2018
Annual Report

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 2015-2019) are:

1. To obtain, isolate and preserve representative viruses from outbreaks and sporadic cases of influenza, and characterise their antigenic and other relevant properties, including resistance to anti-influenza drugs;
2. To exchange information and new antigenic variants of influenza viruses with other WHO Collaborating Centres for Reference and Research on Influenza and with Essential Regulatory Laboratories;
3. To assist WHO in developing recommendations on viruses to be included in influenza vaccines;
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 collect epidemiological information on the prevalence of influenza, especially in countries and areas in the Region;
6. To undertake research to improve the detection, prevention and treatment of influenza;
7. To assist WHO and national health authorities in developing and implementing plans for responding to pandemic influenza; and
8. To comply with the Terms of Reference for WHO Collaborating Centres for Influenza related to work with Pandemic Influenza Preparedness biological materials as specified in Annex 5 of the Pandemic Influenza Preparedness Framework.

Governance

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

Contact information

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Highlights of 2018

Surveillance

The Centre received and processed **3991 samples**, of which **96.9% were tested**. Of viruses tested, more than half **(51.8%)** were **A(H1N1)pdm09 viruses.**

Research

The Centre further developed its research program during 2019, welcoming **Dr Annette Fox** as Senior Research Scientist and continuing numerous influenza-related research projects.

Publications

Centre staff were authors on **47 papers** in peer-reviewed journals. This is the **highest annual total** of publications and included two papers in the New England Journal of Medicine.

A(H3N2)v variant virus

The Centre recorded the first ever detection of a swine **A(H3N2)v** variant virus from a **human** patient in **Australia.**

Centre staff retreat, May 2018

Director's report

It is a pleasure to present the 2018 Annual Report of the WHO Collaborating Centre for Reference and Research on Influenza. The Centre has continued to actively fulfil its commitments to the WHO, National Influenza Centres in the region, and the Commonwealth Government and to participate in training and research activities.

Following a very busy influenza season in 2017, the 2018 influenza season in Australia was quite mild. However, there were more than usual notifications in the 'inter-seasonal period', in December 2018 that extended into the beginning of 2019. The Centre received and processed nearly 4000 influenza samples from 39 laboratories in Australia and 16 other countries during 2018. The largest proportion (>50%) of the samples analysed were A(H1N1)pdm09 viruses and about a quarter were A(H3N2) viruses. As we noted in recent years, there is considerable genetic diversification of the H3 HA gene.

In 2018, the Centre reported the first detection of a swine A(H3N2) variant virus from a human patient in Australia. The virus, from South Australia, contained a combination of influenza genes derived from seasonal influenza A(H3N2) viruses that had circulated in humans in 1996-1997 and A(H1N1)pdm09 viruses, with adaptations that enabled them to circulate in swine. The detection of this virus from a human patient indicates that such influenza A viruses are circulating in pigs in Australia and highlights the potential for zoonotic infections and the importance of surveillance in swine farms.

The integration of Next Generation Sequencing (NGS) techniques into routine surveillance activities has resulted in a large annual number of viruses undergoing full genome sequencing. In 2018, the Centre sequenced 191 full genomes and 1225 partial genomes (HA and NA genes plus MP gene for influenza A viruses).

During 2018 the Centre continued to work on isolation of cell-based and egg-based viruses for vaccine production. The Centre also continued to monitor potential pandemic influenza viruses and seeks to obtain new viruses as they were detected (such as A(H7N9) viruses), to check reagents and prepare virus and RNA stocks. Centre staff participated in training international visitors at the Centre as well as at workshops hosted overseas. Centre staff presented at several domestic and international conferences in 2018.

Centre staff contributed to a total of 47 original research papers, reviews and reports in 2018, the largest number published in a year. Centre staff were successful in obtaining grant funding to support their research from a variety of sources including NHMRC, NIH (USA) and the Coalition for epidemic preparedness innovations (CEPI).

We are very grateful to Dr Mike Catton, Director of VIDRL, and many other members of VIDRL staff, especially Hayley Snelling, Jane Brewster, Anna Ayres and Dallas Wilson, for their support of the Centre's work at every level during 2018. 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 in 2018. It is a privilege to work with the Centre staff and I look forward to working with our partners in 2019 and onwards.

Prof Kanta Subbarao
Centre Director

Surveillance

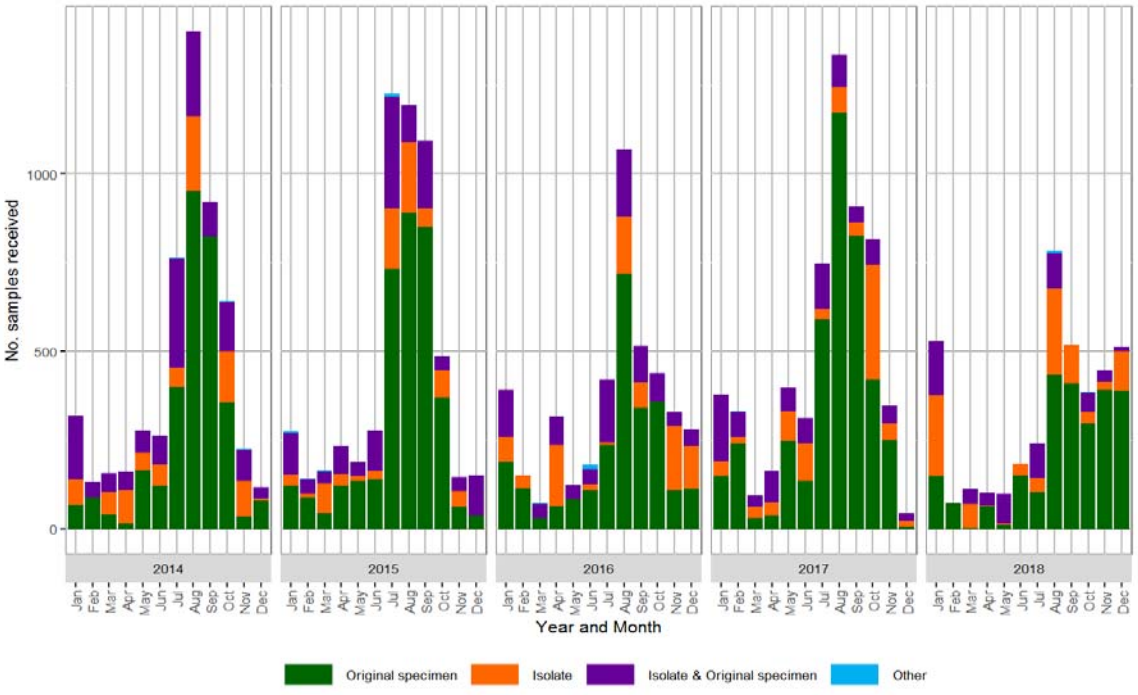
Introduction

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, 2014-2018



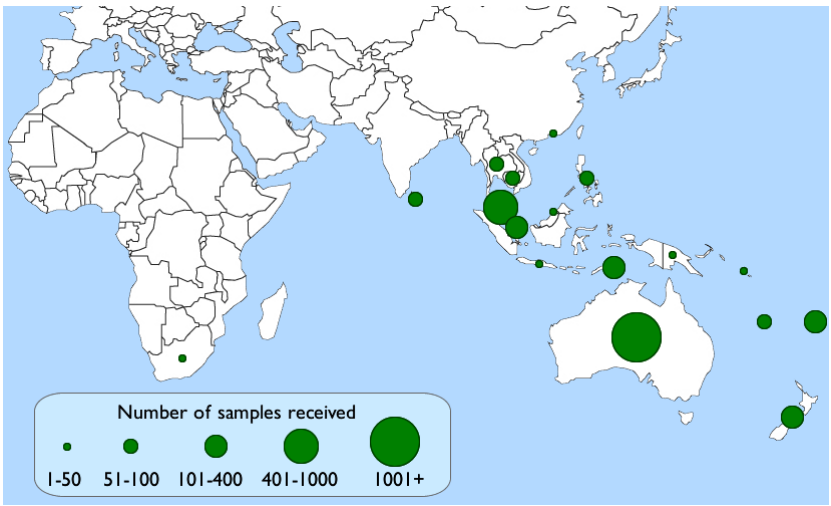


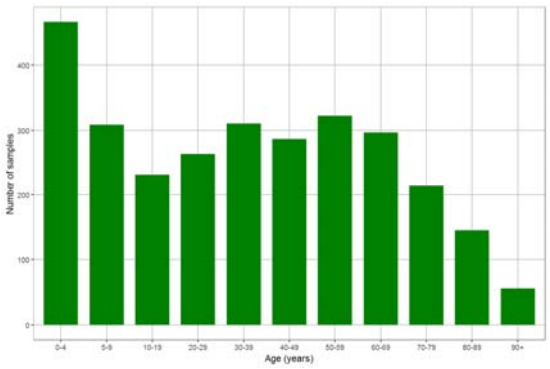
Figure 2. Geographic spread of influenza laboratories sending viruses to the Centre during 2018.

Receipt of Influenza Viruses

During 2018 the Centre received 3991 clinical specimens and/or virus isolates from 39 laboratories in 17 countries (Figures 1 and 2, Table 1). Overall the number of samples received during 2018 was lower compared to previous four years. However, an unusually large number of samples were received during the last two months of 2018, whereas there there is usually a decrease in samples received during this time. Amongst samples received by the Centre for which the age of the patient was known, the largest portion were from subjects aged under 5 years (Figure 3).

A total of 3868 samples (96.9%) were cultured and analysed by haemagglutination inhibition (HI) assay and/or real-time reverse-transcription polymerase chain reaction (RT-PCR). 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, 51.7% were identified as A(H1N1)pdm09, 24.8% were A(H3N2) viruses, 5.6% were B/Victoria and 16.1% were B/Yamagata viruses (Table 2). One sample was an A(H3N2)v variant virus, the first time this variant subtype has been identified from a human patient in Australia (more details on page 12). A total of 427 samples came from Australian general practictioner based surveillance systems (Table 3).

Figure 3. Age distribution of patients from whom samples were received at the Centre in 2018 and the age is known.



Isolation 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.

Table 1. Samples received by the Centre in 2018, by country.

Country	Samples received				% Samples tested
	Specimens	Isolates	Specimen + Isolate	Other (eg. RNA/ DNA/tissue)	
AUSTRALASIA					
Australia	1828	141	379	9	98.1%
New Zealand	38	91			100%
SOUTH PACIFIC					
Fiji	114				100%
New Caledonia	81				100%
Papua New Guinea	9				100%
Solomon Islands	17				100%
SOUTH EAST ASIA					
Brunei	14				100%
Cambodia	52	48			100%
Indonesia	9	16			100%
Malaysia	0	472			83.5%
Philippines	51		36		100%
Singapore		9	167		100%
Thailand	19	66			100%
Timor-Leste	150				100%
EAST ASIA					
Macau SAR, China		40			100%
SOUTH ASIA					
Sri Lanka	83	11			100%
AFRICA					
South Africa		3	38		100%
TOTAL	**2465**	**897**	**620**	**9**	**96.9%**

Table 2. Samples successfully tested by cell culture and/or RT-PCR assay at the Centre in 2018, by country.

Country	Samples tested by cell culture and/or RT-PCR assay								
	A (H1N1)pdm09	A H3N2	A H3N2v	A mixed subtype	A unsubtyped	B/Victoria	B/Yamagata	B lineage undetermined	C
AUSTRALASIA									
Australia	1091	417	1	2	23	19	269	13	1
New Zealand	67	15				3	41		
SOUTH PACIFIC									
Fiji	21	25					28		
New Caledonia	20	6				28	24		
Papua New Guinea	6					2			
Solomon Islands	3				1		1		
SOUTH EAST ASIA									
Brunei	7	1							
Cambodia	40	27				3	15		
Indonesia	6	7		2		3		7	
Malaysia	180	107		1		25	47		
Philippines	6	32				2	2		
Singapore	58	65				23	30		
Thailand	21	29					27		
Timor-Leste	23	9		2		60	10		
EAST ASIA									
Macau SAR	23	13				1	3		
SOUTH ASIA									
Sri Lanka	15	25				7	7		
AFRICA									
South Africa	37	2					2		
TOTAL	**1624**	**780**	**1**	**7**	**24**	**176**	**506**	**20**	**1**

Table 3. Samples received from general practitioner based surveillance systems in Australia, 2019

	No. samples received	No. isolates recovered*	Viruses analysed by HI assay
Australian Sentinel Practices Research Network *(ASPREN)*	185	110	97
Victorian Sentinel Practices Influenza Network *(VicSPIN)*	36	32	28
Influenza Complications Alert Network (*FluCAN*)	206	156	148
TOTAL	**427**	**298**	**273**

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

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. In addition a number of A(H3N2) viruses are also analysed antigenically using a microneutralisation assay known as the Focus Reduction Assay (FRA). Subtypes are based on analysis of the HA and in some cases are confirmed by genetic analysis of the NA gene.

Antigenic analyses 2018

A total of 3750 isolates that were received at the Centre in 2018 were cultured and isolated in MDCK cells, of which 2882 (76.9%) produced a positive result. The largest proportion of viruses were A(H1N1)pdm09 (53.3%), followed by A(H3N2) viruses (25.6%) (Figure 4). This trend similar throughout the different world regions for samples received and successfully analysed at the Centre (Figure 5), the exception being South Asia, where A(H3N2) viruses predominated.

Figure 4. Influenza sub/types and lineages of samples received in 2018 and characterised by antigenic analysis.

