) advice of all equipment and consumables to purchase for a functional PCR laboratory, (iii) regular online meetings for advice and planning to Pacific Island Countries, (iv) development of training materials for PCR, including training videos, lectures, SOPs and other guidance documents, (v) and advice and evaluation regarding the usefulness of automated platforms in the Pacific and (vi) delivery of remote training to Pacific Island Countries that are setting up PCR for the first time. Countries receiving support, advice and training include Vanuatu, Cook Islands, Solomon Islands, Tonga, Tuvalu, Samoa and Kiribati.

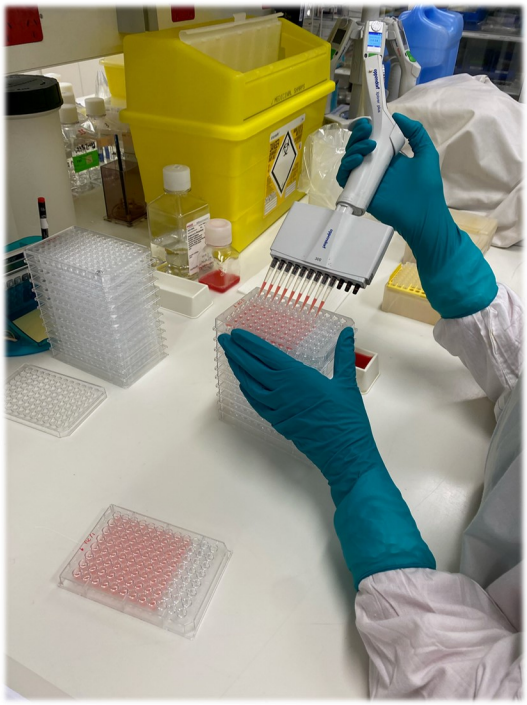
Training Programs and Visits to Regional Laboratories (continued)

Patrick Reading has been working 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.





Patrick Reading has been 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



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

Edin Mifsud, Sook Kwan Leah Brown, Leo Lee, Ankita George, Paulina Koszalka

Research overview

Our research focuses on improving our understanding of the effectiveness of currently approved influenza antivirals and compounds in late-phase human clinical trials, and the risk that drug resistant viruses may spread widely amongst the community.

In understanding viral fitness, it is important to assess the ability of different drug resistant variants to replicate in vitro or in vivo and then to assess the ability of the viruses to transmit between ferrets. This information will provide insights into the likelihood that such viruses could spread amongst the community.

A cooperative research and development agreement (CRADA) with Romark Laboratories which commenced in 2016 has continued to investigate in vitro and in vivo aspects of the repurposed drug nitazoxanide for its effectiveness against human and potentially pandemic avian influenza viruses. In addition a CRADA with Shionogi which commenced in 2018 continued to investigate whether the PA endonuclease inhibitor baloxavir is able to reduce the rate of transmission using the ferret model of infection. A CRADA with Roche commenced in late 2020, investigating the fitness of variant viruses with reduced susceptibility to baloxavir and other neuraminidase inhibitors, which may be used as a future combination therapy.

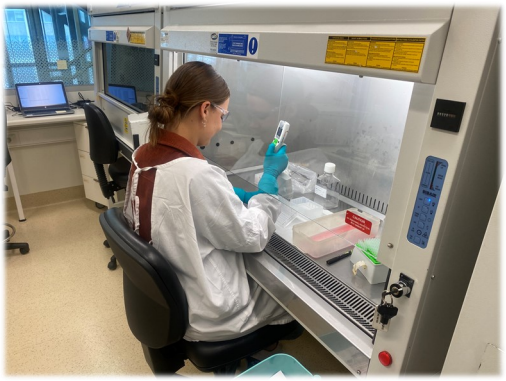
Collaborators

James McCaw 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 AAHL) and Jeff Butler (CSIRO, AAHL)

Highlights and developments 2020

In our baloxavir studies, we found that treating influenza -infected ferrets with baloxavir significantly reduced viral shedding compared to oseltamivir and placebo, and subsequently reduced the risk of virus transmission to untreated ferrets housed in close contact. In collaboration with Shionogi and Imperial College London, our results provide significant supporting evidence for Centerstone, a first-of-its-kind clinical trial on the role of baloxavir to control the spread of influenza from infected patients to household contacts without prophylaxis. A paper was published in PLoS Pathogens addressing the fitness of the PA-I38T variant, which has reduced susceptibility in ferrets. Additionally, we developed a rapid pyrosequencing assay to detect viruses with low baloxavir susceptibility due to PA amino acid substitutions (PA/I38X). Investigations on the fitness costs of the PA/I38T substitution emerging in baloxavir-treated patients using competitive fitness experiments in ferrets have also been performed.

In our studies of the influenza antiviral nitazoxanide, we showed that the combination of nitazoxanide and oseltamivir therapy in ferrets reduced the clinical signs associated with influenza infection and significantly reduced the number of ferrets shedding influenza virus when compared to either nitazoxanide or oseltamivir alone. The results of these studies were accepted for publication in Antiviral Research. Currently we are investigating if this dual combination therapy can reduce disease severity associated with H5N1 and H7N9 influenza viruses, and this work will be done in collaboration with Australian Centre for Disease Preparedness (ACDP).



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)

Highlights and developments 2020

In 2020, we collected and screened 955 swab samples from wild Anseriiformes (ducks) and Charadriiformes (shorebirds and terns) in Victoria, Tasmania and Western Australia, with 22 influenza A virus detections (see Table R1). 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 955 paired serum samples for general anti-influenza A antibodies using a commercial NP-ELISA.

Victoria experienced the largest outbreak of avian influenza in poultry on record during 2020. We contributed expertise as members of the outbreak management team lead by Agriculture Victoria, and screened samples from wild birds as part of the Victoria's proof of freedom following the end of the outbreak. Michelle Wille and Stacey Lynch (Agriculture Victoria) wrote an article for The Conversation explaining the outbreak and what it means for Victorians.

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 will be complete Feb 2021.

In addition to classical approaches to screen for and characterise influenza A viruses, we have continued to utilize RNA sequencing (RNA-seq) to assess the total viral burden in Australian wild birds. Finally, in light of SARS-CoV-2 we have synthesized all data from wild birds, globally, to reveal the ecology and evolution of coronaviruses in birds, now published in FEMS Microbiological Reviews.

Table R1. Samples collected from wild birds in 2020

Avian order	Serum samples		Swab samples	
	Samples collected	*Influenza-positive samples*	*Samples collected*	*Influenza-positive samples*
Anseriformes	201	46	201	1
Charadriiformes	754	55	754	21

Epidemiology

Centre staff

Sheena Sullivan, Vivian Leung, Arseniy Khvorov (University of Melbourne, UoM), Leslie Dowson (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.

Highlights and developments 2020

We continued to work with the Australian Sentinel Practices Research Network (ASPREN), the Victorian General Practice Sentinel Surveillance (VicSPIN) network, and the Influenza Complications Alert Network (FluCAN) to estimate influenza vaccine effectiveness for the WHO Vaccine Consultation Meetings to monitor influenza activity, which was extremely low in 2020.

The group was successful in securing funding to conduct a large longitudinal cohort study to understand the long-term effects of repeated vaccination in hospital workers, led by Drs Sheena Sullivan and Annette Fox (Immunology unit) at the Centre, and Adam Kucharski (London School of Hygiene and Tropical Medicine). This study commenced in 2020, with recruitment in six Australian cities, and all laboratory analysis to be conducted at the Centre. The study has been expanded to include analysis of COVID-19 infection and vaccination among hospital workers.

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).

Continuing work on the burden of disease project undertaken with the Telethon Kids Institute, the University of Western Australia and University of Hong Kong in 2017-2018, we have prepared several manuscripts for publication. Dr Sullivan was also successful in gaining access to the OptumLabs data (with Annette Regan and Onyebuchi Arah, UCLA) to understand the burden of influenza during pregnancy, and this work has been extended to COVID-19.

The group was also involved in the COVID-19 response, providing epidemiological support at the Victorian Department of Health (Sheena Sullivan, Chris Bailie) and the Royal Melbourne Hospital (Vivian Leung, Chris Bailie). Vivian Leung and Chris Bailie worked with the Infection Prevention and Surveillance Service at the Royal Melbourne Hospital to manage the healthcare worker (HCW) contact tracing data and assist with the development a contact tracing database.

Collaborators

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

Burden of disease: Hannah Moore (Telethon Kids Institute); George Milne (University of Western Australia); Benjamin Cowling and Jessica Wong (University of Hong Kong); Annette Regan, Onyebuchi Arah (UCLA)

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).

Human Immunity to Influenza

Centre staff and student

Annette Fox, Louise Carolan, Ryan (Yeu-Yang) Tseng, Sheena Sullivan, Vivian Leung, Maria Auladell Bernat

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. In particular, memory B cells that cross-react with shared epitopes in subsequent strains may out-compete naïve B cells for the resources required for activation, so that responses become focused on epitopes from old strains, and are not updated towards 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.