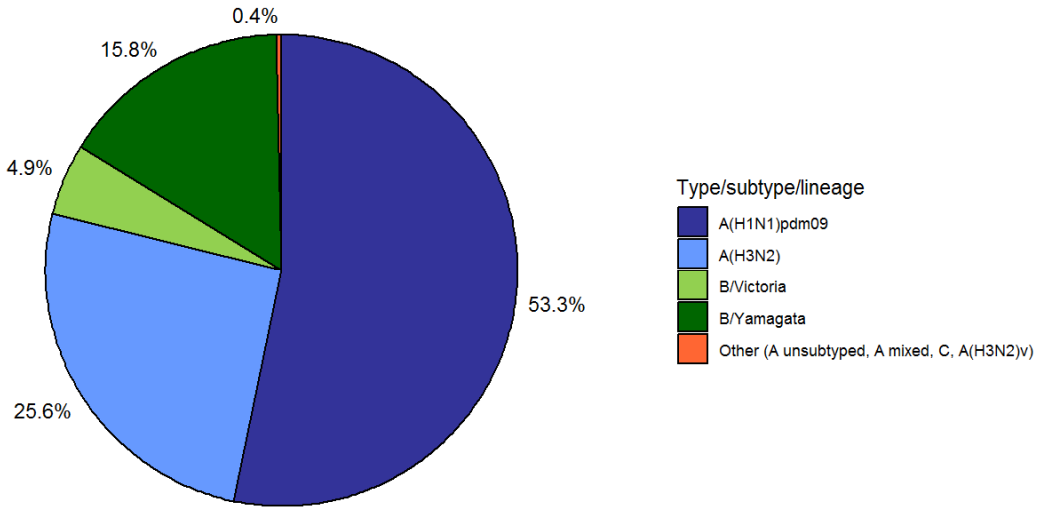
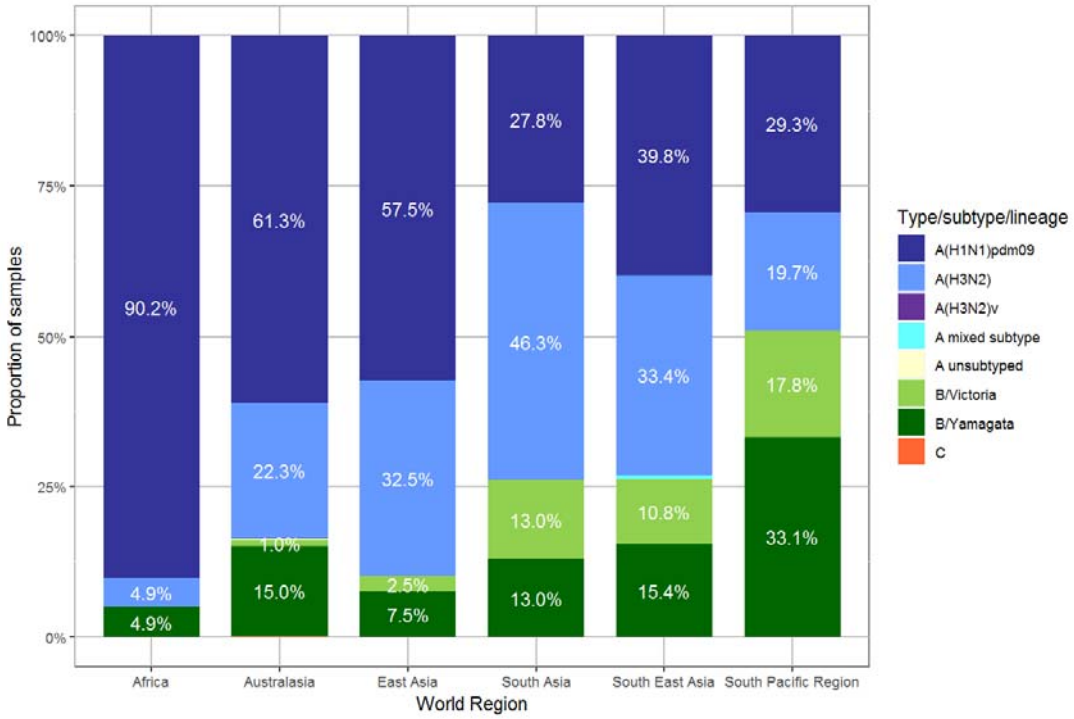


Figure 5. Influenza sub/types and lineages of isolates received from different world regions during 2018 as determined by antigenic analysis.



Genetic Analysis of Influenza

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 have been increasingly employed at the Centre for efficient and cost-effective sequencing of whole genomes of viruses, and/or selected influenza virus genes.

Figure 6. Sanger and NGS sequence analysis of samples received at the Centre in 2018.

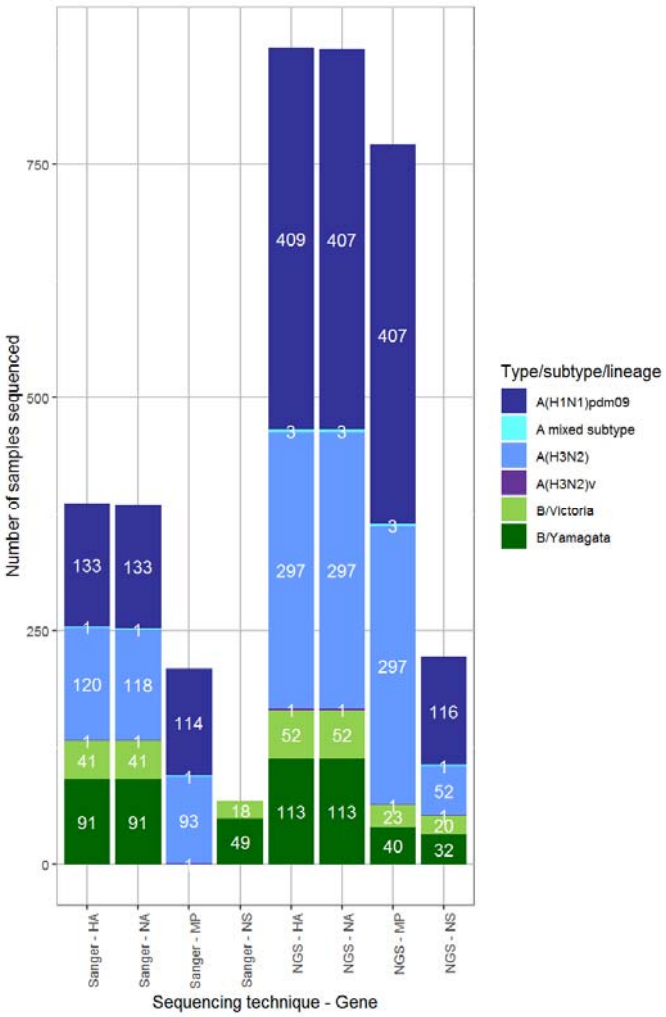
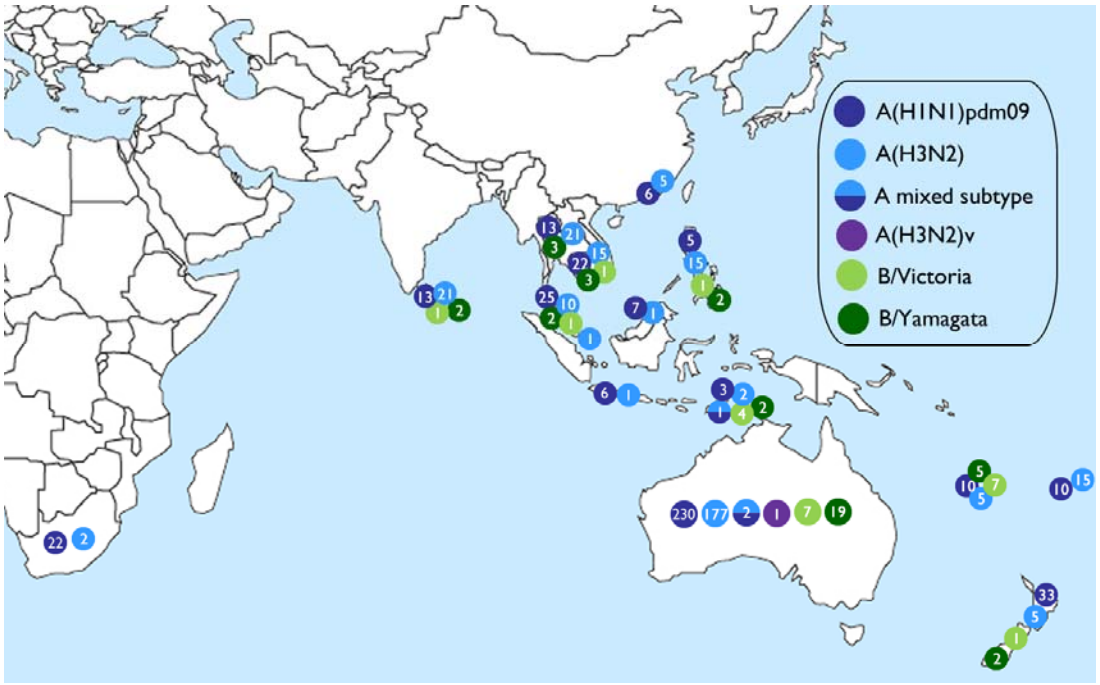


Figure 7. Geographic spread of submitting laboratories and numbers of viruses received at the Centre in 2018 with HA, NA and MP (Influenza A only) genes sequenced using NGS at the Centre.



Sequencing 2018

In 2018, 1225 HA, 1224 NA, 958 MP and 285 NS genes from 1231 human viruses received at the Centre were analysed by Sanger sequencing or NGS (Figure 6). In addition, the HA, NA and MP genes of 705 influenza A and 165 influenza B (HA and NA only, 63 MP genes) viruses were sequenced by NGS techniques (Figures 6 and 7).

Full genome sequencing was performed on 191 viruses, using NGS techniques (Figures 8 and 9). 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. Number of viruses analysed by full genome sequencing 2010-2018 using Sanger sequencing and NGS techniques.

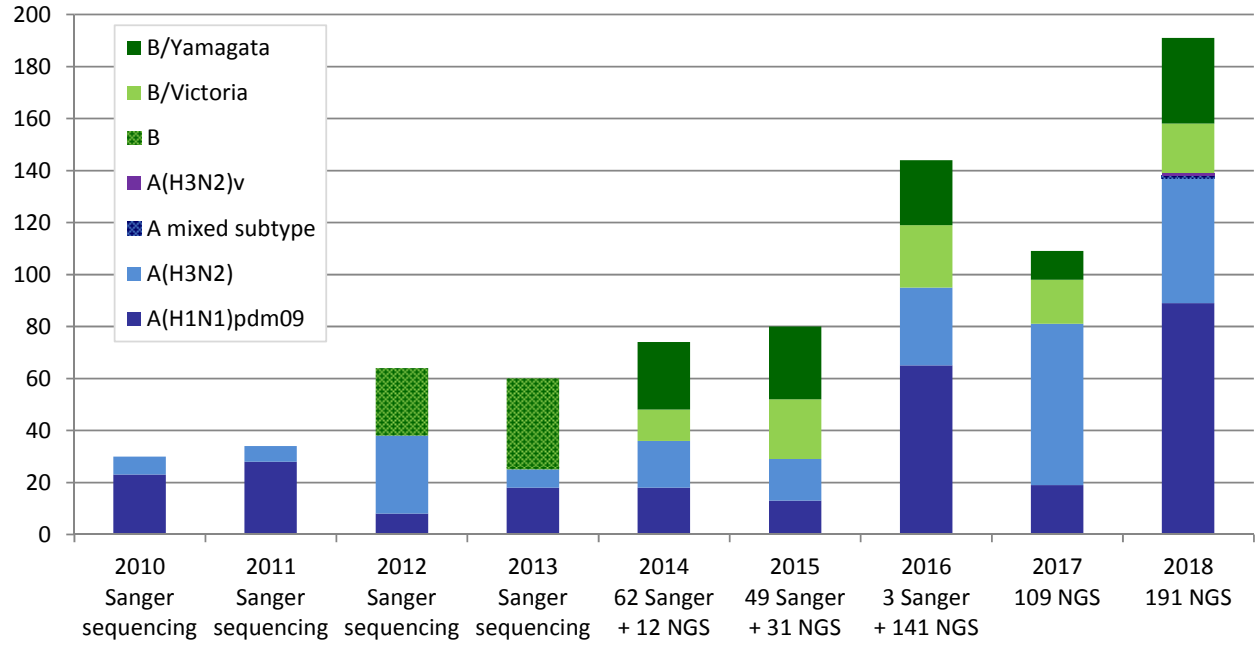
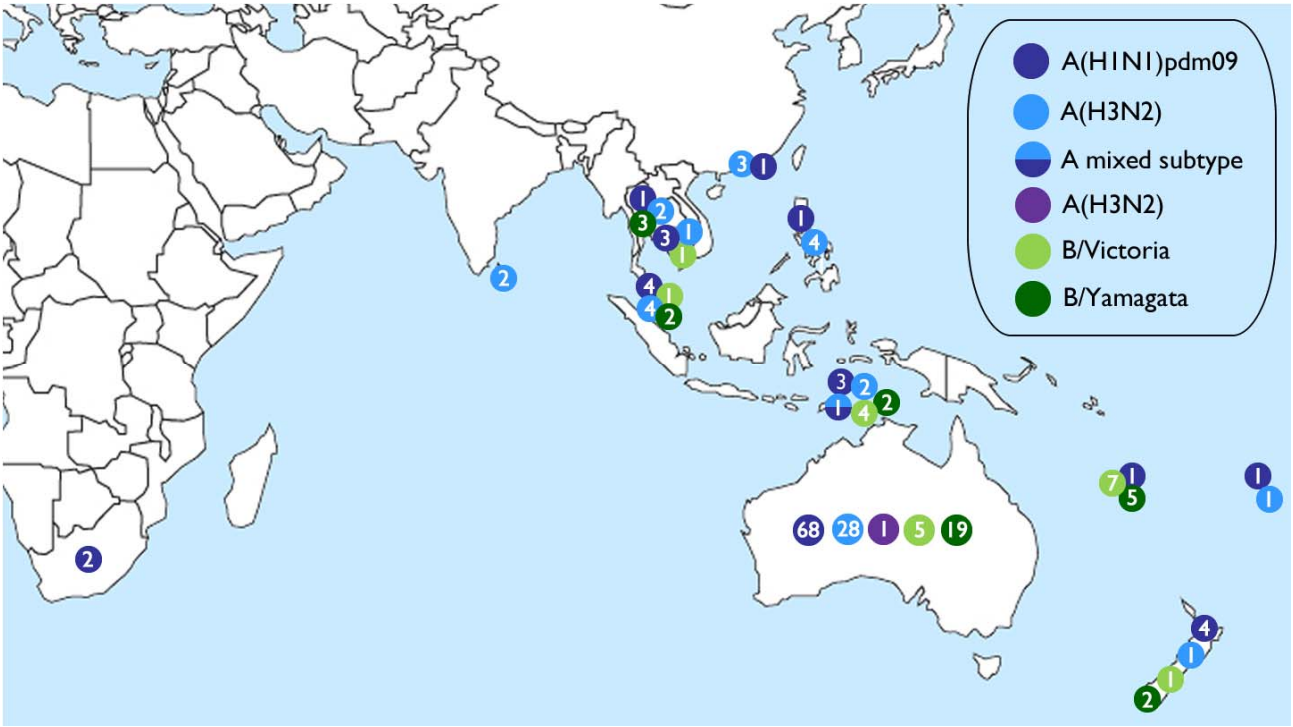


Figure 9. Geographic spread of submitting laboratories and numbers of viruses analysed by full genome sequencing using NGS techniques at the Centre in 2018.



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 2018

A total of 4891 gene sequences from 1524 viruses were deposited with GISAID in 2018 (Table 4). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 124 influenza viruses were also represented in the Centre's submissions (data not shown).

Table 4. Genetic sequences submitted to GISAID by the Centre in 2018.*

Gene / Type/ Subtype/	HA	NA	MP	NS	PB1	PB2	PA	NP	Total
A(H1N1)pdm09	467	463	412	26	26	26	23	26	**1469**
A(H3N2)	760	755	675	74	73	73	74	74	**2558**
B/Victoria	90	90	15	34	15	14	16	15	**289**
B/Yamagata	206	205	18	75	18	18	18	17	**575**
Total	**1523**	**1513**	**1120**	**209**	**132**	**131**	**131**	**132**	**4891**

** Counts include all sequences submitted to GISAID during 2018, which includes viruses received in previous years and viruses sequenced for research purposes.*

Detection and characterisation of an A(H3N2) variant virus from a human patient

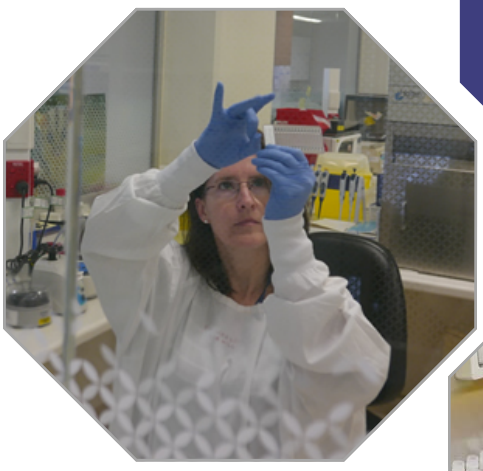
Background

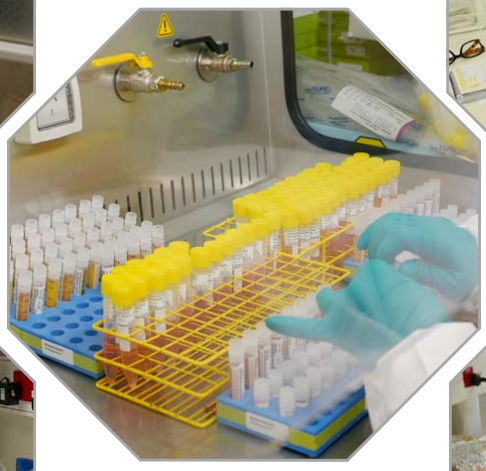
Since 2009, human infections with swine A(H3N2) variant viruses (A(H3N2)v) have been sporadically detected in the U.S.A. These zoonotic viruses usually circulate only in pigs, however occasionally may be transmitted to humans in circumstances of close and prolonged exposure to swine. To date, very limited human-to-human transmission has been detected, with no sustained or community spread of these viruses. Although zoonotic influenza viruses are known to circulate in Australian swine, until 2018 no cases of A(H3N2)v transmission to humans had been detected.

A(H3N2)v variant detected in Australia

In 2018 the Centre recorded the first ever detection of a swine A(H3N2)v virus from a human patient in Australia. This virus, which was from South Australia, was characterised by full genome sequencing using NGS techniques. Phylogenetic analysis revealed that the virus contained a combination of influenza genes that are derived from seasonal A(H3N2) viruses that circulated in humans during 1996-1997 and A(H1N1) pdm09 viruses, but contain adaptions that enable them to circulate in swine. The detection of this virus from a human patient indicates that zoonotic influenzas circulating in Australian swine can infect humans and could potentially pose a pandemic threat if further adaption that would enable circulation in humans occurs. This highlights the importance for vigilant surveillance in swine farms and for people who work with swine to reduce influenza infections at the human–swine interface.

Around the laboratories





Surveillance Results by Influenza Subtype or Lineage

Viruses were analysed by comparison with reference viruses recommended by WHO for the 2018 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 1506 A(H1N1)pdm09 isolates were analysed by HI assay in 2018. Almost all of these viruses (99.3%) displayed similar antigenic properties to the cell-grown vaccine reference strain A/Michigan/45/2015 (Figure 10, Table 5).

Haemagglutinin gene sequencing

Sequencing was performed on a total of 521 HA genes. Phylogenetic analysis showed that the majority of circulating A(H1N1)pdm09 viruses sent to the Centre during 2017 were in subclade 6B.1 and genetically similar to the vaccine strain A/Michigan/45/2015 (Figure 11).

Table 5. Antigenic characterisation of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/Michigan/45/2015 reference virus.

A(H1N1)pdm09 reference strain: A/Michigan/45/2015		
Region	**Like**	**Low reactor (%)**
Africa	36	1 (2.7 %)
Australasia	1070	6 (0.6 %)
East Asia	23	0
South Asia	15	0
South East Asia	307	3 (1.0 %)
Pacific	45	0
TOTAL	**1496**	**10 (0.7 %)**

Figure 10. 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.

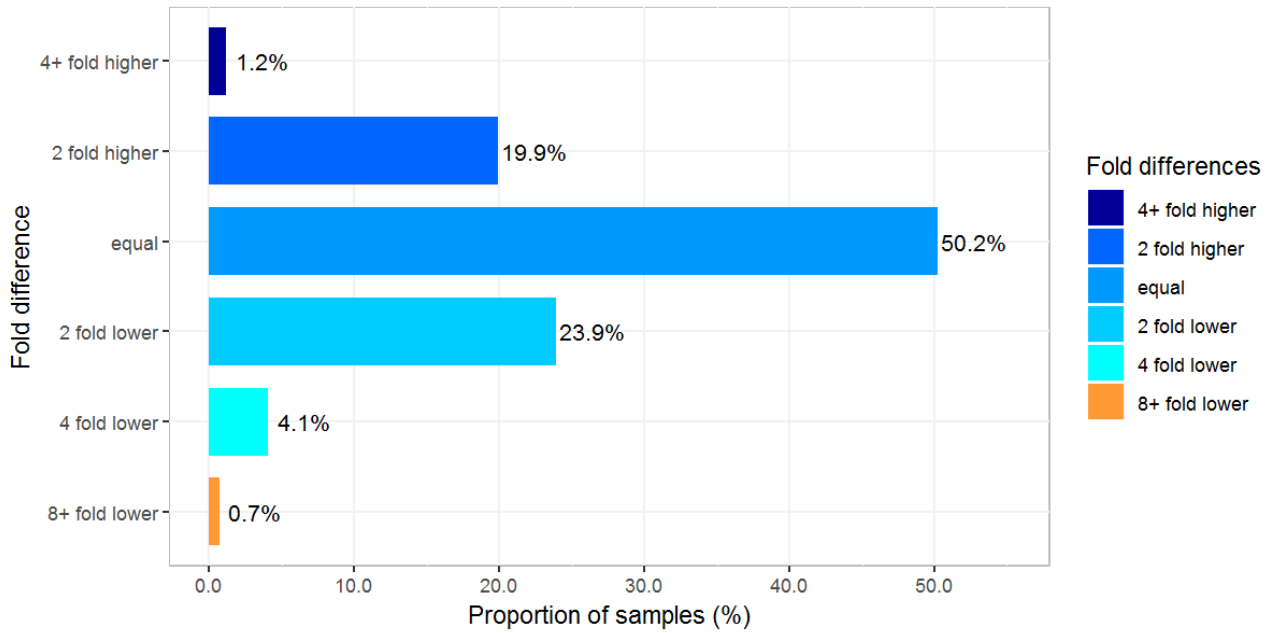
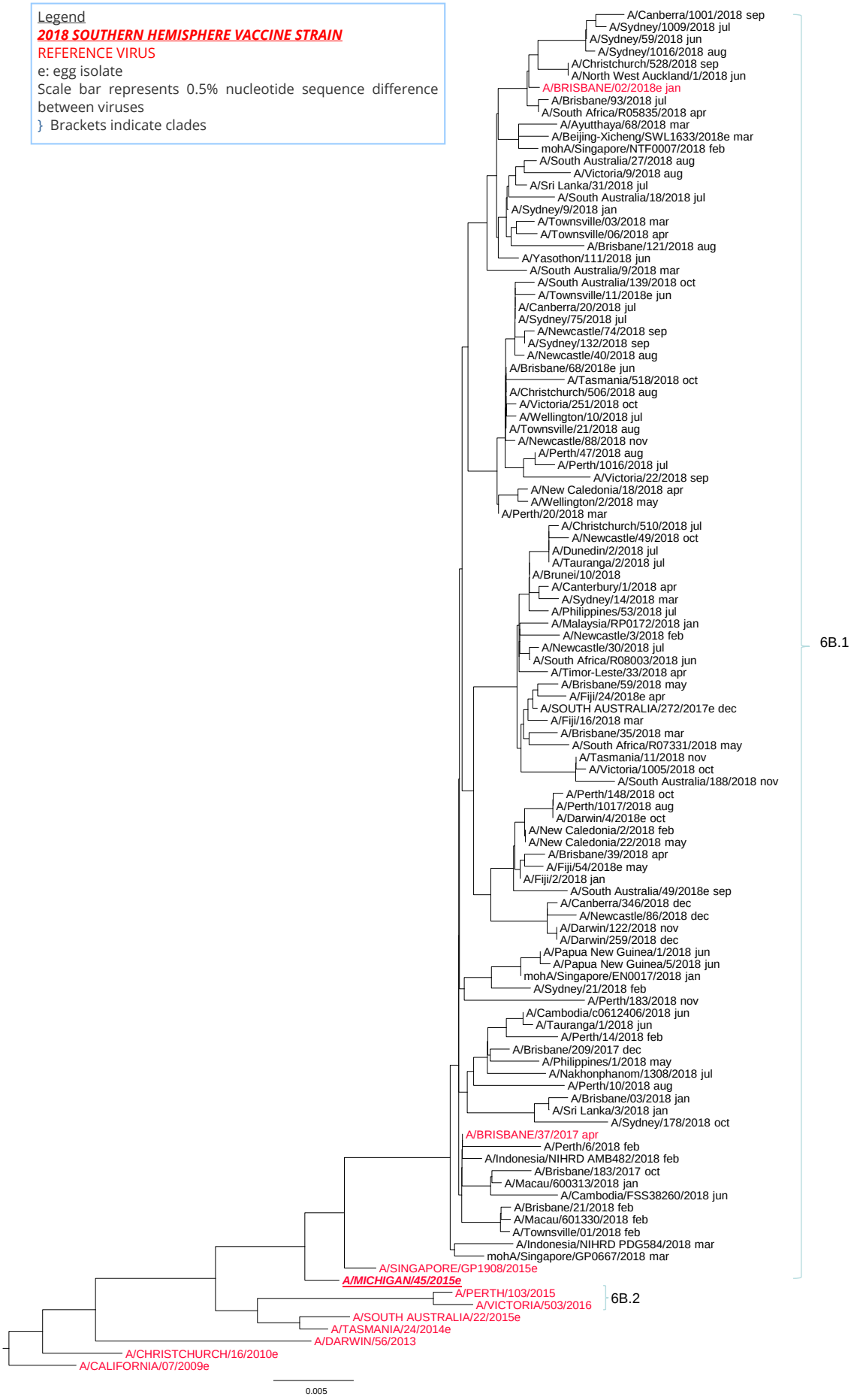


Figure 11. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2018.



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 the FRA are required to test the antigenic characteristics of these viruses. During 2018 FRAs were performed on a regular basis and continue to be integrated into the Centre's routine surveillance activities.

Of 503 A(H3N2) subtype isolates analysed by HI assay compared to the cell-propagated reference strain A/Singapore/INFIMH-16-0019/2016 (Figure 12, Table 6), the majority were antigenically similar to the reference virus when using ferret antisera generated to cell grown A(H3N2) viruses. However, a larger portion (27.5%) of viruses were low reactors when compared to A/Singapore/INFIMH-16-0019/2016 virus grown in eggs (data not shown).

A total of 65 A(H3N2) viruses that could not be analysed by HI assay were analysed by FRA. Of these viruses, 9.2% werelow reactors to cell-grown A/Singapore/INFIMH-16-0019/2016 (Figure 13).

Haemagglutinin gene sequencing

A total of 410 HA genes from A(H3N2) viruses were sequenced. Phylogenetic analysis indicate that most circulating viruses fell into clade 3C.2a1b or subclade 3C.2a2, represented by the new reference strain A/Switzerland/8060/2017, which was recommended by WHO for inclusion in Southern Hemisphere vaccine in 2018 (Figure 14).

Table 6. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the cell-grown A/Singapore/INFIMH-16-0019/2016 reference virus.

A(H3N2) reference strain: A/Singapore/INFIMH-16-0019/2016		
Region	**Like**	**Low reactor (%)**
Australasia	255	6 (2.3 %)
East Asia	7	0
South Asia	24	0
South East Asia	196	2 (1.0 %)
Pacific	10	3 (23.1 %)
TOTAL	**492**	**11 (2.2 %)**

Figure 12. Summary of fold differences in HI titres of A(H3N2) viruses analysed at the Centre compared to the A/Singapore/INFIMH-16-0019/2016 reference virus.