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).

Highlights and developments 2020

During 2020 we commenced a longitudinal cohort study to investigate the effects of repeated influenza vaccination in hospital workers, led 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 complications due to COVID-19 restrictions 605 of a target of 1500 participants were recruited from 6 hospitals across Australia. 1905 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.

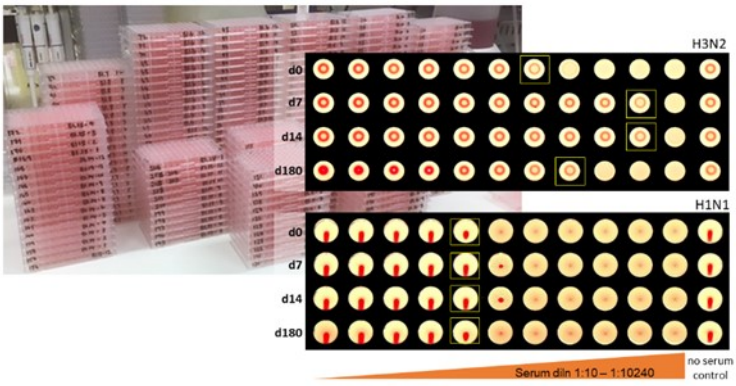


Figure R1. *Vaccine study serology. Assay plates are shown in the back-ground, and scanned plate images are shown in the foreground for sera collected on days 0 – 180 of vaccination tested against H3N2 and H1N1 antigens.*

Vaccination induced antibodies that have biased recognition of egg over cell-grown antigen for H3N2 but not H1N1 (Figure R2).

The proportions of participants who seroconverted varied by vaccine component (Table R2) and by hospital (not shown), but tended to be low. This was in part explained by prior vaccination and high pre-existing antibody titres: as the number of prior vaccinations increased seroconversion rates decreased (Table R3); and pre-vaccination titres increased (Figure R3). However, post-vaccination titres and titre rises were lowest among the most highly vaccinated group although pre-vaccination titres were similar to less vaccinated groups.

Human Immunity to Influenza (continued)

Together these preliminary findings provide further indication that prior vaccination may attenuate influenza vaccine immunogenicity, and that egg-grown A(H3N2) vaccine viruses induce relatively poor antibody titres against equivalent cell-grown strains in accordance with egg-adaptive changes within an immunodominant antibody binding site.

Figure R2. *HI antibody responses induced by vaccination of hospital workers in 2020. Scatter plots show titres against cell versus egg grown vaccine antigens on d14 post-vaccination. Two-by-two table show numbers seroconverting (4-fold rise) against egg versus cell grown viruses by day 14.*

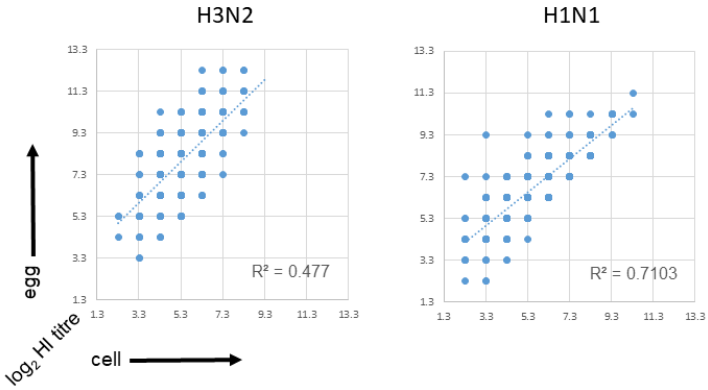


Table R2. *Proportion of hospital workers (n=587) that seroconverted after vaccination against cell- and egg-grown versions of the four component strains in the vaccine.*

H3N2		H1N1		B Vic		B Yam	
cell	egg	cell	egg	cell	egg	cell	egg
22.5 %	30.5 %	26.9 %	25.0 %	17.2 %	18.7 %	13.8 %	13.5 %

Table R3. *Proportion of hospital workers that seroconverted by number of prior influenza vaccinations.*

Prior	*N*	H3N2		H1N1		B Vic		B Yam	
		cell	egg	cell	egg	cell	egg	cell	egg
0	*46*	60.9	89.1	73.9	80.4	67.4	52.2	60.9	37.0
1	*62*	29.0	37.1	32.3	24.2	22.6	27.4	21.0	19.4
2	*59*	18.6	30.5	27.1	27.1	11.9	20.3	13.6	11.9
3	*56*	17.9	26.8	5.4	12.5	14.3	19.6	8.9	8.9
4	*62*	17.7	22.6	14.5	16.1	6.5	8.1	4.8	8.1
5	*224*	16.1	18.8	21.9	20.9	8.5	8.5	5.4	8.5

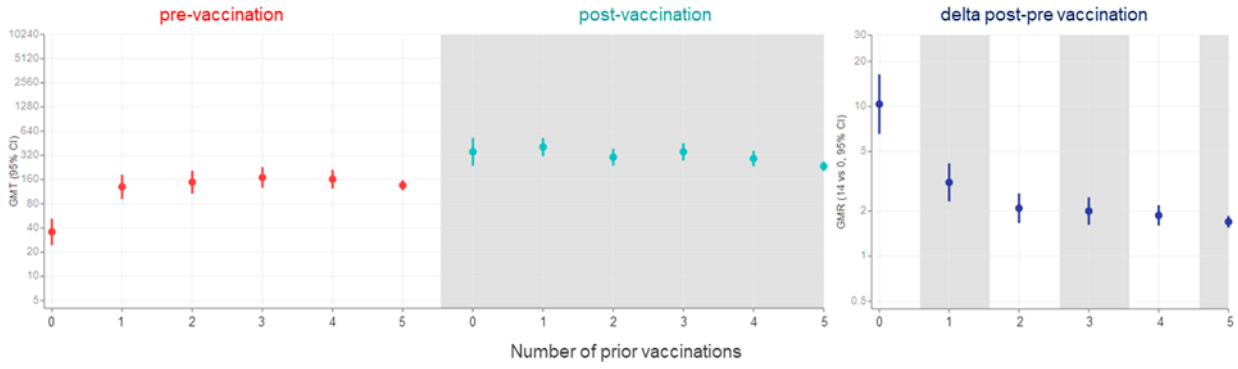
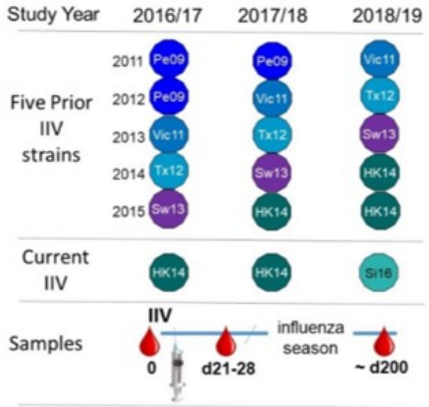


Figure R3. *HI antibody titres and tire rises against an egg-grown virus representing the H3N2 component of the vaccine among hospital workers who had 0-5 prior vaccinations. Prior vaccination was associated with higher pre, but not post vaccination titres.*

Human Immunity to Influenza (continued)

A similar study to assess the effects of prior vaccination on vaccine immunogenicity among health care personnel (HCP) in Peru and Israel is near completion. The clinical component of this study was led by Mark Thompson (CDC). To date over 30000 HI tests have been performed to assess titres of pre-vaccine, post-vaccine and post-season sera from 298 HCP against 35 A (H3N2) viruses. Preliminary analysis of a subset of the data indicates that prior vaccination was associated with attenuated immunogenicity of the 2018/19 vaccine among HCP from Israel.



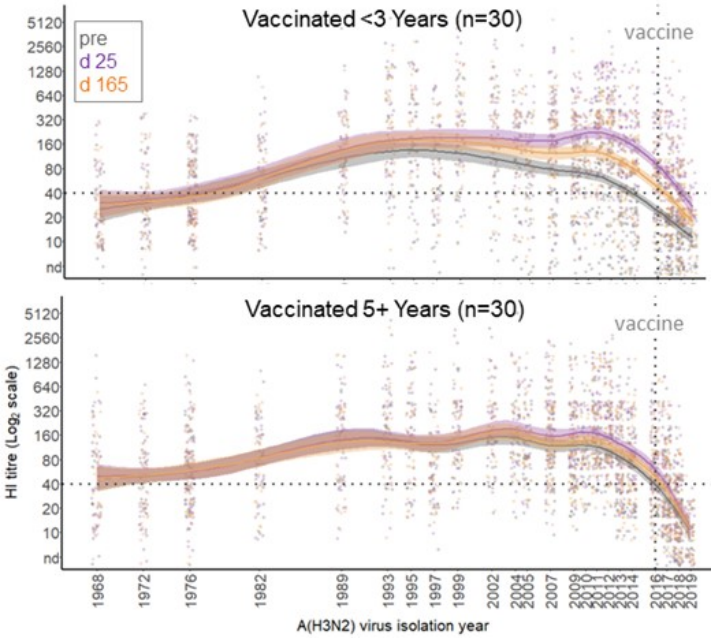


Figure R4. *Multi-year study to examine effects of repeated influenza vaccination among health care personnel in Israel and Peru. Sera were collected pre and post vaccination during 2016, 2017, or 2018/19. Vaccinations during the five prior years were recorded. Selected HCP who had been vaccinated during 5 prior years or in less than three prior years were assessed to detect antibodies against 35 viruses spanning 1968 to 2019. Antibody titre landscapes across the viruses are shown for HCP from Israel vaccinated during 2018/19 including 30 highly vaccinated and 30 less frequently vaccinated. The former exhibited little vaccine induced titre rise and had lower post-vaccine titres against subsequently circulating strains. This is likely to compromise protection.*