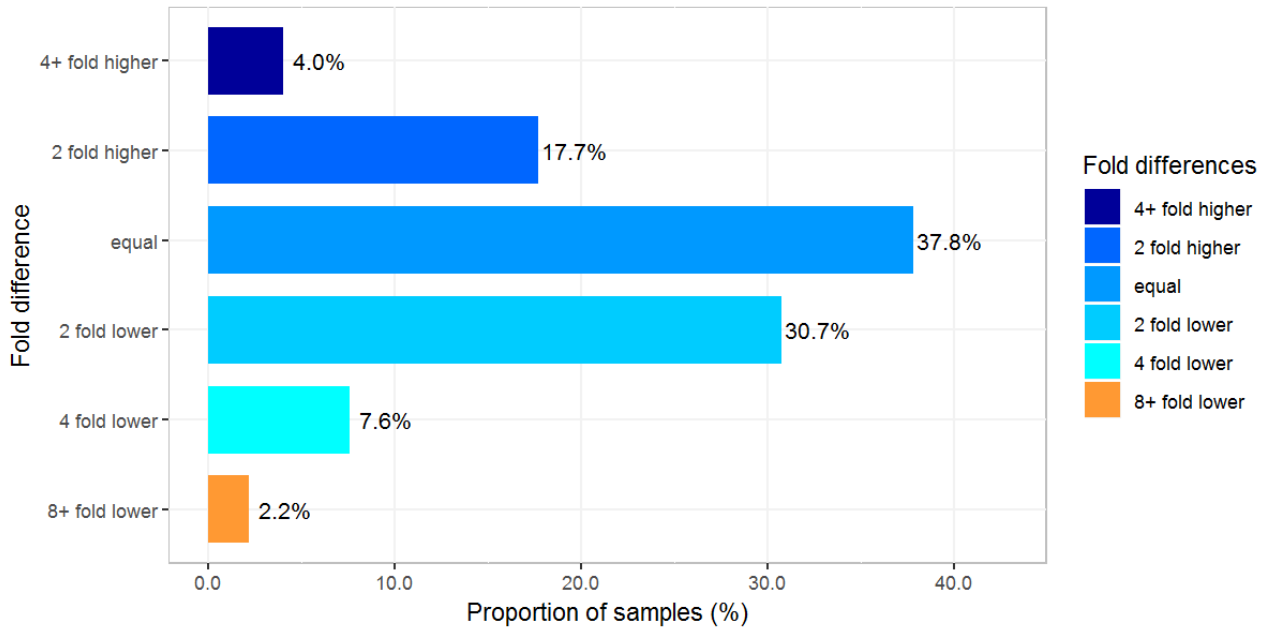


Figure 13. Summary of fold differences in titres of A(H3N2) viruses analysed at the Centre by FRA assay compared to the A/Singapore/INFIMH-16-0019/2016 reference virus.

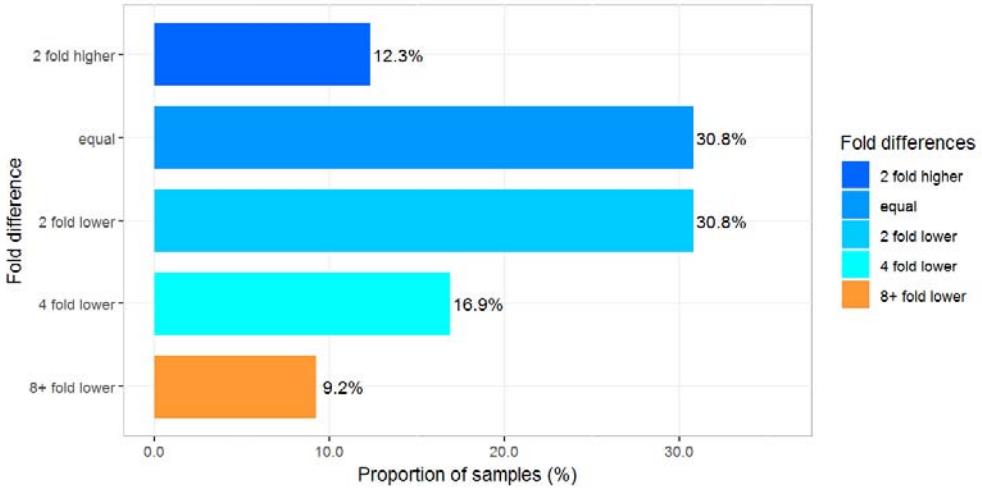


Figure 14. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2018.

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 2016 vaccine strain B/Brisbane/60/2008) and the B/Yamagata/16/88 lineage (represented by the southern hemisphere 2015 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 2018 the Centre received many more B/Yamagata lineage viruses compared to B/Victoria lineage viruses.

Antigenic Analysis

A total of 112 B/Victoria viruses were analysed by HI assay. While the majority of viruses that were compared to B/Brisbane/60/2008 were antigenically similar to the cell-grown reference virus, a growing proportion of circulating viruses were low reactors (Table 7, Figure 15). This was consistent with data from other Collaborating Centre, leading to a change to B/Colorado/6/2017 in the recommended strain for the B./Victoria component of the southern hemisphere vaccine in 2018.

Haemagglutinin gene sequencing

Phylogenetic analysis of 87 genes from B/Victoria lineage viruses showed the growth of the subclade V1A.1. This subclade contains the new recommended vaccine strain B/Colorado/6/2017, which has two amino acid deletions in the HA gene and is genetically distinct from the previous vaccine strain (B/Brisbane/60/2008) (Figure 17).

Table 7. Antigenic characterisation of B Victoria viruses received at the Centre during 2018 compared to the B/Brisbane/60/2008 and B/Colorado/6/2017 reference viruses.

	B/Victoria reference strain: B/Brisbane/60/2008		B/Victoria reference strain: B/Colorado/6/2017*	
Region	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**
Australasia	8	3 (27.3 %)	2	1 (33.3%)
East Asia	1	0 (0 %)	0	0
South Asia	0	2 (100 %)	0	0
South East Asia	39	9 (18.8 %)	17	2 (10.5%)
Pacific	28	0 (0 %)	0	0
TOTAL	**76**	**14 (15.6 %)**	**19**	**3 (13.6%)**

** A small number of B/Victoria viruses were received in 2018 but tested by HI assay against the newly recommended vaccine strain B/Colorado/6/2017 in 2019.*

Figure 15. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to the B/Brisbane/60/2008 reference virus.

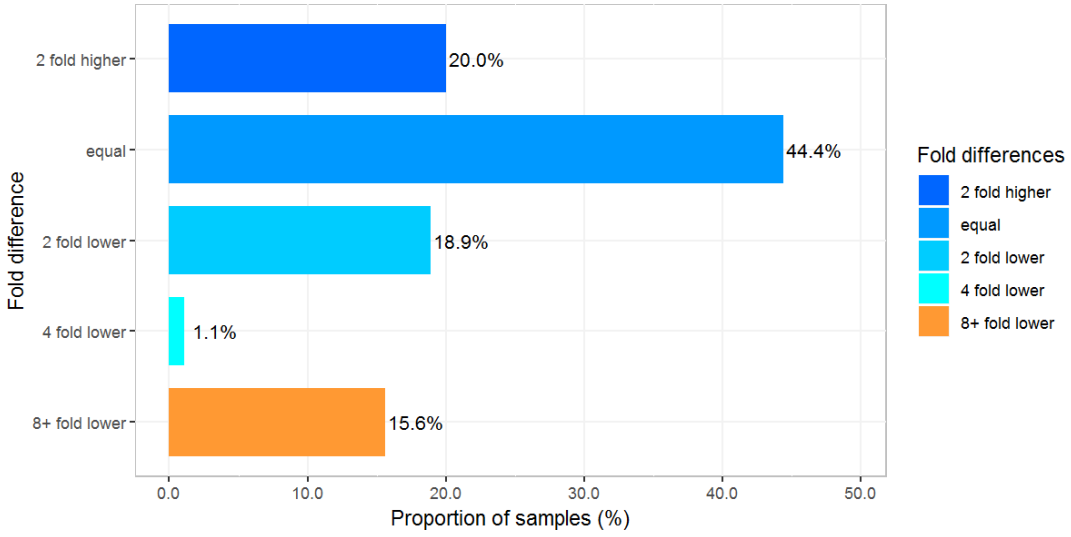


Figure 16. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to the B/Colorado/6/2017 reference virus.

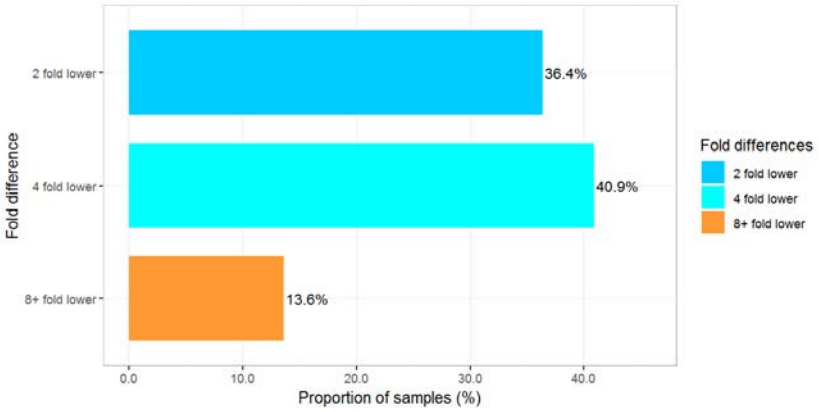


Figure 17. Phylogenetic tree of representative HA genes of B/Victoria viruses received by the Centre during 2018.

Influenza B/Yamagata

Antigenic analysis

A total of 353 B/Yamagata viruses were analysed by HI assay, of which almost all were antigenically similar B/Phuket/3073/2013 virus. Grown in cells (Figure 18, Table 8).

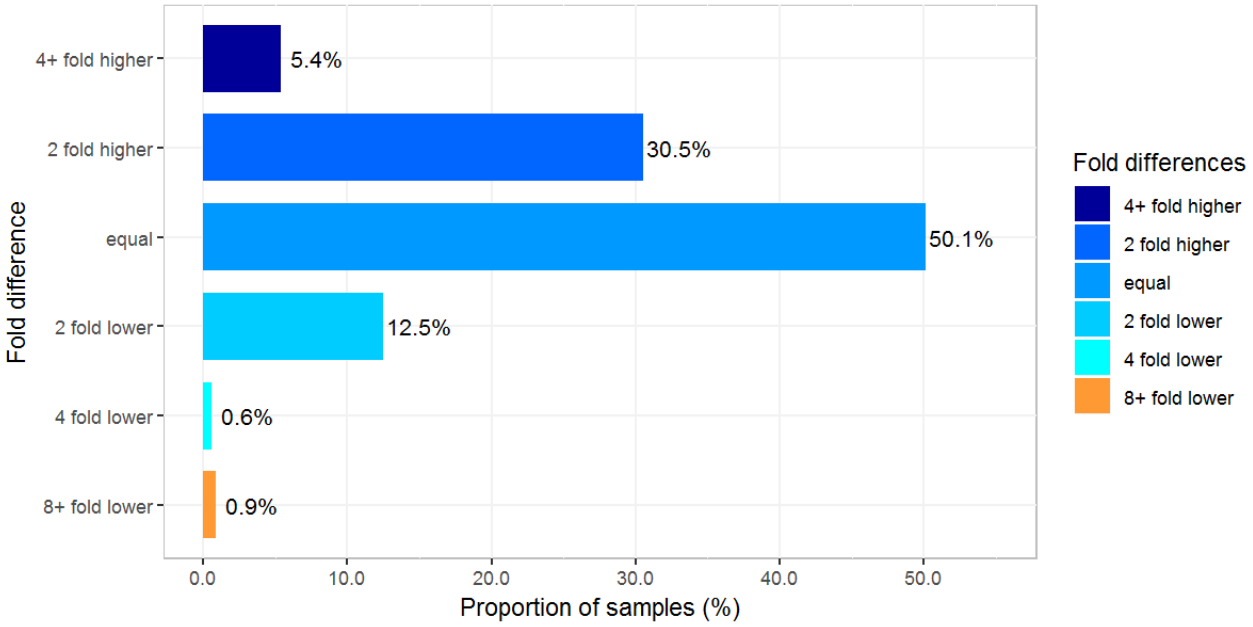
Haemagglutinin gene sequencing

Sequencing was performed on 203 B/Yamagata viruses were sequenced. Phylogenetic analysis showed that almost all of these viruses belonged to the clade represented by B/Phuket/3073/2013 (Figure 19).

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 reference strain: B/Phuket/3073/2013	
Region	**Like**	**Low reactor (%)**
Africa	2	0
Australasia	240	2 (0.8 %)
East Asia	3	0
South Asia	2	0
South East Asia	68	0
Pacific	35	1 (2.8 %)
TOTAL	**350**	**3 (0.9 %)**

Figure 18. Summary of fold differences in HI titres of B/Yamagata viruses analysed at the Centre compared to the B/Phuket/3073/2013 reference virus.



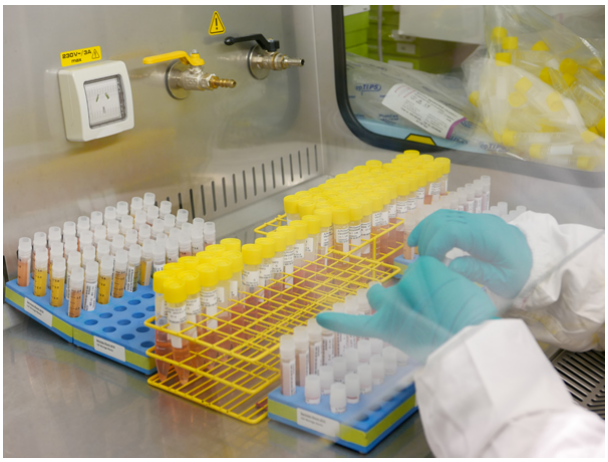
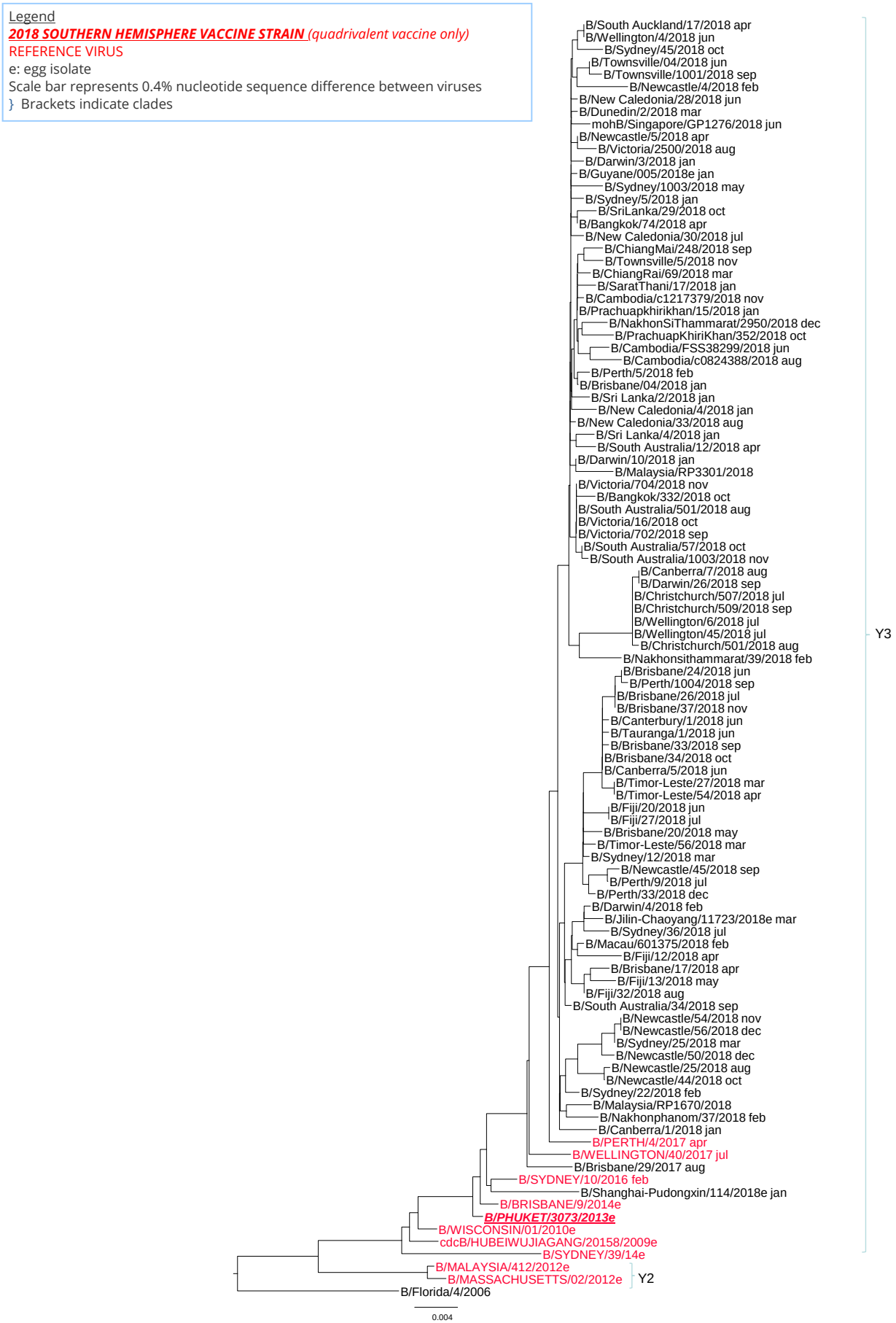


Figure 19. Phylogenetic tree of representative HA genes of B/Yamagata viruses received by the Centre during 2018.



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 2018 and tested by NAI assay, by country.

Type/subtype/ lineage / Country	A(H1N1) pdm09	A (H3N2)	A Mixed type	B/ Victoria	B/ Yamagata	TOTAL
Australasia						
Australia	1028	379	2	15	228	1652
New Zealand	67	7		3	41	118
South Pacific						
Fiji	21	25		0	28	74
New Caledonia	20	5		28	24	77
Papua New Guinea	4					4
South East Asia						
Brunei	7	1				8
Cambodia	40	27		3	15	85
Indonesia	6	4		3		13
Malaysia	179	107	1	25	47	359
Philippines	6	32		1	2	41
Singapore	58	65		23	30	176
Thailand	21	29			27	77
Timor-Leste	5	3	2	32	4	46
East Asia						
Macau SAR	23	12		1	3	39
South Asia						
Sri Lanka	15	25		7	7	54
Africa						
South Africa	37	2			2	41
TOTAL	**1537**	**723**	**5**	**141**	**458**	**2864**

Antiviral resistance analyses 2018

NAI assays were used to analyse 2864 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 7 viruses (3 A(H1N1)pdm09, 2 B/Victoria and 2 B/Yamagata) were found to have 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, for example histidine to tyrosine at position 275 (H275Y) of the neuraminidase protein of A(H1N1)pdm09 viruses, which reduces inhibition by oseltamivir, or the equivalent H273Y mutation in B viruses (Table 11).

Table 10. Neuraminidase inhibitor sensitivity of viruses received by the Centre in 2018.*

Type/Subtype/ Lineage	No. tested	Oseltamivir		Peramivir		Laninamivir		Zanamivir	
		RI	HRI	RI	HRI	RI	HRI	RI	HRI
A(H1N1)pdm09	1537		3 (0.2%)	1 (0.07%)	2 (0.13%)			1 (0.07%)	
A(H3N2)	723	2 (0.28%)		1 (0.14%)		1 (0.14%)		2 (0.28%)	
A mixed subtype	5								
B/Victoria	141	1 (0.71%)	1 (0.71%)		2 (1.42%)		1 (0.71%)		1 (0.71%)
B/Yamagata	458	3 (0.66%)		1 (0.22%)	2 (0.44%)			1 (0.22%)	
TOTAL	**2864**	**6 (0.21%)**	**4 (0.14%)**	**3 (0.1%)**	**6 (0.21%)**	**1 (0.03%)**	**1 (0.03%)**	**4 (0.14%)**	**1 (0.03%)**

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 2017-2018. **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 2018 with highly reduced inhibition by NAIs.

Type/Subtype/ Lineage	Country/city of submitting laboratory	NAI(s) with highly reduced inhibition (marked with *)				Mutation detected
		Oseltamivir	Peramivir	Laninamivir	Zanamivir	
A (H1N1)pdm09	Singapore	*	*			H275Y
	Singapore	*	*			H275Y
	Malaysia	*				H275Y
B/Victoria	Malaysia	*	*	*	*	G140R
	Malaysia		*			T146P
B/Yamagata	Malaysia		*			E117E/G
	Malaysia		*			T146K

Resistance to Adamantanes

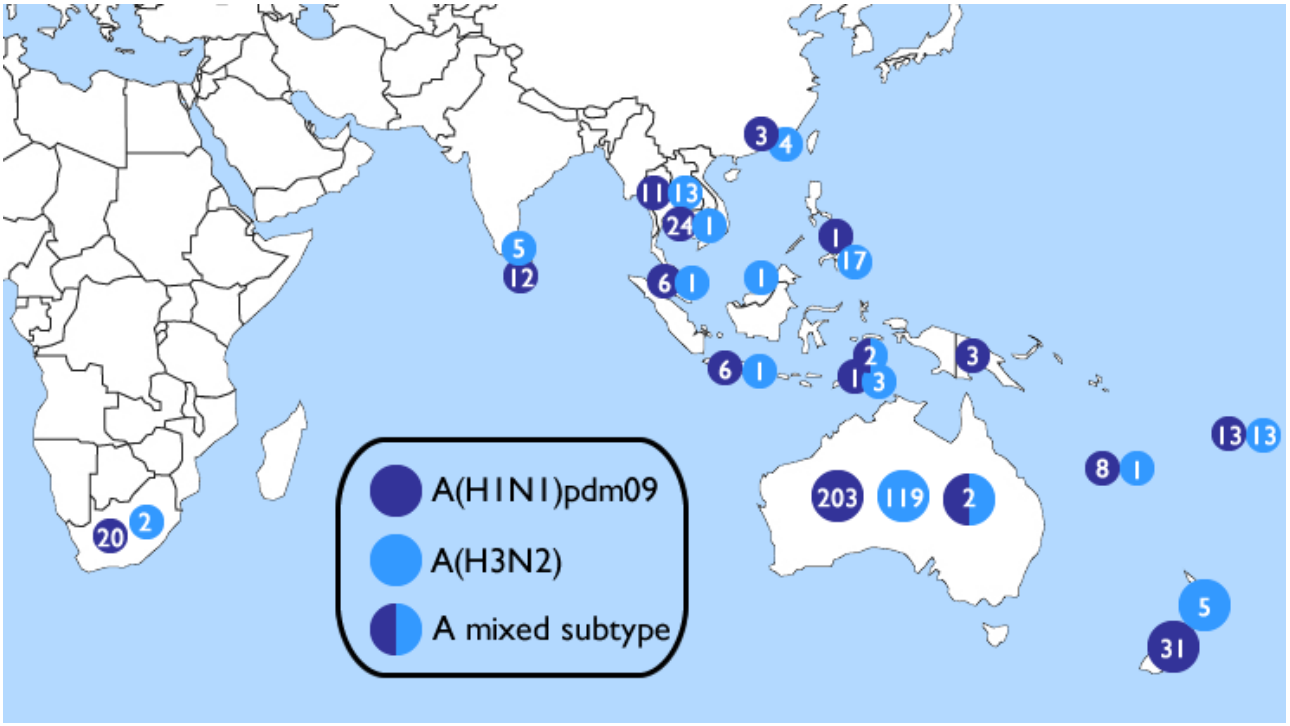
Background

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 2018

Real-time PCR or sequencing was used to analyse 531 influenza A viruses, which were representative of those submitted to the Centre during 2018 (Figure 20). Almost all of the tested influenza A viruses carried the S31N mutation, indicating that they would be resistant to adamantanes. One A(H3N2) virus from Australia contained a S31D mutation in the matrix protein; this virus also remains resistant to adamantanes. One A(H1N1)pdm09 from Australia and three A(H3N2) viruses (one each from Australia, New Zealand and Thailand) contained a serine residue at position 31 in the matrix protein, which would render them susceptible to adamantanes.

Figure 20. Geographic spread of viruses received at the Centre during 2018 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 hen's 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 2018

In 2018, a total of 60 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 69.0% (Tables 12 and 13).

Table 12. Virus isolation in eggs at the Centre in 2018.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	22	20	90.9
A(H3N2)	48	28	58.3
B/Victoria	10	8	80.0
B/Yamagata	7	4	57.1
Total	**87**	**60**	**69.0**

Table 1. Potential candidate vaccine strains isolated in eggs at the Centre in 2018 .

A(H1N1)pdm09	A(H3N2)	
A/South Australia/272/2017	A/Brisbane/185/2017	A/Singapore/GP0077/2018
A/Brisbane/02/2018	A/Brisbane/190/2017	A/Singapore/KK0130/2018
A/Victoria/897/2017	A/Brisbane/192/2017	A/Singapore/GP0454/2018
A/Brisbane/70/2018	A/Christchurch/516/2017	A/South Australia/10/2018
A/Brisbane/72/2018	A/Brisbane/01/2018	A/Singapore/KK0199/2018
A/Townsville/11/2018	A/South Australia/273/2017	A/Singapore/KK0259/2018
A/Brisbane/68/2018	A/South Australia/274/2017	A/Brisbane/43/2018
A/Townsville/08/2018	A/Sri Lanka/93/2017	
A/Fiji/24/2018	A/Kentucky/03/2018	**B/Victoria**
A/Brisbane/59/2018	A/Kentucky/1/2018	B/Sri Lanka/17/2017
A/SouthAfrica/R07338/18	A/Maine/2/2018	B/Singapore/EN0958/2017
A/Fiji/54/2018	A/Nebraska/01/2018	B/Sri Lanka/14/2017
A/Newcastle/45/2018	A/Rhode Island/02/2018	B/Sri Lanka/14/2018
A/South Australia/27/2018	A/Rhode Island/01/2018	B/Singapore/KK0234/2018
A/Christchruch/506/2018	A/Wisconsin/04/2018	B/Singapore/KK0248/2018
A/Christchurch/515/2018	A/Brisbane/34/2018	B/Singapore/KK0686/2018
A/South Australia/49/2018	A/Brisbane/28/2018	B/Singapore/KK0148/2018
A/Darwin/6/2018	A/Brisbane/40/2018	
A/Darwin/4/2018	A/Brisbane/36/2018	**B/Yamagata**
A/Tasmania/505/2018	A/Brisbane/32/2018	B/New Caledonia/25/2017
	A/Sydney/22/2018	B/Sri Lanka/15/2017
		B/Christchurch/500/2018
		B/South Australia/25/2018

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 2018, 47 candidate vaccine viruses that had been received from other WHO Collaborating Centres and laboratories were passaged in eggs at the Centre (Table 14).

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 14. Potential candidate vaccine viruses from other WHO Collaborating Centres isolated at the Centre during 2018.

A(H1N1)pdm09	B/Victoria
A/Tokyo/EH1608/2017	NYMC BX-65A (B/Florida/78/2015)
A/Beijing-Dongcheng/SWL331/2017	B/Zhejiang-Wuxin/113/2018
A/Michigan/272/2017	B/Hebei-Cixian/149/2018
IVR-180 (A/Singapore/GP1908/2015)	**B/Yamagata**
A/Switzerland/3330/2017	BVR-1B (B/Phuket/3073/2013)
A/Slovenia/2794/2017	B/Beijing-Chaoyang/12977/2017
A/Switzerland/2656/2017	B/Shanghai-Pudongxin/114/2018
A/Hunan-Wuling/SWL1468/2018	B/Jilin-Chaoyang/11723/2018
A/Beijing-Xicheng/SWL1633/2018	B/Guyane/005/2018
A(H3N2)	**A(H5N1)**
A/Kanagawa/ZC1617/2017	A/Anhui1/2005(H5N1)-PR8-IBCDC-RG6
A/Wisconsin/19/2017	A/India/NIV/2006(H5N1)-PR8-IBCDC-RG7
NYMC X-301 (A/Washington/16/2017)	A/Egypt/321/2007(H5N1)-PR8-IDCDC-RG11
NYMC X-301A (A/Washington/16/2017)	A/Egypt/3300-NAMRU3/2008(H5N1)-PR8-IDCDC-RG13
NYMC X-307 (A/Singapore/INFIMH-16-0019/2016)	A/Cambodia/X0810301/2013/(H5N1)-PR8-IDCDC-RG34B
NYMC X-307A (A/Singapore/INFIMH-16-0019/2016)	A/CK/Bangladesh/11RS1984-30/2011(H5N1)PR8IDCDCRG36
IVR-186 (A/Singapore/INFIMH-16-0019/2016)	IDCDC-RG12(A/Chicken/Vietnam/NCVD-016/2008)
A/Bretagne/1565/2017	
A/Switzerland/8060/2017	**A(H5N6)**
NYMC X-311 (A/Brisbane/1/2018)	A/Hubei/29578/2016 (CNIC RG)
A/Kansas/14/2017	
A/Kanagawa/IC1618/2017	**A(H7N9)**
NIB-112 (A/Switzerland/8060/2017)	A/Anhui/1/2013/(H7N9)-PR8-IDCDC-RG33A
A/Kanagawa/AC1709/2017	A/Shanghai/2/2013/(H7N9)-PR8-IDCDC-RG32A
A/Kanagawa/AC1740/2018	A/Shanghai/2/2013(H7N9)-PR8-IDCDC-RG32A.3
A/Kanagawa/IC1718/2018	NIBRG-375 (A/Guangdong/17SF003/2016)
A/Kanagawa/IC1745/2018	(CBER-RG7C) A/Guangdong/17SF003/2016

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 15). Serum panels from children, younger adults (20-64 years old) and older adults (≥ 65 years old) are assessed.