Research is ongoing to determine the cellular and molecular mechanisms underpinning the attenuating effects of prior vaccination on responses to attenuated influenza vaccine. Several approaches are being used to explore the hypothesis that vaccine responses are dominated by recalled memory B cells that recognize limited epitopes that are shared with prior strains. A large panel of reverse engineered viruses that vary from the vaccine strain in a single antigen have been produced. Serum titres are compared against wild-type versus mutant viruses to determine the relative amount of antibody that is directed

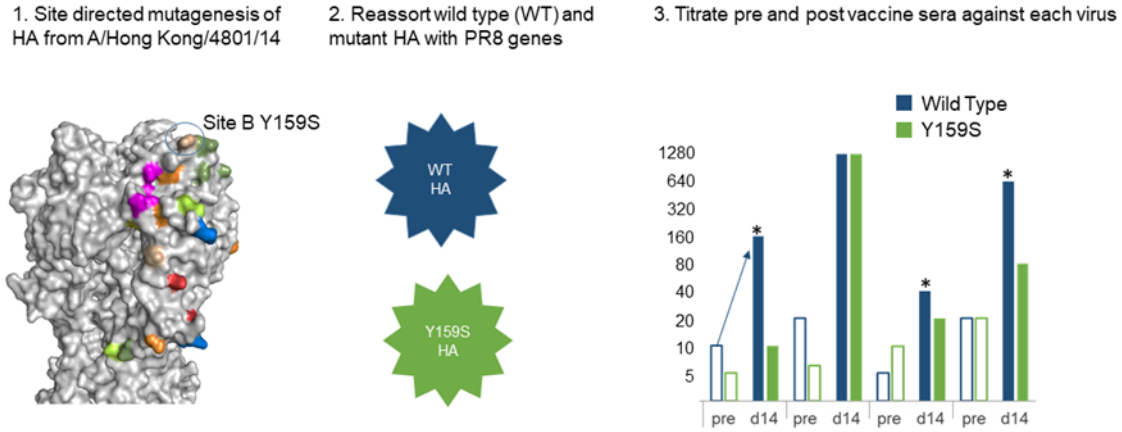


Figure R5. *Use of reverse engineered viruses to determine titres of antibodies induced against individual antigenic sites. Viruses are reverse engineered to introduce substitutions within single antigenic sites. Column graphs show titres of pre-vaccine (open bars) and post-vaccine (filled bars) sera from three vaccinees against wild type versus Y159S (site B) mutant viruses. Asterisks indicate participants who had strong titre rises against the wild-type vaccine antigen (blue bars) but not against the site B mutant (green bars) indicating that a substantial fraction of vaccine-induced antibody was directed against site B.*

Early Recognition and Response to Influenza Infection

Centre staff

Patrick Reading, James Barnes

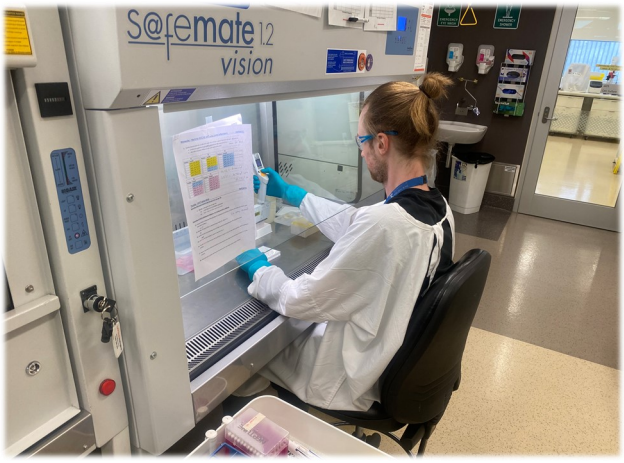
Research overview

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, Lorena Brown, Carol Hartley and Joanne Devlin (The University of Melbourne)



Highlights and developments 2020

During 2020, our research focussed on understanding and characterising particular intracellular proteins (termed restriction factors) that are expressed or induced in host cells and can block the replication of influenza and/or other respiratory viruses. We are now using approaches to ectopically overexpress or delete putative restriction factors to determine their role in blocking virus replication and to characterise their mechanism/s of antiviral activity. 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.

In 2020 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'). Dr Ruby Farrukee also joined the research group on a Roche Postdoctoral Fellowship (RFP) Programme to examine aspects of cellular responses to respiratory syncytial virus (RSV) infection.

Overall, our research contributed to four peer-reviewed publications during 2020, in journals such as Viruses, Frontiers in Immunology and Virology. In 2020, Prof Reading led a research group at the University of Melbourne consisting of four post-doctoral scientists, four Ph.D. students and one Master of Biomedical Science student. Prof Reading is co-supervisor of an additional four Ph.D. students enrolled at the University of Melbourne. Prof Reading also supervises James Barnes, a research assistant based at the Centre, who has been developing assays to measure antibody-dependent cell-mediated cytotoxicity to vaccination, as well as assessing novel vaccines in ferret models of infection.

Evolution, Modelling and Serological Responses to Influenza Viruses

Centre staff

Ian Barr, Malet Aban, Manisha Patel, 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), has been 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 been undertaken. In March-July 2020, Sam Wilks a post-doctoral researcher from Cambridge University visited the Centre.

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 has been placed on hold for most of 2020 due to Dr Dai taking a year off for maternity leave.

Highlights and developments 2020

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.

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 Bolongia (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).

Collaborative Agreements

The Centre is party to four 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 Romark Laboratories: Studies of the influenza antiviral nitazoxanide (2016-2020)

Centre staff: Edin Mifsud, Danielle Tilmanis, Aeron Hurt

Overview: The Centre is evaluating the effectiveness of the influenza antiviral nitazoxanide *in vitro* and *in vivo* (ferret and mouse models) using both seasonal influenza viruses and potentially pandemic viruses influenza vaccines

Highlights and developments 2019: *In vitro* studies have shown that nitazoxanide and oseltamivir have an additive to synergistic interaction. In a ferret model, combination treatment of the nitazoxanide and oseltamivir was more effective at preventing influenza virus infection and lower respiratory tract replication compared to oseltamivir treatment alone. In 2019 the results of these studies were accepted for publication in Antiviral Research.

Cooperative Research and Development Agreement with Shionogi TechnoAdvance Research (2018-2020)

Centre staff: Leo Lee, Edin Mifsud, Paulina Koszalka, Aeron Hurt

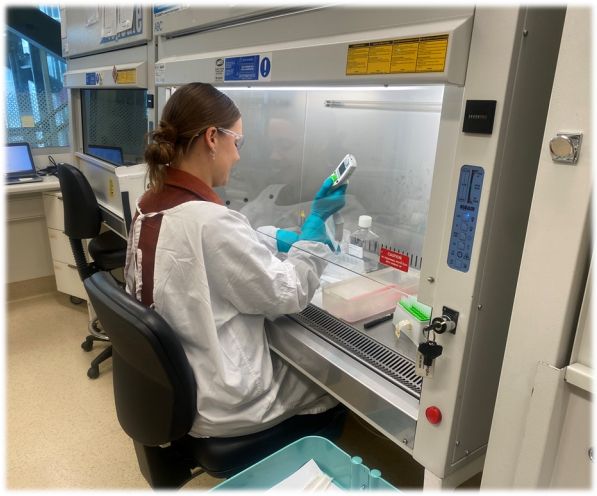
Overview: The Centre is evaluating the effectiveness of the influenza antiviral baloxavir in preventing the transmission of influenza virus.

Highlights and developments 2019: We found that treating influenza-infected ferrets with baloxavir significantly reduced viral shedding and reduced the risk of virus transmission to untreated ferrets. Our results provide significant evidence supporting the role of baloxavir to control the spread of influenza from infected patients to household contacts without prophylaxis. We also developed a rapid pyrosequencing assay to detect amino acid substitutions (eg. I38X) in the PA gene which would reduce the susceptibility of viruses to baloxavir. We are also investigating the fitness costs of the PA/I38T substitution emerging in baloxavir-treated patients using competitive

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** and Vijaykrishna Dhanasekaran (Monash University).



Research Funding and Awards

Centre staff members are Chief Investigators in grants awarded in 2020:

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

Sheena Sullivan was awarded $30,000 in top-up funding. 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.

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

Kanta Subbarao is Co-investigator for this fund, for the period 2020-2021.

Victorian Department of Health and Human Services COVID-19 Victorian Consortium Antiviral Pillar

$200,000 awarded to **Kanta Subbarao**, who is lead investigator, to stablish an in vitro antiviral testing platform, for the period 2020-2021.

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**, alongside Prof Ben Cowling and Bing Yi at the University of Hong Kong. The project aims to compare hotel quarantine approaches in Australia and Hong Kong.

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

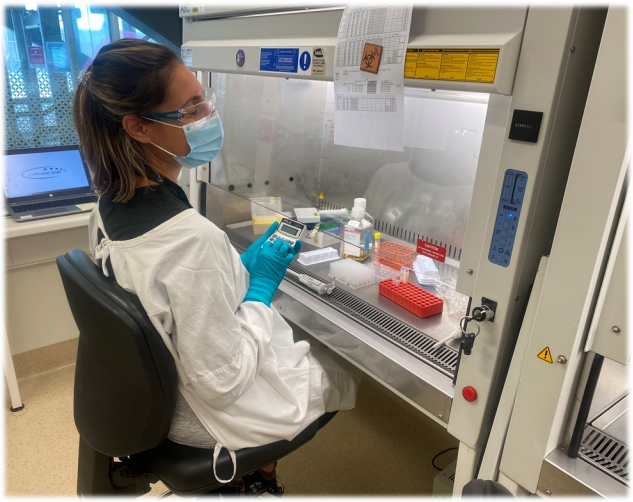
$200,000 awarded to **Kanta Subbarao**, who is Co-investigator, for the period 2020-2021.

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 awarded to **Kanta Subbarao**, who is chief investigator, for the period 16 June 2020– 30 June 2021.

NIH NIAID Sub-award from NYICE Center of Excellence for Influenza Research: ***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 awarded to **Kanta Subbarao** and **Annette Fox** (Kanta Subbarao is chief investigator for Australian sites) for the period 2020-2022.



Communications and Advisory Activities

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

Publications and Reports

The Centre continued to build its research and surveillance profile with the publication of 50 original research papers, reviews and reports in 2020.

Centre Publications 2020

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2. **Deng YM**, Wong FYK, **Spirason N**, **Kaye M**, Beazley R, Grau MLL, Shan S, Stevens V, **Subbarao K**, **Sullivan S**, **Barr IG**, **Dhanasekaran V**. 2020. Locally Acquired Human Infection with Swine-Origin Influenza A(H3N2) Variant Virus, Australia, 2018. Emerg Infect Dis 26:143-147.
3. **Wille M**. 2020. Unravelling virus community ecology in bats through the integration of metagenomics and community ecology. Mol Ecol 29:23-25.
4. Hung SJ, Hsu YM, Huang SW, Tsai HP, **Lee LYY**, **Hurt AC**, **Barr IG**, Shih SR, Wang JR. 2020. Genetic variations on 31 and 450 residues of influenza A nucleoprotein affect viral replication and translation. J Biomed Sci 27:17.
5. Londrigan SL, Wakim LM, Smith J, Haverkate AJ, Brooks AG, **Reading PC**. 2020. IFITM3 and type I interferons are important for the control of influenza A virus replication in murine macrophages. Virology 540:17-22.
6. Vanderven HA, **Barr I**, Reynaldi A, Wheatley AK, Wines BD, Davenport MP, Hogarth PM, Kent SJ. 2020. Fc functional antibody responses to adjuvanted versus unadjuvanted seasonal influenza vaccination in community-dwelling older adults. Vaccine 38:2368-2377.
7. Takashita E, Daniels RS, Fujisaki S, Gregory V, Gubareva LV, Huang W, **Hurt AC**, Lackenby A, Nguyen HT, Pereyaslov D, **Roe M**, Samaan M, **Subbarao K**, Tse H, Wang D, Yen HL, Zhang W, Meijer A. 2020. Global update on the susceptibilities of human influenza viruses to neuraminidase inhibitors and the cap-dependent endonuclease inhibitor baloxavir, 2017-2018. Antiviral Res 175:104718.
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13. **Mifsud EJ**, Tilmanis D, Oh DY, Ming-Kay Tai C, Rossignol JF, **Hurt AC**. 2020. Prophylaxis of ferrets with nitazoxanide and oseltamivir combinations is more effective at reducing the impact of influenza a virus infection compared to oseltamivir monotherapy. Antiviral Res 176:104751.

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17. Rockman S, Laurie K, **Barr I**. 2020. Pandemic Influenza Vaccines: What did We Learn from the 2009 Pandemic and are We Better Prepared Now? Vaccines (Basel) 8.

18. Bedford JG, Infusini G, Dagley LF, Villalon-Letelier F, Zheng MZM, Bennett-Wood V, **Reading PC**, Wakim LM. 2020. Airway Exosomes Released During Influenza Virus Infection Serve as a Key Component of the Antiviral Innate Immune Response. Front Immunol 11:887.

19. Weinman AL, **Sullivan SG**, Vijaykrishna D, Markey P, Levy A, Miller A, Tong SYC. 2020. Epidemiological trends in notified influenza cases in Australia's Northern Territory, 2007-2016. Influenza Other Respir Viruses doi:10.1111/irv.12757.

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23. Lam EKS, Morris DH, **Hurt AC**, **Barr IG**, Russell CA. 2020. The impact of climate and antigenic evolution on seasonal influenza virus epidemics in Australia. Nat Commun 11:2741.

24. **Tilmanis D**, **Koszalka P**, **Barr IG**, Rossignol JF, **Mifsud E**, **Hurt AC**. 2020. Host-targeted nitazoxanide has a high barrier to resistance but does not reduce the emergence or proliferation of oseltamivir-resistant influenza viruses in vitro or in vivo when used in combination with oseltamivir. Antiviral Res 180:104851.

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26. Xia J, Adam DC, Moa A, Chughtai AA, **Barr IG**, **Komadina N**, MacIntyre CR. 2020. Comparative epidemiology, phylogenetics, and transmission patterns of severe influenza A/H3N2 in Australia from 2003 to 2017. Influenza Other Respir Viruses doi:10.1111/irv.12772.

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45. Lau YC, Perera R, Fang VJ, Luk LH, Chu DKW, Wu P, **Barr IG**, Peiris JSM, Cowling BJ. 2020. Variation by lineage in serum antibody responses to influenza B virus infections. PLoS One 15:e0241693.

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47. Tosif S, Neeland MR, Sutton P, Licciardi PV, Sarkar S, Selva KJ, Do LAH, Donato C, Quan Toh Z, Higgins R, Van de Sandt C, Lemke MM, Lee CY, Shoffner SK, Flanagan KL, Arnold KB, Mordant FL, Mulholland K, Bines J, Dohle K, Pellicci DG, Curtis N, McNab S, Steer A, Saffery R, **Subbarao K**, Chung AW, Kedzierska K, Burgner DP, Crawford NW. 2020. Immune responses to SARS-CoV-2 in three children of parents with symptomatic COVID-19. Nat Commun 11:5703.

Centre Publications (continued)

48. **Sullivan SG**. 2020. The need for robust epidemiological evidence during a pandemic. Clin Infect Dis 71(16):2289-90. doi:10.1093/cid/ciaa770.

49. Khoury DS, Wheatley AK, Ramuta MD, Reynaldi A, Cromer D, **Subbarao K**, O'Connor DH, Kent SJ, Davenport MP. 2020. Measuring immunity to SARS-CoV-2 infection: comparing assays and animal models. Nat Rev Immunol 20:727-738.

50. Farrukee R, Ait-Goughoulte M, Saunders PM, Londrigan SL, **Reading PC**. 2020. Host Cell Restriction Factors of Paramyxoviruses and Pneumoviruses. Viruses 12.

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.