Serum panel analyses in February 2018

In February the Centre analysed serum panels from recipients of seasonal quadrivalent influenza vaccines in Australia, USA and Europe, as well as serum panels from vaccinated subjects in China (trivalent influenza vaccine).

The combined data from all WHO Collaborating Centres and ERLs showed that for the majority of panels tested, geometric mean HI titres (GMT) of anti-HA antibodies against recent A(H1N1)pdm09 viruses were somewhat reduced compared to GMTs against the cell-grown vaccine strain A/Michigan/45/2015, but these reductions were greater when measured against egg-propagated vaccine virus.

GMTs of antibodies against representative recent A(H3N2) lineage viruses were significantly reduced compared to A/Hong Kong/4801/2014 vaccine virus grown in eggs, but not compared to cell culture-propagated vaccine virus. These findings were similar to geometric mean titres determined using microneutralisation assays (GMNT).

Serum panel analyses of influenza B viruses showed that GMT of antibodies against some representative recent B/Victoria/2/87 lineage viruses were reduced compared to vaccine virus B/Brisbane/60/2008 grown in both eggs and cell culture, but reductions were not as great when compared to vaccine virus grown in cells. Antibodies induced by B/Brisbane/60/2008 vaccine viruses in very young children had reduced titres against B/Victoria/2/87–lineage viruses containing two– and three-amino acid deletions in the HA protein.

GMTs against representative recent B/Yamagata/16/88 lineage viruses were similar to HI titres to the B/Phuket/3073/2013 vaccine virus grown in cells.

Serum panel analyses in September 2018

In September, the Centre analysed serum panels from recipients of seasonal quadrivalent or trivalent (≥ 65years old in Australia) influenza vaccines Australia and USA .

The combined data from all ERLs and WHO Collaborating Centres showed that GMTs of antibodies against some representative recent cell culture-propagated A(H1N1)pdm09 viruses were significantly reduced compared to the A/Michigan/45/2015 vaccine virus grown in eggs and cells, however the GMTs of the majority of viruses tested were not significantly reduced.

GMTs of antibodies against representative recent A(H3N2) lineage viruses grown in cell culture or eggs were significantly reduced compared to titres against the egg-propagated vaccine virus A/Singapore/INFIMH-16-0019/2016. However, cell culture-propagated viruses did not show significant reductions in GMTs compared to A/Singapore/INFIMH-16-0019/2016 grown in cells. In virus neutralisation tests, all A(H3N2) viruses grown in cell culture showed significant reductions in GMT compared to titres against egg-propagated A/Singapore/INFIMH-16-0019/2016. Some of these viruses also showed significant reductions in GMTs compared to cell culture-propagated A/Singapore/INFIMH-16-0019/2016 grown in cell culture.

Comparison of GMTs of antibodies against some representative recent B/Victoria/2/87 lineage viruses showed moderate reductions in post-vaccination HI GMTs against representative recent B/Victoria/2/87- lineage viruses containing two– or three-amino acid deletions in the HA protein compared to B/Brisbane/60/2008-like vaccine reference viruses grown in eggs or cells.

GMTs of antibodies against most representative recent B/Yamagata/16/88-lineage viruses were similar to or somewhat reduced compared to titres against the cell-grown B/Phuket/3073/2013-like reference viruses.

Table 15. Representative and vaccine candidate strains used for serological analyses during 2018. All viruses are egg grown unless indicated otherwise.

FEBRUARY	SEPTEMBER
A(H1N1)pdm09	**A(H1N1)pdm09**
A/Michigan/45/2015 [E, C]	A/South Africa/R07331/2018 [C[]
A/Michigan/272/2017 [E,C]	A/Michigan/45/2015 [E, C]
A/Sydney/709/2017 [C]	A/South Africa/VW0454/2018 [C]
	A/Hunan-Wuling/SWL1468/2018 [E,C]
	A/Victoria/897/2017 [E,C]
	A/Brisbane/78/2018 [C]
A(H3N2)	**A(H3N2)**
A/Hong Kong/4801/2014 [E]	A/Hong Kong/4801/2014 [E]
A/Michigan/15/2014 [C]	A/Brisbane/192/2017 [E]
A/Singapore/INFIMH-16-0019/2016 [E]	A/Singapore/INFIMH-16-0019/2016 [E,C]
A/Victoria/653/2017 [E]	A/Brisbane/28/2018 [E,C]
A/Wisconsin/19/2017 [E]	A/South Australia/10/2018 [C]
	A/Brisbane/60/2018 [C]
B/Victoria	**B/Victoria**
B/Phuket/3073/2013 [E]	B/Phuket/3073/2013 [E]
B/Victoria/570/2017 [E, C]	B/Saitama/51/2018 [C]
B/Sydney/5/2016 [C]	B/Jilin-Chaoyang/11723/2018 [E]
	B/Victoria/541/2017 [E,C]
B/Yamagata	**B/Yamagata**
B/Brisbane/60/2008 [E]	B/Brisbane/60/2008 [E]
B/Colorado/6/2017 [E, C]	B/Colorado/6/2017 [E]
B/Chongqing-Banan/1840/2017 [C]	B/Hong Kong/269/2017 [E]
B/Townsville/7/2016 [C]	B/Darwin/109/2017 [E, C]
	B/Hubei-Maojian/1219/2018 [C]
	B/Wellington/1/2018 [C]

**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).

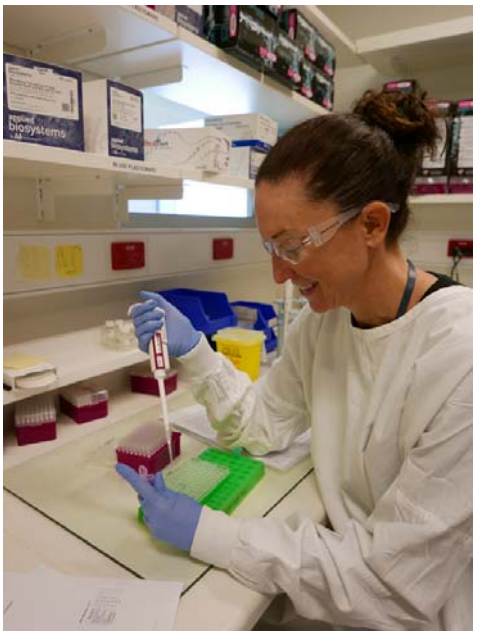
The Centre Director and Deputy Director participate in preparatory teleconferences and then meet at the face-to-face Consultation with WHO, representatives from the other WHO Collaborating Centres and the four Essential Regulatory Laboratories (Center for Biologics Evaluation and Research, US Food and 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 2018 WHO made the recommendations reported below.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2018–2019, Geneva, Switzerland, 19 - 21 February 2018

It is recommended that vaccines for use in the 2018–2019 influenza season (northern hemisphere winter) contain the following:

- an A/Michigan/45/2015 (H1N1)-like virus;
- an A/Hong Kong/4801/2014 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013* -like virus (B/Yamagata/16/88 lineage).

It is recommended that the influenza B virus component of trivalent vaccines for use in the 2018-2019 northern hemisphere influenza season be a B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage.



WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2018, Atlanta GA, USA, 24–26 September 2018

It is recommended that vaccines for use in the 2019 influenza season (southern hemisphere winter) contain the following:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Switzerland/8060/2017 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013* -like virus (B/Yamagata/16/88 lineage).

It is recommended that egg based trivalent vaccines for use in the 2019 southern hemisphere influenza season contain the following:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Switzerland/8060/2017 (H3N2)-like virus; and
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage).

It is recommended that the A(H3N2) component of non-egg based vaccines for use in the 2019 southern hemisphere influenza season be an A/Singapore/INFIMH-16-0019/2016*-like virus together with the other vaccine components as indicated above.

[*] *Viruses originally isolated 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 2018 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/Singapore/GP1908/2015 (Feb, Sept)	A/Singapore/TT1384/2016 (Sept)
A(H3N2)	A/Brisbane/1/2018 (Sept) A/Brisbane/192/2017 (Sept)	A/Canberra/7/2016 (Feb, Sept)
B/Yamagata	B/Brisbane/9/2014 (Feb, Sept) B/Phuket/3073/2013 (Sept)	B/Singapore/INFKK-16-0569/2016 (Feb, Sept) B/Singapore/INFKK-16-0610/2016 (Feb, Sept) B/Brisbane/9/2014 (Feb, Sept)

Photo courtesy of Centers for Disease Control and Prevention

Australian Seasonal Influenza Vaccine Recommendation

Whereas 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 AIVC.

The AIVC met on 10 October 2018 and recommended that the following viruses be used for influenza vaccines in the 2019 southern hemisphere influenza season:

Egg based quadrivalent vaccines:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Switzerland/8060/2017 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

Egg based trivalent vaccines:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Switzerland/8060/2017 (H3N2)-like virus; and
- a B/Phuket/3073/2013-like (B/Yamagata/16/88 lineage)

Non-egg based vaccines:
A(H3N2) component: A/Singapore/INFMH-16-0019/2016 (H3N2)-like virus other components the same as above indicated for egg based vaccines

Notably, the recommendation for the Australian trivalent vaccine as recommended by AIVC for 2019 included a B/Yamagata lineage virus, rather than the B/Victoria lineage virus recommended by WHO. This is because in Australia, the vast majority of circulating influenza B viruses during 2018 were of the B/Yamagata lineage, while few B/Victoria lineage viruses were detected.

Preparation and Distribution of Diagnostic Reagents

Reagents for Antigenic Typing of Influenza Viruses

Each year the Centre prepares and distributes kits to regional and reference laboratories to enable influenza preliminary analysis and characterisation of influenza specimens prior to submission of samples to the Centre. The kits contain polyclonal sera and viral antigens for reference influenza strains. During 2018, 39 kits were sent to 19 laboratories in 13 countries. Each kit contained 10 mL each of the reference antigens A/Michigan/45/2015, A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like, B/Brisbane/60/2008 and B/Phuket/3073/2013 and homologous antisera.

Recipients of the 2018 Kit

AUSTRALIA: Queensland Health Scientific Services, Brisbane, Queensland; Vaxxas, Brisbane, Queensland; Flinders Medical Centre, Adelaide; Westmead Hospital, Sydney, New South Wales; University of New South Wales, Sydney

CAMBODIA: Institut Pasteur, Phnom Penh

HONG KONG SAR: University of Hong Kong

INDIA: University of Delhi, Delhi

KENYA: Center for Virus Research, Kenya Medical Research Institute, Nairobi

MACAU SAR: Public Health Laboratory

MALAYSIA: Institute for Medical Research, Kuala Lumpur;

NEW ZEALAND: Canterbury Health Laboratories, Christchurch; Institute of Environmental Science and Research, Wellington, New Zealand

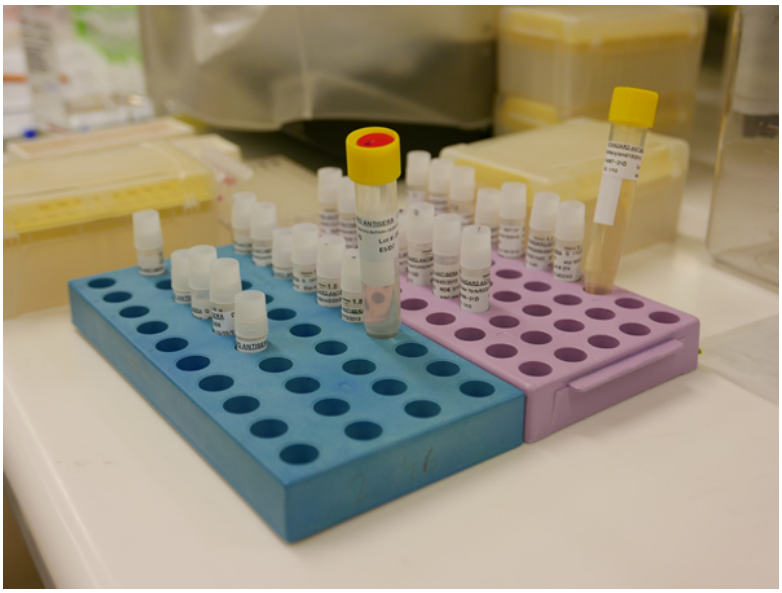
PHILIPPINES: Research Institute for Tropical Medicine, Mutinlupa City

SINGAPORE: Singapore General Hospital; Duke-NUS Graduate Medical School

SOUTH AFRICA: National Institute for Communicable Diseases, Johannesburg

TAIWAN: Taiwan Center for Disease Control, Taipei

THAILAND: National Institute of Health, Bangkok



Training

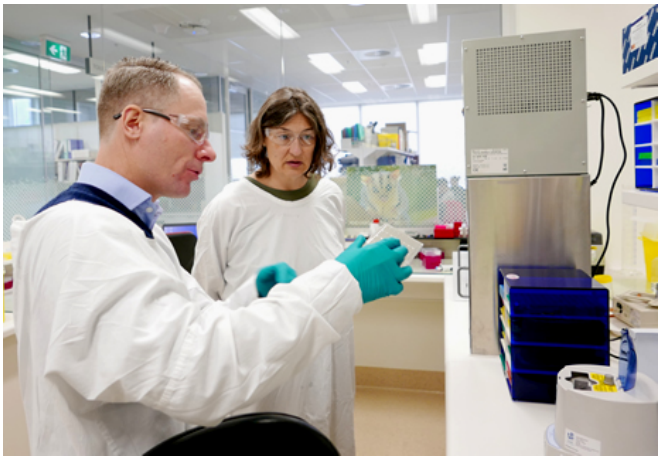
Training and Support of National Influenza Centres

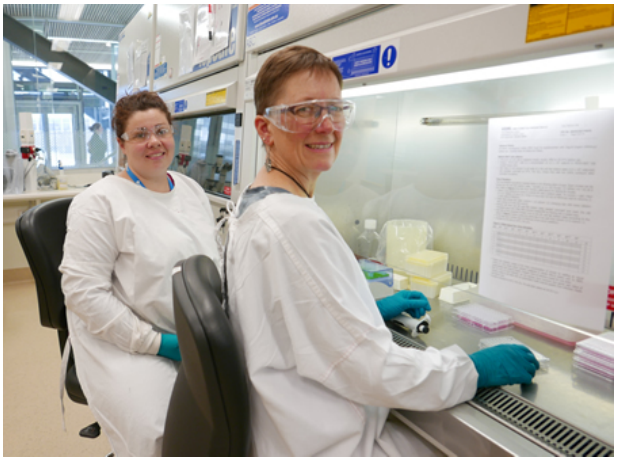
The Centre provides support in the form of training and advice to WHO National Influenza Centres (NICs) and other diagnostic laboratories, especially in the Asia-Pacific region. Strengthening technical capabilities and infrastructure for surveillance work in regional laboratories increases their capacity 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.