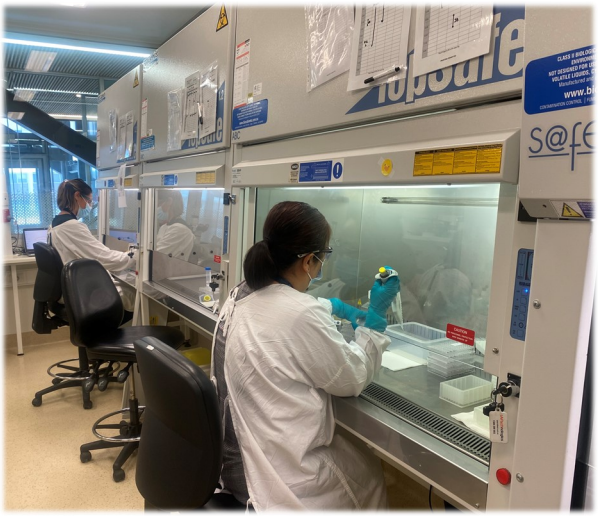
ORAL PRESENTATIONS

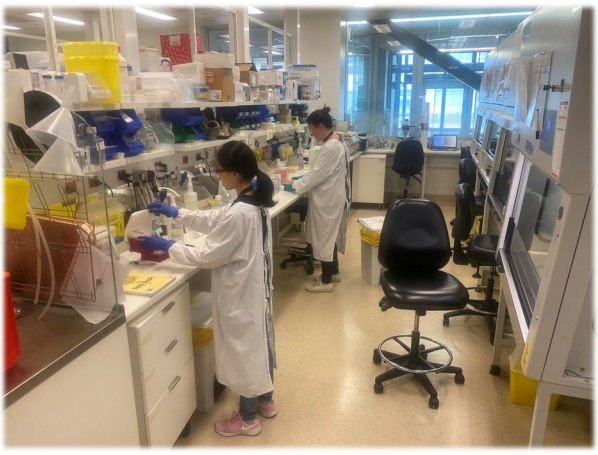
Event/Institute; Location, date	SPEAKER, Title(s)
Special Doherty Institute seminar: 2019-nCoV outbreak; Melbourne, 6 February 2020	KANTA SUBBARAO: Comparing nCoV-2019 and SARS.
2020 New Zealand Influenza Symposium; Auckland, New Zealand, 19-20 February 2020	KANTA SUBBARAO: International update on influenza and vaccines.
National Centre for Immunisation Research and Surveillance; Sydney, 10 March 2020	KANTA SUBBARAO: Update on Influenza and Influenza Vaccines in NCIRS 2020 Influenza program update.
RCPA National Microbiology Webinar, 11 March 2020	KANTA SUBBARAO: What's new about influenza in 2020?
CEPI Brighton Collaboration panel discussion on animal models for SARS-CoV-2, 12-13 March 2020	KANTA SUBBARAO: Lessons from SARS animal models: relevance for COVID-19
Thoracic Society of Australia and New Zealand (virtual), Melbourne, 31 March 2020	KANTA SUBBARAO: Global Transmission of Influenza and COVID -19
RMH Department of Medicine Seminar, 1 May 2020	KANTA SUBBARAO: COVID-19: A Virologist's view
RMH Grand Rounds, 11 June 2020	KANTA SUBBARAO: A tale of two pandemics: influenza and COVID-19: a focus on vaccines
US National Institutes of Health Seminar, 16 June 2020	KANTA SUBBARAO: COVID-19: the Australian experience and a perspective through a SARS-1 lens
School of Biomedical Sciences MinE conference, The University of Melbourne, 24 June 2020	KANTA SUBBARAO: COVID-19: a Virologist's view
Deakin University, Centre of Integrative Ecology Seminar Series, 10 July 2020	MICHELLE WILLE: Wild birds: neglected reservoirs for Coronaviruses
Student run Expo, UWA School of Human Sciences, 15 July 2020	KANTA SUBBARAO: COVID-19: A Virologist's view
Global Virus Network Webinar, 23 July 2020	KANTA SUBBARAO: COVID-19 through a SARS-1 lens
Hall Group Lab meeting, CSIRO, 24 July 2020	MICHELLE WILLE: Wild birds: neglected reservoirs for Coronaviruses
Seabirder Sessions Zoom Seminar Series, 29 July 2020	MICHELLE WILLE: Viruses of Antarctic Penguins and Their Ticks

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
Peter Doherty Institute for Infection and Immunity, A COVID Affair Seminar Series, 29 July 2020	MICHELLE WILLE: Wild birds: neglected reservoirs for Coronaviruses
Washington University School of Medicine in St Louis Symposium on 'COVID-19, Scientific Advances and its Impact on Women's Health', 11 September 2020	KANTA SUBBARAO: A different perspective on COVID-19: a look back from down under
I-MOVE 13th annual meeting, virtual sessions, 16-30 September 2020	SHEENA SULLIVAN: Measuring influenza VE during SARS-CoV-2 co-circulation – results, challenges and lessons learnt
ESCMID Conference on Coronavirus Disease (ECCVID), virtual forum, 23-25 September 2020	SHEENA SULLIVAN: Influenza-SARS-CoV-2 co-circulation: lessons from the Southern hemisphere
International Shorebird Twitter Conference. #ISTC20, 7-8 October 2020	MICHELLE WILLE: Shorebirds as hosts for an array of viral species
Monash University Bioinformatics Seminar Series, 7 October 2020	MICHELLE WILLE: Towards an understanding of virus community ecology in birds
University of Sydney Virus Evolution Seminar, 8 October 2020	MICHELLE WILLE: Factors affecting the RNA virus diversity in birds
Second COVID-19 Virtual Diagnostics Workshop, virtual forum, 9 October 2020	SHEENA SULLIVAN: The utility of serology for COVID-19 detection in a cohort of returned travellers with mild infection
18th International Congress of Virology, 12-16 October 2020	KANTA SUBBARAO: Adaptive changes in the influenza hemagglutinin: Implications for transmissibility and vaccine development
Polar Wildlife Health Webinar, 20-21 October 2020	MICHELLE WILLE: Birds – knowledge gaps
World Influenza Conference, 1 November 2020	KANTA SUBBARAO: Seasonal and pandemic influenza vaccines: principles and challenges
First East Asian-Australasian Flyway Shorebird Science Meeting, 3-5 November 2020	MICHELLE WILLE: Shorebirds as hosts for an array of viral species
University of Melbourne Department of Rural Health Seminar, 5 November 2020	KANTA SUBBARAO: COVID-19: The virus and vaccines
MicroSeq Conference, 10-11 November 2020	MICHELLE WILLE: Factors affecting RNA virus diversity in wild birds
EMBL Australia Postgraduate Symposium 2020, 11-13 November 2020	KANTA SUBBARAO: COVID-19: A virologist's view
VERENA Consortium Lightning Talk Series, 14 November 2020	MICHELLE WILLE: Factors affecting the RNA virus diversity in birds
59th ASMR National Scientific Conference, Firkin Oration, 18-19 November 2020	KANTA SUBBARAO: COVID-19: A virologist's view
Cell Conference, 'COVID-19: Understand, manage, control', 19-21 November 2020	KANTA SUBBARAO: COVID-19: Understanding the virus

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	**SPEAKER, Title(s)**
Harvard University Leadership updates on COVID-19 for clinicians, 2 December 2020	KANTA SUBBARAO: COVID-19 vaccines: Progress and challenges
NIH workshop on post-acute sequealae of COVID-19, 4 December 2020	KANTA SUBBARAO: Approaches to researching post-acute sequealae of SARS-CoV-2 infection
Australasian Virology Society Symposium, 7 December 2020	KANTA SUBBARAO: The pandemic potential of coronaviruses

Unfortunately there were no Poster presentations during 2020.





Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2020.

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*

Influenza and other respiratory viruses, *Editorial Board*

Public Health Laboratory Network (Department of Health), *Committee member*

Michelle Chow *(until March 2020)*

Doherty Institute Communications Working Group, *Member*

Yi-Mo Deng

WHO Working Group for GISRS PCR detection for influenza surveillance, *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*

Influenza and Other Respiratory Viruses, *Editorial board*

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

Kanta Subbarao

National Influenza Surveillance Committee (Department of Health)

Australian Influenza Vaccine Committee (Therapeutic Goods Administration)

Doherty Institute Leadership Group, *Member*

Doherty Institute Operational Management Committee, *Member*

Doherty Institute, *Discipline leader, Global Health*

Scientific Advisory Board for the Universal Influenza Vaccine Project at Mount Sinai School of Medicine, New York City NY, USA, *Member*

External Advisory Board, FLUCOP consortium, *Member*

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 Working Group for the Vaccine Research Center, NIAID, National Institutes of Health, Bethesda, MD, USA

External Advisory Group, NIAID Collaborative Influenza Vaccine Innovation Centers (CIVICs), NIAID, NIH, Bethesda, MD, USA, *Chair*

Vaccine Advisory Group, Vaccine Alliance Aotearoa New Zealand, *Member*

Committees and Advisory Groups

Kanta Subbarao (continued)

Department of Biotechnology, Government of India COVID-19 Vaccine Expert Committee, *Member*

ACT Accelerator COVAX Pillar Independent Product Group, *Member*

Advisory Group for CDC funded grant 'Prospective Assessment of COVID-19 in a Community (PACC) to Marshfield Clinic, Wisconsin, USA, *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*

Australian Technical Advisory Group on Immunisation (ATAGI) COVID-19 Working Group, *Member*

Steering Committee for BCG vaccination to reduce the impact of COVID-19 in healthcare workers (BRACE) trial, Melbourne, *Member*

Scientific Advisory Committee for Maddie Riewoldt's Vision, Australia, *Member*

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

WHO Working group on Influenza Preparedness and Response 2019, *Member*

WHO Pandemic Influenza Preparedness (PIP) Framework Partnership Contribution Independent Technical Expert Mechanism (PCITEM) 2017-present, *Member*

WHO Advisory Group on Human Challenge Studies for COVID-19 Vaccines, *Member*

PLoS Pathogens, *Section Editor*

mBio, *Editorial board*

Cell Host and Microbe, *Editorial board*

Journal of Virology, *Editorial board*

Med, *Editorial board*

Sheena Sullivan

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

Doherty Institute, *Equity and Diversity in Science Committee*

Australasian Epidemiology Association, *Secretary, Victorian Convenor*

WHO SAGE Working Group on Influenza Vaccines, *Member*

Angela Todd *(until November 2020)*

Victorian Infectious Diseases Reference Laboratory Safety Committee, *Member*

Michelle Wille

National Avian Influenza Wild Bird Surveillance, *Steering Committee*

Wildlife Health Australia, *Member*

Victorian Wader Study Group, *Member*

Visitors to the Centre

The Centre was pleased to host the following visitors during 2020.

Date	VISITOR and affiliation
3-7 February 2020	A/PROF ADAM KUCHARSKI; London School of Hygiene and Tropical Medicine, London UK; Collaborator
3-7 February 2020	PROF BENJAMIN COWLING; University of Hong Kong, Hong Kong SAR; Collaborator
17-Feb 2020	DR SEBASTIAN MAURER-STROH; Bioinformatics Institute (BII), A*STAR Biomedical Sciences Institute, Singapore; Collaborator
20-Feb 2020	PROF COLIN RUSSELL; University of Amsterdam, Amsterdam, Netherlands; Collaborator,
11 March-28 July 2020	DR SAM WILKS, Cambridge University, UK

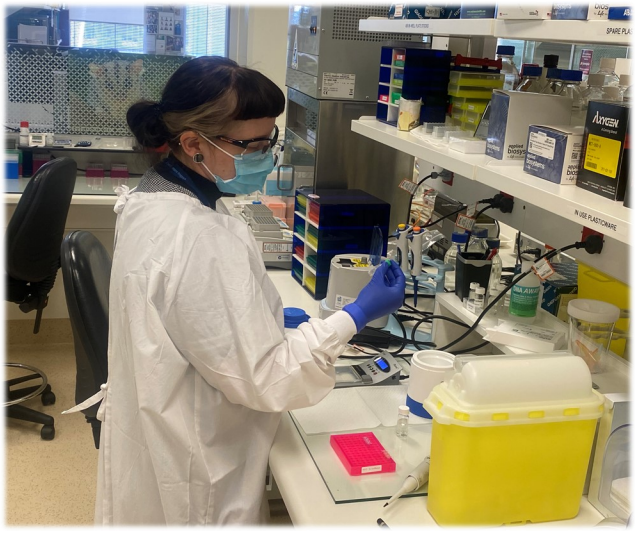
Engagement in WHO activities

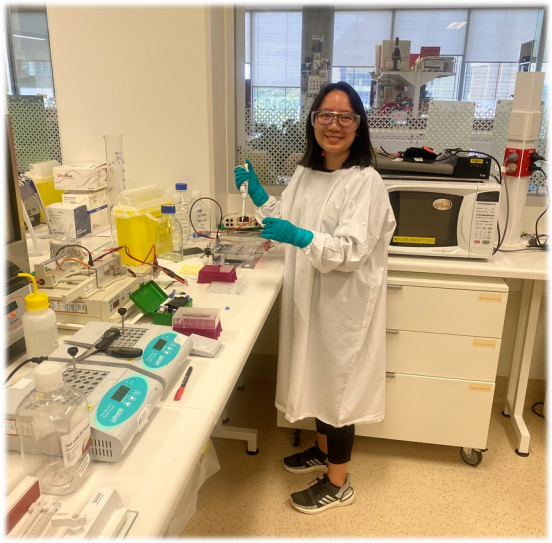
Event; Location, Date	Centre staff involved
WHO R&D Blueprint for action to prevent epidemics: Global Research and Innovation forum towards a roadmap for the 2019 novel coronavirus; Geneva, Switzerland, 10-14 February 2020	Kanta Subbarao attended.
WHO Consultation on the Composition of Influenza Vaccines for the northern hemisphere 2020-2021; Geneva, Switzerland, 24-28 February 2020	Ian Barr, Kanta Subbarao, Yi-Mo Deng attended.
WHO Consultation on the Composition of Influenza Vaccines for the southern hemisphere 2021 (e-Consultation), 21-25 September 2020	Heidi Peck, Ian Barr, Kanta Subbarao, Sheena Sullivan, Yi-Mo Deng attended
WHO Consultation to Adapt Influenza Sentinel Surveillance Systems for Including COVID-19, 6-8 October 2020	Ian Barr, Sheena Sullivan attended
WHO/EURO Expert group on protocols COVID-19 vaccine effectiveness, 18-19 November 2020	Sheena Sullivan attended
Strategic Advisory Group of Experts (SAGE) on Immunization Influenza vaccines Working Group, 8 December 2020	Sheena Sullivan attended

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
Immunisation Coalition Annual Scientific Meeting; Melbourne, 2-3 February 2020	Ian Barr, Kanta Subbarao, Sheena Sullivan attended.
TSANZSRS Annual Scientific Meeting 2020; Melbourne, 27 -31 March 2020	Kanta Subbarao
Master of Bioinformatics program, The University of Melbourne, 14-21 September 2020	Michelle Wille taught the subject BINF90004 Case Studies in Bioinformatics
8th Australasian Vaccines and Immunotherapeutics Development (AVID) Meeting, 8-11 November 2020	Ian Barr attended
Wild and Comparative Immunology Conference, 8-10 December 2020	Michelle Wille attended





Community Engagement

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

James Barnes

- Featured in an article on The Courier Mail titled, 'UQ vaccine: Meet the people racing to build the COVID-19 jab', published 20 November 2020; https://www.couriermail.com.au/news/queensland/uq-vaccine-meet-the-104-people-racing-to-build-the-covid19-jab/news-story/4abad86dab0b47e3ed235686e1e3a5aa

Ian Barr

- Participated in an interview with ABC News for the article "Flu season which struck down 310,000 Australians 'worst on record' due to early outbreaks", published 11 February 2020; https://www.abc.net.au/news/2020-02-11/early-outbreaks-to-blame-for-worst-flu-season-on-record/11949320
- Participated in an interview with The New Daily for the article "Coronavirus symptoms: The difference between the flu and the virus", published 6 March 2020; https://thenewdaily.com.au/life/wellbeing/2020/03/06/coronavirus-flu-difference-symptoms/
- Participated in an interview with The Age on 'Early flu shots a "risk worth taking"', published 31 March 2020; https://www.theage.com.au/national/early-flu-shots-a-risk-worth-taking-20200330-p54fcc.html
- Participated in an interview with Body and Soul on 'Why do doctors want us to get the flu vaccine, ASAP?', published 31 March 2020; https://www.bodyandsoul.com.au/health/health-news/why-do-doctors-want-us-to-get-the-flu-vaccine-asap/news-story/8e68071aa7bddfcc499e0320265f0111
- Participated in an interview with Gizmodo on 'You Can Catch The Flu And Coronavirus At The Same Time, But Don't Panic', published 1 April 2020; https://www.gizmodo.com.au/2020/04/can-you-catch-coronavirus-flu-same-time/
- Participated in an interview with AccuWeather on 'Is the US ready for how the coronavirus may impact the next flu season?', published 2 April 2020; https://www.accuweather.com/en/health-wellness/is-the-us-ready-for-how-the-coronavirus-may-impact-the-next-flu-season/712010
- Participated in an interview with the ABC on 'A winter flu season means Australia's coronavirus lockdown could last for months', published 10 April 2020; https://www.abc.net.au/news/2020-04-10/flu-season-with-coronavirus-could-mean-extended-lockdown-covid19/12136870
- Participated in an interview with Fairfax Media on 'Can my workplace force me to get an influenza vaccination?', published 10 May 2020; https://www.thecourier.com.au/story/6750915/can-my-work-force-me-to-get-the-flu-jab/
- Participated in an interview with Healthline on 'What If Flu and COVID-19 Overlap? Australia Is Trying to Avoid That Scenario', published 11 May 2020; https://www.healthline.com/health-news/australia-dealing-with-possible-flu-covid-combination
- Participated in an interview with newsGP on 'Is Australia at risk of a rebound flu season?', published 16 June 2020; https://www1.racgp.org.au/newsgp/clinical/is-australia-at-risk-of-a-rebound-flu-season
- Participated in an interview with ABC news on 'Flu deaths drop in Australia as coronavirus restrictions save hundreds of lives', published 23 July 2020; https://www.abc.net.au/news/2020-07-23/coronavirus-restrictions-cause-flu-cases-to-drop-australia/12480190
- Participated in an interview with MiNDFOOD magazine titled 'A Vaxing Question', published 15 August 2020; https://www.pressreader.com/australia/mindfood/20200806/283772791292743

Community Engagement (continued)

Ian Barr (continued)