In-house Training

Dr Anja Werno (*below, at right)*, from Canterbury Health Services, Christchurch, New Zealand, visited the Centre on 6–10 August. During her visit she learned techniques in genetic analysis, HI assays, FRAs and data analysis.

Mrs Jacqui Ralston (*below, at right)*, from the Institute of Environmental Science and Research, Wellington, New Zealand, visited the Centre on 3–15 September to undertake training in FRAs.





Mr Songha Tok and Ms Sonita Kol, from Institute Pasteur, Phnom Penh, Cambodia, and Ms Sovandara Om (*at right)*, from the National Institute of Public Health, Phnom Penh, Cambodia, visited the Centre on 22 October – 2 November. Ms Kol and Ms Om undertook training in surveillance techniques for influenza detection and characterisation, while Mr Tok was trained in specialised serology techniques.

L to R: Mr Songha Tok, Ms Sonita Kol and Ms Sovandara Om.

Training Programs and Visits to Regional Laboratories

Naomi Komadina led a workshop on GISAID Bioinformatics Training at the WHO South-East Asia and Western Pacific Region National Influenza Centre Meeting on 13 July in Nepal, Kathmandu (*below*).

Patrick Reading visited the Sri Lankan National Influenza Centre at the Medical Research Centre in Colombo, Sri Lanka, on 25 August – 9 September (*below*). He trained staff in cell culture and virus isolation techniques

Photo courtesy of Jude Jayamaha, Medical Research Centre

Patrick Reading was an influenza specialist at the Workshop to Strengthen Influenza-like Illness (ILI) & Severe Acute Respiratory Infections (SARI) Surveillance, held in Suva, Fiji, on 6–10 August (*below*). The meeting was attended by laboratory representatives from the Cook Islands, Fiji, French Polynesia, Kiribati, New Caledonia, Niue, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna and Guam. Prof Reading participated as a discussion panel member, facilitated table-top exercises, led a one-day practical component and presented five lectures.

Photo courtesy of the Secretariat of the Pacific Community

Patrick Reading was an influenza specialist at the Workshop to Strengthen Influenza-like Illness & Severe Acute Respiratory Infections (SARI) Surveillance in the Solomon Islands on 2–4 October. The workshop was attended by over 30 doctors, nurses and surveillance representatives from different provinces of the Solomon Islands. Prof Reading was a discussion panel member and presented three lectures.

Research

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

Epidemiology

Centre staff and students

Sheena Sullivan, Vivian Leung, Olivia Price, Ximena Tolosa, Angelyna Lee

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, including the Australian Sentinel Practices Research Network (ASPREN; Nigel Stocks, Monique Chilver), the Victorian General Practice Sentinel Surveillance (VicSPIN; James Fielding) network, and the Influenza Complications Alert Network (FluCAN; Allen Cheng) to estimate influenza vaccine effectiveness in the community. Ongoing work with the University of Hong Kong (Ben Cowling) and University of Melbourne (David Price) examines bias in vaccine effectiveness studies to improve the utility of these estimates for influenza vaccine strain selection. The group also contributed to various Department of Health contracts, including quantification of the influenza burden in Australia, and pandemic vaccine prioritization and supply.

Collaborators

Nigel Stocks, Monique Chilver (University of Adelaide, Adelaide SA); James Fielding, Kylie Carville and Kristina Grant (VIDRL); Ben Cowling and Jessica Wong (University of Hong Kong, Hong Kong SAR); Hannah Moore and Tom Snelling (Telethon Kids Institute, Perth WA); George Milne and Joel Kelso (University of Western Australia, Perth WA); Annette Regan (Curtin University, Perth WA); David Price (The University of Melbourne, VIDRL); Adam Kucharski (London School of Hygiene and Tropical Medicine, London, UK).

Highlights and developments 2018

We continued to work with VicSPIN and ASPREN to estimate influenza vaccine effectiveness for the WHO Vaccine Consultation Meetings. In addition, Ms Price worked with VicSPIN and VIDRL to conduct a time series analysis of respiratory virus data to search for patterns in seasonality of influenza and other respiratory viruses.

For the Australian Government Department of Health, we worked on a project combining influenza disease burden estimates with mathematical modelling to inform vaccination policy. This was a collaborative effort with colleagues at the Telethon Kids Institute, the University of Western Australia and the University of Hong Kong. The epidemiology team lead Phase I of this project, to estimate the burden of influenza in Australia. The results were used to inform a dynamic transmission model to test various vaccination scenarios in the Australian context. The study will provide valuable additional information to support these policies.

The pandemic influenza preparedness framework includes a goal to calculate a global burden estimate. To that end, the group also worked with WPRO to provide assistance to Cambodia, Laos, Mongolia and Vietnam in the estimation of their influenza burden using sentinel surveillance data. Some of this work was completed by the Centre's first Master of Applied Epidemiology scholar, Dr Ximena Tolosa, who subsequently published influenza burden estimates from Cambodia.

The group also participated in several serological studies. One is an APPRISE-funded project to establish routine serosurveillance in Australia and is being led by PathWest Laboratory Medicine (Perth, WA) and VIDRL. The second is also APPRISE-funded and is concerned with conducting surveillance among people who work at the human-animal interface, coordinated by Dr Tolosa. Additional serological and mathematical/ statistical work was also conducted on a healthcare worker cohort study conducted in 2016 to better understand antibody responses to vaccination, particularly repeat vaccination. This latter topic was the focus of several applications for funding, which may see fruition in 2019.

Antivirals and Viral Fitness

Centre staff and students

Aeron Hurt, Danielle Tilmanis, Edin Mifsud, Sook Kwan Leah Brown, Leo Lee, Merryn Roe, Rubaiyea Farrukee, 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 commenced in 2018 to investigate whether the PA endonuclease inhibitor baloxavir is able to reduce the rate of transmission using the ferret model of infection.

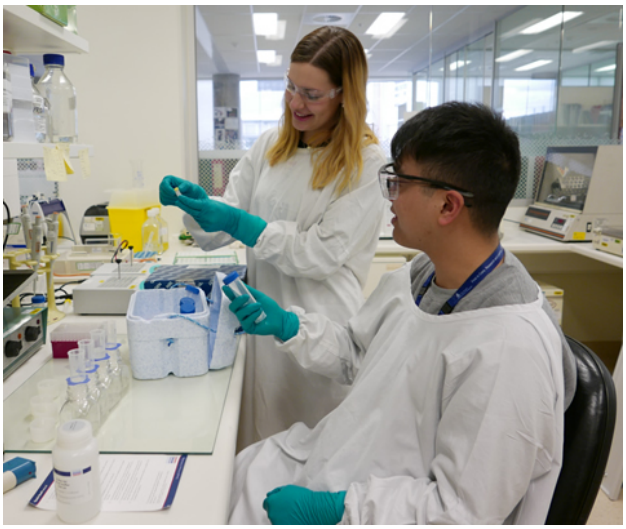
Collaborators

James McCaw and Alex Zarebski (University of Melbourne); Jessie Bloom (Fred Hutchinson Cancer Research Centre, Seattle WA, USA); Jean-Francois Rossignol (Romark Laboratories, Tampa FL, USA); Takao Shishido (Shionogi TechnoAdvance Research, Osaka, Japan)

Highlights and developments 2018

In 2018 we assessed the fitness cost of numerous substitutions in the N9 neuraminidase of A(H7N9) influenza viruses. Our results showed that while the fitness cost of NA substitutions differed depending on whether the virus was from the Yangtze River or Pearl River lineage. We also completed a substantial project to correlate *in vitro* IC_{50} data with clinical effectiveness of oseltamivir in ferrets to determine if certain variant viruses were clinically resistant.

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. Currently, *in vitro* and *in vivo* studies are being carried out to determine if combination therapy can prevent the selection of oseltamivir resistant influenza viruses.



Animal Influenza Viruses

Centre staff

Michelle Wille, Malet Aban, Aeron Hurt

Research overview

Animal influenza viruses can pose a threat to humans via direct infection from an animal 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. As part of ongoing analyses of avian influenza in Antarctica, further samples from penguins in Antarctica were collected by our Chilean collaborators.

Collaborators

Marcel Klaassen (Deakin University, Victoria), Bethany Hoye (University of Wollongong, Woollongong VIC); Simone Warner (Victorian Department of Primary Industries, Victoria); Edward Holmes (University of Sydney, Sydney NSW); Daniel González Acuña (University of Concepción, Bío Bío Region, Chile); Frank Wong (Australian Animal Health Labs, Geelong VIC); Andrew Breed (Australian Government Department of Agriculture)

Highlights and developments 2018

In 2018, we collected and screened 1746 swab samples from wild Anseriiformes (ducks) and Charadriiformes (shorebirds and terns) in Victoria, Tasmania and Western Australia, with 79 influenza A virus detections (*see table p.##*). These samples are being characterised and isolated in embryonated hens' eggs and will assist in the understanding of the ecology of avian influenza viruses in Australia. 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 serum samples for general anti-influenza A antibodies using a commercial NP-ELISA. In 2018 blood samples were collected from the 1101 birds, most of which were collected from long distant migrant Red-necked Stint (n=149, from two states) and Ruddy Turnstones (n=325). Samples from long distance Red-necked Stint and nomadic Pacific Black Duck since 2012 were further being assayed for antibodies against H5 antibodies, to which migratory Red-necked Stint may have been exposed on their migrations to the northern hemisphere. The project was completed in January 2019 and was funded by the Department of Agriculture.

In addition to classical approaches to screen for and characterise influenza A viruses, we have embarked on a new collaboration to use RNA sequencing (RNA-seq) to assess the total viral burden in Australian wild birds. A critical finding was that the presence of influenza A virus infection is associated with higher overall viral burden and viral diversity in shorebirds and ducks as compared to birds that were not infected with influenza A virus. This research has further allowed us to identify a number of other RNA viruses in wild birds that are important reservoir hosts for influenza A virus.

Photo courtesy of Mark Smith, Victorian Wader Study Group

Samples collected from wild birds in 2018

Avian order	Species	State	Serum samples		Swab samples	
			Samples collected	*Influenza-positive samples*	*Samples collected*	*Influenza-positive samples*
Charadriiformes	Crested tern	Tas			67	
	Double-banded plover	Tas	8		8	
	Red-necked stint	Tas	1		1	
	Ruddy turnstone	Tas	325	96	319	20
	Silver gull	Tas	1		1	
	Curlew sandpiper	Vic	148	1	149	1
	Red-necked stint	Vic	79	14	79	3
	Sharp-tailed sandpiper	Vic	55	1	55	4
	Bar-tailed godwit	WA	32	1	32	
	Curlew sandpiper	WA	25	1	25	1
	Great knot	WA	35		35	
	Greater sandplover	WA	35	1	35	
	Grey-tailed tattler	WA	32	1	32	1
	Red knot	WA	63	11	63	13
	Red-necked stint	WA	70	14	70	1
	Ruddy turnstone	WA	6		6	
	Terek sandpiper	WA	22		22	
Anseriformes	Hardhead	Vic			23	1
	Australian shelduck	Vic			17	
	Chestnut teal	Vic	63	30	175	10
	Grey teal	Vic	8	2	183	10
	Pacific black duck	Vic	61	20	241	10
	Pacific black duck x domestic duck	Vic	9	3	19	2
	Wood duck	Vic	3		21	1
	Pink-eared duck	Vic			46	1
Other	Crested pigeon	Vic	14		14	
	Australian magpie	Vic	3		3	
	Magpie-lark	Vic	2		2	
	Noisy miner	Vic			1	
	Rainbow lorikeet	Vic	1		1	
	Galah	Vic			1	
	Grand Total		**1101**	**196**	**1746**	**79**

Kinetics of the Antibody Response to Seasonal Influenza Vaccines

Centre staff

Kanta Subbarao, Sheena Sullivan, Olivia Price, Heidi Peck, Ian Barr

Research overview

Our research, which is undertaken at the Centre and at the University of Melbourne, investigates how long the immune response to the seasonal influenza vaccine lasts in adults of different age groups and whether the timing of the vaccination campaign, relative to the start, peak and end of the last five influenza epidemics in Victoria, is optimal for protection.

Collaborators

Caroline Marshall (Royal Melbourne Hospital); Monica Slavin and Leon Worth (Peter MacCallum Cancer Centre).

Highlights and developments 2018

Study subjects were recruited to participate in the study among staff aged 18-50 years and volunteers aged 65+ years ("ambulatory elderly") at two hospitals and residents aged 65+ years ("frail elderly") at two aged care facilities. Participants aged under 65 years received the 2018 southern hemisphere quadrivalent vaccine and those aged over 65 years received enhanced trivalent vaccine (either high dose or adjuvanted). Serum samples were collected at prior to vaccination and 1, 2, 4, and 6 months post-vaccination. Antibody titres against vaccine antigens will be measured by HI and virus neutralization assays. Geometric mean titres (GMTs) will be estimated using random effects regression. Based on the preliminary data from the study, we will request a 12 month post-vaccination blood sample from the study participants.