- Participated in an interview with newsGP on 'Flu boosters unnecessary as influenza all but vanishes', published 18 August 2020; https://www1.racgp.org.au/newsgp/clinical/flu-boosters-unnecessary-as-influenza-all-but-vani
- Participated in an interview with The Sydney Morning Herald on 'Overall death rates are down - now the bad news', published 21 August 2020; https://www.smh.com.au/national/overall-death-rates-are-down-now-the-bad-news-20200821-p55nxm.html
- Participated in an interview with Healthline titled, 'Why Australia Had a Mild Flu Season and What That Means for the United States', published 6 September 2020; https://www.healthline.com/health-news/australia-mild-flu-season-what-means-for-the-united-states
- Participated in an interview with CTV News titled, 'What Canada can learn from the Southern Hemisphere's season of "virtually no influenza"', published 10 September 2020; https://www.ctvnews.ca/health/what-canada-can-learn-from-the-southern-hemisphere-s-season-of-virtually-no-influenza-1.5099934
- Participated in an interview with The Guardian titled, 'Southern hemisphere has record low flu cases amid Covid lockdowns', published 17 September 2020; https://www.theguardian.com/society/2020/sep/17/falling-flu-rates-in-southern-hemisphere-offers-hope-as-winter-approaches-coronavirus
- Participated in an interview with KBS World on the interaction of influenza and COVID-19, published 21 September 2020; http://world.kbs.co.kr/service/program_listenagain.htm?lang=e&procode=korea_24
- Participated in an interview with Healthline titled, 'What We Can Learn from Australia Before Flu Season', published 2 October 2020; https://www.healthline.com/health-news/what-we-can-learn-from-australia-before-flu-season
- Participated in an interview with The Indian Express titled, 'Explained: How will the novel coronavirus behave in the winter?', published 16 October 2020; https://indianexpress.com/article/explained/explained-how-will-novel-coronavirus-behave-in-winter-6709100/
- Quoted by a Chemical & Engineering news article titled, 'Combined COVID-19 and flu tests could help overwhelmed hospitals', published 18 November 2020; https://cen.acs.org/analytical-chemistry/diagnostics/Combined-COVID-19-flu-tests/98/i45
- Participated in an interview with The Medical Republic titled, 'Respiratory deaths fell during second COVID-19 wave', published 7 December 2020; https://medicalrepublic.com.au/respiratory-deaths-fell-during-second-covid-19-wave/38109

Leo Lee

- Participated in an interview with ScienceDaily on 'Influenza: researchers show that new treatment reduces spread of virus' which featured findings of Lee L et. al. 2020 Plos Pathog, published 16 April 2020; https://www.sciencedaily.com/releases/2020/04/200416091947.htm
- Participated in an interview with News Medical on 'New antiviral drug reduces transmission of influenza, study shows' which featured findings of Lee L et. al. 2020 Plos Pathog, published 16 April 2020; https://www.news-medical.net/news/20200416/New-antiviral-drug-reduces-transmission-of-influenza-study-shows.aspx

Community Engagement (continued)

Patrick Reading

- Featured in a Doherty article titled, 'Cold and flu and the search for similarities to target for better treatment', published 25 August 2020; https://www.doherty.edu.au/news-events/news/cold-and-flu-and-the-search-for-similarities-to-target-for-better-treatment
- Participated in a podcast interview with Contain This titled, 'Contain This: The Latest in Global Health Security', published 7 September 2020; https://www.buzzsprout.com/620797/5327071
- Featured in an article on The Courier Mail titled, 'UQ vaccine: Meet the people racing to build the COVID-19 jab', published 20 November 2020; https://www.couriermail.com.au/news/queensland/uq-vaccine-meet-the-104-people-racing-to-build-the-covid19-jab/news-story/4abad86dab0b47e3ed235686e1e3a5aa

Kanta Subbarao

- Participated in an interview with the Smithsonian Magazine for the article "As the World Faces One of the Worst Flu Outbreaks in Decades, Scientists Eye a Universal Vaccine", published 17 January 2020; https://www.smithsonianmag.com/science-nature/world-faces-worst-flu-outbreak-decades-scientists-eye-universal-vaccine-180974005/
- Participated in an interview with ABC News for the article "Coronavirus 'super-spreaders' a potential risk as strain spreads from Wuhan to cities outside of China", published 22 January 2020; https://www.abc.net.au/news/2020-01-22/coronavirus-super-spreaders-a-risk-as-virus-threatens-go-global/11885028
- Participated in an interview with ABC Radio Sydney for the segment "Australia prepares for new strain of coronavirus", published 22 January 2020; https://www.abc.net.au/radio/sydney/programs/am/australia-prepares-for-new-strain-of-coronavirus/11888352
- Participated in an interview with The Age for the video segment "Coronavirus explained", published 7 February 2020; https://www.theage.com.au/world/coronavirus-explained-20200207-5izsa.html
- Appeared on ABC News Breakfast to talk about about the newly emerged coronavirus COVID-2019, published 17 February 2020; https://www.abc.net.au/news/2020-02-17/who-virologist-on-the-coronavirus/11971182
- Participated in an interview with The Age for the article "Why children aren't getting sick from coronavirus", published 3 March 2020; https://www.theage.com.au/national/why-children-aren-t-getting-sick-from-coronavirus-20200302-p545x8.html
- Participated in an interview on COVID19 with Mornings with Virginia Trioli on ABC Radio Melbourne, published 4 March 2020; https://www.abc.net.au/radio/melbourne/programs/mornings/mornings/12004956
- Participated in an interview with STAT on 'From ferrets to mice and marmosets, labs scramble to find right animals for coronavirus studies', published 5 March 2020; https://www.statnews.com/2020/03/05/coronavirus-labs-scramble-to-find-right-animals-for-covid-19-studies/
- Participated in an interview with Cell Host and Microbe for a special feature on Gender Inclusion in Microbial Sciences, published 11 March 2020; https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30121-9; https://www.cell.com/cell-host-microbe/pdf/S1931-3128(20)30121-9.pdf
- Participated in an interview with The Scientist on 'Possible Biological Explanations for Kids' Escape from COVID-19', published 17 March 2020; https://www.the-scientist.com/news-opinion/possible-biological-explanations-for-kids-escape-from-covid-19-67273
- Participated in an interview with ABC Radio Sydney on COVID-19, published 21 March 2020; https://www.abc.net.au/radio/sydney/programs/weekendmornings/weekend-mornings/12057198

Community Engagement (continued)

Kanta Subbarao (continued)

- Participated in an interview with the National Geographic on 'The coronavirus spares most kids. These theories may help explain why.', published 25 March 2020; https://www.nationalgeographic.com/science/2020/03/coronavirus-spares-most-kids-these-theories-may-help-explain-why/
- Participated in an interview with PNAS on 'News Feature: Avoiding pitfalls in the pursuit of a COVID-19 vaccine', published 30 March 2020; https://www.pnas.org/content/117/15/8218
- Participated in an interview with COSMOS on 'The COVID-19 spread: What do we know?', published 7 April 2020; https://cosmosmagazine.com/features/what-do-we-know-about-covid-19-transmission/
- Participated in an interview with News Corp on 'How newly approved drug could stop flu in its tracks' which featured findings of Lee L et. al. 2020 Plos Pathog, published 16 April 2020; https://www.dailytelegraph.com.au/news/how-newly-approved-drug-could-stop-flu-in-its-tracks/news-story/fbaf34a344f7fa0ce252a48db2b08c80?btr=d512b91fd37edab4c80438c17a7e2199
- Participated in an interview with Nature on 'Antibody tests suggest that coronavirus infections vastly exceed official counts', published 17 April 2020; https://www.nature.com/articles/d41586-020-01095-0
- Participated in an interview with Good Weekend Talks on 'What did we learn, or miss, from the Spanish flu?', published 19 April 2020; https://www.smh.com.au/national/what-did-we-learn-or-miss-from-the-spanish-flu-20200415-p54jz6.html
- Participated in an interview with InSight on 'Flu in the time of COVID-19? “All bets are off”', published 20 April 2020; https://insightplus.mja.com.au/2020/15/flu-in-the-time-of-covid-19-all-bets-are-off/
- Participated in an in interview with the Sydney Morning Herald on 'Flu season that looked like 'a big one' beaten by hygiene, isolation', published 20 April 2020; https://www.smh.com.au/national/flu-season-that-looked-like-a-big-one-beaten-by-hygiene-isolation-20200420-p54lh7.html
- Participated in an interview with The Australian on 'Coronavirus: Hopes up for an Australian vaccine by September', published 29 April 2020; https://www.theaustralian.com.au/nation/coronavirus-hopes-up-for-an-australian-vaccine-by-september/news-story/cd6006a8e7c449fb442a9fd962eda45f?btr=694a863d25c61c1c2b9135620a735b16
- Participated in an interview with News Corp on 'UQ COVID-19 vaccine hits new milestone in preclinical trials', published 29 April 2020; dailytelegraph.com.au/news/queensland/uq-covid19-vaccine-hits-new-milestone-in-preclinical-trials/news-story/7c28e8d591c488f826e7c7a69c02934c?btr=48b60f01c727ef4443db63bc08e7d4b3
- Participated in an interview with SBS on 'Coronavirus vaccine breakthrough as Queensland scientists raise high levels of antibodies in testing', published 29 April 2020; https://www.sbs.com.au/news/coronavirus-vaccine-breakthrough-as-queensland-scientists-raise-high-levels-of-antibodies-in-testing
- Participated in an interview with 7.30 Report (ABC) on 'Winter is coming and there are concerns the coronavirus could flare up', published 5 May 2020; https://www.abc.net.au/7.30/winter-is-coming-and-there-are-concerns-the/12213766
- Wrote an article on Cell Host and Microbe 'SARS-CoV-2: A New Song Recalls an Old Melody', published 13 May 2020; https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30246-8
- Participated in an interview with Lifehacker on 'PSA: Your Flu Shot Won't Give You A Mild Flu', published 14 May 2020; https://www.lifehacker.com.au/2020/05/psa-your-flu-shot-wont-give-you-a-mild-flu/
- Participated in a podcast with the Melbourne Vaccine Education Centre on 'COVID19 Road to a vaccine podcast episode 4: Professor Kanta Subbarao', published 17 June 2020; https://mvec.mcri.edu.au/covid19-road-to-a-vaccine-podcast-episode-4-professor-kanta-subbarao/

Community Engagement (continued)

Kanta Subbarao (continued)

- Participated in an online webinar with BioForum titled, 'Developing an Australian Novel Vaccine: UQ Coronavirus Vaccine Development Project', published 26 June 2020; https://biomelbourne.org/event/bioforum-developing-an-australian-novel-vaccine-the-uq-cepi-csl-coronavirus-vaccine-development-project/
- Participated in an interview with NDTV on 'Senior WHO Official Speaks To NDTV On Herd Immunity, COVID Vaccine', published 31 July 2020; https://www.ndtv.com/video/shows/coronavirus-facts-vs-myths/senior-who-official-speaks-to-ndtv-on-herd-immunity-covid-vaccine-556143
- Participated in an interview with ABC news titled 'The coronavirus is mutating, just like most viruses, but the effect isn't as pronounced as some headlines suggest', published 15 August 2020; https://www.abc.net.au/news/health/2020-08-15/coronavirus-new-strains-mutation-vaccine-headlines/12519576
- Participated in a webinar with Glen Waverley High School titled 'Pandemic Past and Present', published 19 August 2020;
- Participated in an interview with NPR titled, 'From Southern Hemisphere, Hints That U.S. May Be Spared Flu On Top Of COVID-19', published 26 August 2020; https://wamu.org/story/20/08/26/from-the-global-south-hints-that-u-s-may-be-spared-flu-on-top-of-covid-19/
- Participated in an interview with Science News titled, 'What will happen when COVID-19 and the flu collide this fall?', published 18 September 2020; https://www.sciencenews.org/article/covid19-coronavirus-flu-season-fall
- Participated in an interview with The Smithsonian Magazine titled, 'What to Expect When Covid-19 and the Flu Season Collide', published 7 October 2020; https://www.smithsonianmag.com/science-nature/what-expect-when-covid-19-and-flu-season-collide-180976000/
- Co-authored an article on The Conversation titled, 'Infecting volunteers with coronavirus may be one way to test potential vaccines. But there are risks', published 13 October 2020; https://theconversation.com/infecting-volunteers-with-coronavirus-may-be-one-way-to-test-potential-vaccines-but-there-are-risks-147349
- Hosted a COVID-19 webinar series, 'COVID-19: The Virus and Vaccines' for the Faculty of Medicine, Dentistry and Health Sciences at The University of Melbourne, published 6 November 2020; https://unimelb.zoom.us/webinar/register/WN_DXZuX77_S029zZDEVSdLeA
- Participated in a webinar titled, 'COVID-19 The Virus and Vaccines' for the Department of Rural Health at The University of Melbourne, published 17 November 2020; https://medicine.unimelb.edu.au/school-structure/rural-health/news-and-events/covid-19-the-virus-and-vaccines
- Participated in an interview with The Atlantic titled, 'The End of the Pandemic Is Now in Sight', published 19 November 2020; https://www.theatlantic.com/health/archive/2020/11/vaccines-end-covid-19-pandemic-sight/617141/
- Featured in an article on The Courier Mail titled, 'UQ vaccine: Meet the people racing to build the COVID-19 jab', published 20 November 2020; https://www.couriermail.com.au/news/queensland/uq-vaccine-meet-the-104-people-racing-to-build-the-covid19-jab/news-story/4abad86dab0b47e3ed235686e1e3a5aa
- Participated in an interview with Norman Swan on the 7.30 report (ABC) titled, 'Will this new vaccine be a game changer?', published 3 December 2020; https://www.abc.net.au/7.30/will-this-new-vaccine-be-a-game-changer/12948848
- Participated in an interview with Virginia Trioli for ABC Melbourne Radio, published 9 December 2020; https://www.abc.net.au/radio/melbourne/programs/mornings/

Community Engagement (continued)

Kanta Subbarao (continued)

- Quoted in an article with The Scientific Times titled, 'Children's Adaptive Immune System Seems Key to Beating COVID-19', published 16 December 2020; https://www.sciencetimes.com/articles/28669/20201216/childrens-adaptive-immune-system-seems-key-to-beating-covid-19.htm

Sheena Sullivan

- Co-authored an article on The Conversation titled, 'Why do some COVID-19 tests come back with a 'weak positive', and why does it matter?', published 7 October 2020; https://theconversation.com/why-do-some-covid-19-tests-come-back-with-a-weak-positive-and-why-does-it-matter-147258

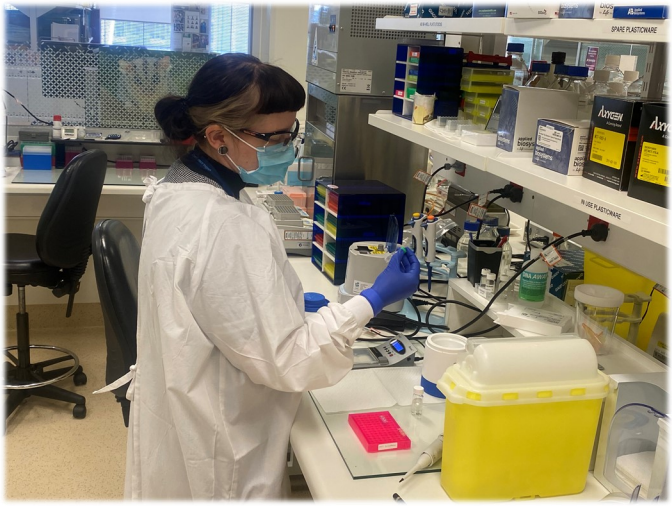
Michelle Wille

- Wrote an article on the Pursuit on 'Penguin viruses in the frozen continent', published 15 April 2020; https://pursuit.unimelb.edu.au/articles/penguin-viruses-in-the-frozen-continent
- Work has been featured in the Wild Bird News newsletter, published 7 October 2020; https://www.wildlifehealthaustralia.com.au/Portals/0/Documents/ProgramProjects/N2_Wild_Bird_News_Jun_2019.pdf
- Co-authored an article on The Conversation titled, 'Nearly half a million poultry deaths: there are 3 avian influenza outbreaks in Victoria. Should we be worried?', published 7 October 2020; https://theconversation.com/nearly-half-a-million-poultry-deaths-there-are-3-avian-influenza-outbreaks-in-victoria-should-we-be-worried-145325

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. The website was also redesigned in October 2020, whilst retaining the content of the original site. During 2020, the website was viewed by 5,284 unique users from 126 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 2020. The Centre's Twitter profile gained 252 followers during the year, with a total of 670 followers by 31 December 2020.



Management and staff

Director
Prof Kanta Subbarao

Deputy Director
Prof Ian Barr

Administrative officer
Jayde Simpson

Quality & Regulatory Officer
Katie Milne

Educator/Research scientist
Prof Patrick Reading

Laboratory Manager/
Senior Medical Scientist
Dr Paul Whitney

Communications officer
Dr Michelle Chow (until Mar)
Dr Miku Kuba*

Surveillance

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

GENETIC ANALYSIS
Head: Dr Yi-Mo Deng
Medical scientists:
Pina Iannello
Hilda Lau
Jean Moselen
Natalie Spirason
Angela Todd (until Nov)
Bioinformatician:
Miguel Grau Lopez (until Feb)

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

BIOINFORMATICS
Manager: Naomi Komadina
Bioinformatician: 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

IMMUNE RESPONSES TO INFLUENZA
Senior research scientist:
Dr Annette Fox
Post-Doctoral researchers
Dr Ryan (Yeu-Yang) Tseng*
Research assistant
Louise Carolan

ANTIVIRALS AND ANIMAL INFLUENZAS
Senior research scientist:
Dr Mariana Baz
Post-Doctoral researchers
Dr Edin Mifsud
Dr Nikita Deshpande*
Dr Michelle Wille (until Jun— now Honorary)
Research assistants:
Malet Aban
Ankita George
Leo Lee (until May)
Manisha Patel (until Oct)
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
Research assistant:
Arseniy Khvorov
MAE Candidate:
Chris Bailie

**New staff members in 2020*