Human Immunity to Influenza

Centre staff and student

Annette Fox, Louise Carolan, Maria Auladell Bernat, Sheena Sullivan, Vivian Leung

Research overview

A key goal of our work is to identify strategies to improve the immunogenicity and therefore 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, which was first described in the 1950's and is referred to as original antigenic sin, may be due to interference by antibodies or B cells induced by prior influenza exposures. 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, resulting in a focused immune response, and reduced potential to recognise 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); 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)

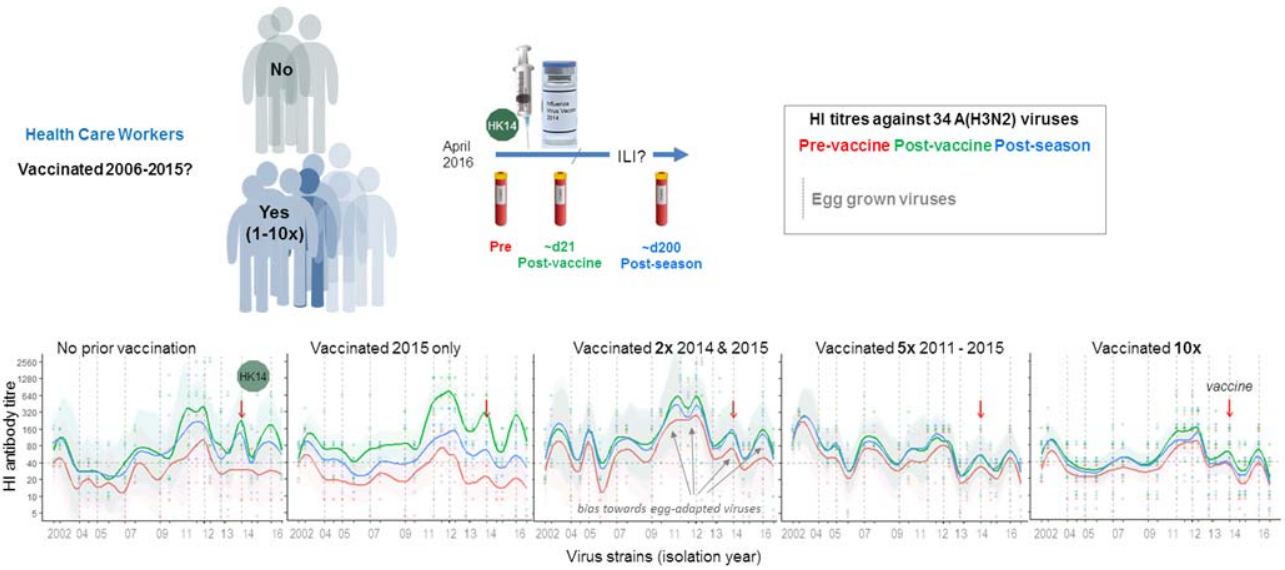
Highlights and developments 2018

Antibody landscapes (*figure below*), which fit heamagglutuination inhibiting (HI) antibody titres against prevailing, past and future virus strains, were used to examine the breadth of A(H3N2) virus-reactive antibody responses to influenza vaccination. Evolution of A(H3N2) viruses since 1968 has meant that HI assay conditions have been altered over the years. Most recently, oseltamivir has been added to increase sensitivity for detecting HI antibodies by preventing neuraminidase (NA)-mediated agglutination. We further investigated effects of oseltamivir and verified that NA-mediated agglutination is largely restricted to a small fraction of viruses that acquire NA D151G/N mutations upon propagation in MDCK cells. However, oseltamivir also appeared to have effects on HI titres that were unrelated to NA mutations. We therefore produced a panel of 35 viruses spanning 1968-2016 that lacked NA D151G/N mutations, performed well in HI assays without oseltamivir, and included cell and egg-grown virus pairs to understand whether vaccination with egg-grown strain induces responses that are skewed epitopes present in egg- but not cell-grown strains.

Antibody landscapes were produced using pre- and post-vaccination sera from two cohorts, both vaccinated in 2016. Analysis of a sera collected at three time-points from 49 Health Care Workers (HCW, collaboration with Sheena Sullivan and Vivian Leung) demonstrates a striking attenuation of titres against an increasingly broad array of A(H3N2) strains as the number of prior vaccinations increased (*figure below*). We also assessed 600 sera collected pre- and post-vaccination from 100 previously vaccine-naïve people in Vietnam who had been actively followed for nine years to detect influenza infections. Contrary to prior-vaccination, prior A(H3N2) infection was associated with higher titres against vaccine, prior and future strains, and with faster boosting and better titre maintenance.

Antibody responses could be poor among repeatedly vaccinated HCW because memory B cells have become increasingly focused, limiting the pool that is able to respond. To investigate the role and specificity of memory B cells it is necessary to distinguish acutely responding B cells that are memory versus naïve-derived. We used an optimised *in vitro* activation protocol to compare the post-activation phenotype of sorted human naïve and memory B cells. The results indicate that a panel of B cell differentiation markers can be used to distinguish these B cell subsets up to six days after activation. This panel is being combined with fluorescent- labelled influenza HA proteins representing vaccine and prior strains to dissect the specificity and origin (naïve or memory) of responding B cells, detected in *ex vivo* samples collected acutely following influenza vaccination.

HI antibodies are the only accepted correlate of influenza vaccine protection and have been a primary focus of our work. However, influenza vaccination also induces antibodies that protect by inhibiting neuraminidase. We therefore examined the effect of repeated vaccination on neuraminidase inhibiting antibody (NI) titres in HCW. Like HI titres, NI titres were attenuated among repeatedly vaccinated HCW indicating that the mechanisms that impact HI titres may operate more broadly. In future studies we will examine the breadth of the NI antibody response. We will also use HA antigenic site-specific monoclonal antibodies in competition ELISA, and reverse-engineered viruses containing mutations within individual antigenic sites to examine the epitope specificity and focusing of serum antibodies. These studies will help to understand the effects of exposure history, and if and how vaccination can extend the B cell response to recognize epitopes in new strains.



Effect of prior influenza vaccination on the magnitude and breadth of antibodies against A(H3N2) viruses. *Increasing prior vaccination was associated with attenuated titres and titre rises against 2004-2016 A/H3N2 viruses, particularly strains circulating after the vaccine strain.*

Early Recognition and Response to Influenza Infection

Centre staff

Patrick Reading

Research overview

Our research is undertaken at the Centre and at the University of Melbourne. We investigate 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. 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 and (iii) utilizing approaches to simulate host innate immunity to limit the impact of subsequent infection with influenza or other respiratory viruses.

Collaborators

Paul Young (University of Queensland, Brisbane QLD); Nathan Bartlett (University of Newcastle, Newcastle NSW); Kirsten Spann (Queensland University of Technology, Brisbane QLD); Lara Herrero (Griffith University, Brisbane QLD); 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 2018

During 2018, we have focussed on understanding the different responses elicited in epithelial cells versus immune cells following infection by influenza and other respiratory viruses. Virus infection of epithelial cells promotes virus replication and release, whereas infection of immune cells (such as macrophages) results in an abortive infection. Based on these findings, we hypothesised that macrophages express particular factors (termed restriction factors) that can block the replication of influenza and other respiratory viruses. Therefore, we performed RNA sequencing to examine the transcriptional signatures in epithelial cells versus macrophages in the presence or absence of influenza virus infection, allowing us to identify putative restriction factors expressed in macrophages, but no epithelial cells. These studies were recently published in The Journal of Virology. We are now using approaches to ectopically overexpress (in epithelial cells) or delete (in macrophages) these putative restriction factors to determine their role in blocking virus replication and to characterise their mechanism/s of antiviral activity.

Overall, our research contributed to six peer-reviewed publications during 2018, in journals such as The Journal of Virology, The Journal of Infectious Diseases and Nature Communications. Dr Reading presented several research talks at conferences and institutes during the year, including at the Negative Strand Virus Meeting in Italy and as a invited speaker and session chair at the Australian Society for Microbiology Meeting in Brisbane. In addition, he was a Chief Investigator on a successful NHMRC Development Grant (2019-2021, 'Clamp stabilised vaccines to provide broad spectrum protection against influenza') as well as a multi-million dollar grant from the Coalition of Epidemic Preparedness Innovations (2019-2021, 'Rapid response pipeline for stabilised subunit vaccines') to fund research with collaborators at the University of Queensland investigating novel recombinant vaccines against influenza viruses.

In 2018, Dr Reading's research group consisted of one post-doctoral scientist, four PhD students and one Master of Biomedical Science student, all enrolled through the University of Melbourne. Dr Reading also is co-supervisor of an additional four PhD students and one Masters student enrolled at the University of Melbourne.

Evolution, Modelling and Serological Responses to Influenza Viruses

Centre staff

Ian Barr, Aeron Hurt, Malet Aban, Yi-Mo Deng, Sheena Sullivan, Annette Fox

Research overview

We are continuing with several collaborative projects both with international and local groups to investigate various aspects of influenza virus evolution and the immune responses to influenza viruses and vaccines.
One of these projects is in collaboration with colleagues at the University of Cambridge and the University of Amsterdam (Edward Lam, Dylan Morris, Colin A. Russell) who analysed antigenic and genetic data on influenza viruses processed at the Centre from 2000-2015. The study measured the variability in influenza epidemics and compared epidemiological patterns with previously hypothesized environmental and virological drivers of influenza virus epidemics.

In another ongoing collaboration with Vijaykrishna Dhanasekaran (Monash University) and the J. Craig Venter Institute, we have continued to analysing sequence data from over 700 B/Yamagata lineage viruses collected from Australia, New Zealand and Singapore during 2012-2014 as well as completing another series of full genome sequences on almost 600 A(H3N2) viruses collected in Australia from 2012-2016. Results from these studies are being compiled for publication.

The Centre is also participating in a US based CEIRS (Centers of Excellence for Influenza Research and Surveillance) project titled “Advanced vaccination and immunity management strategies to protect from influenza virus infection”. This project aims to identify future influenza viruses in advance of them becoming widespread and generate vaccine candidate viruses that could provide enhanced protection compared the current system of selecting viruses that may no longer be in circulation when the vaccine is available some 9-10 months after the vaccine viruses have been chosen. Work has been progressing on extensive antigenic testing (using both HI and virus microneutralisation assays) of mutated viruses generated by human serum escape mutants and reverse engineered viruses containing selected mutations.

Highlights and developments 2018

Our study on variability in influenza epidemics found that the timing of local epidemics in Australia is not associated with anomalous fluctuations in temperature and humidity and that virus antigenic change does not have an observable effect either on the magnitude or timing of local epidemics. Variation in epidemic size appears instead to be driven principally by heterosubtypic competition: epidemics that start earlier in the year tend to be larger than those that start later, and epidemics of a particular virus type or subtype are smaller and less likely to occur at all if viruses of another type or subtype have already circulated. This study has been submitted for publication.

Other serology projects with collaborators in Hong Kong and Singapore were completed in 2018, resulting in two publications:

Six-monthly versus annual influenza vaccination in older adults in the tropics: an observer-blind, active-comparator controlled, randomised superiority trial. Young B, Sadarangani S, Sen Yew H, Yung CF, Barr I, Connolly J, Chen M, Wilder-Smith A. Clin Infect Dis. 2018 (epub ahead of print October 2018).

Incidence of influenza A(H3N2) virus infections in Hong Kong in a longitudinal sero-epidemiological study, 2009-2015. Wei VWI, Wong JYT, Perera RAPM, Kwok KO, Fang VJ, Barr IG, Peiris JSM, Riley S, Cowling BJ. PLoS One. 2018 May 24;13(5):e0197504.

Collaborators

Derek Smith (Cambridge University, UK); Yoshihiro Kawaoka (The University of Wisconsin, Madison, WI, USA and The University of Tokyo, Japan); Vijaykrishna Dhanasekaran (Monash University); Gavin Smith and Yvonne Su (Duke-NUS Graduate Medical School, Singapore); Ron Fouchier (Erasmus University, Rotterdam, The Netherlands); Edward Bolongia (Marshfield Clinic Research Foundation, Marshfield WI, USA); Alan Durbin and Gene Tan (J. Craig Venter Institute, Rockville and San Diego, USA); Edward Holmes and Jemma Geohagan (University of Sydney, NSW); Malik Peiris and Benjamin Cowling (University of Hong Kong, Hong Kong); Mark Chen and Barnaby Young (Tan Tock Seng Hospital, Singapore); Steven Kent (University of Melbourne)

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 the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) (2017-2018)

Centre staff: Hilda Lau, Robert Shaw, Ian Barr, Heidi Peck, Cleve Rynehart

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

Highlights and developments 2018: A total of 60 egg isolates were obtained from 88 inoculations with original clinical specimens from various geographical locations. Isolation rates varied from 57% to 87% according to virus type/subtype and lineage. Suitable isolates were made available to other laboratories and industry for reassortment and assessment as vaccine candidates.

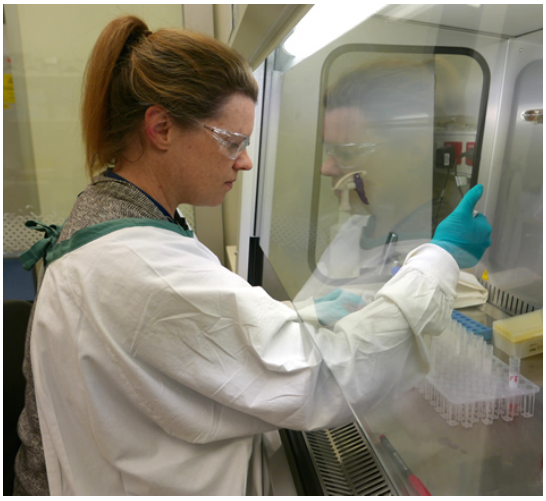
Cooperative Research and Development Agreement with Seqirus: Development and provision of influenza virus strains isolated on MDCK 33016PF cells for vaccine production (2017-2020)

Centre staff: Heidi Peck, Cleve Rynehart, Sally Soppe, Ian Barr

Project overview: Using a proprietary Seqirus cell line to isolate influenza viruses, the Centre produces potential candidate vaccine viruses (CVVs) for cell-based influenza vaccine manufacture. A number of original clinical specimens are used to isolate viruses directly into the MDCK33016PF cell line. The resultant isolates undergo analysis of their growth, antigenic characteristics and other properties

Highlights and developments 2018: During 2018, 103 clinical specimens were cultured in MDCK 33016PF cells, of which 91 (88%) produced isolates. As in previous years, this was much higher than the rate of isolation in eggs. The isolates, which comprised A(H1N1)pdm09 and A(H3N2) viruses, were sent to Seqirus in Holly Springs NC, USA, for further evaluation as potential vaccine candidates produced by cell culture.

Three out of four vaccine components (A(H3N2), B/Victoria and B/Yamagata) included in the cell-based influenza vaccine are to be fully derived from cells. The B/Yamagata component of the Seqirus cell-based vaccine for the Northern Hemisphere 2019-2020 season continues to use B/Singapore/INFTT-16-0610/2016, a cell-derived seed isolated at the Centre.



Agreement with Romark Laboratories: Studies of the influenza antiviral nitazoxanide (2016-2019)

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

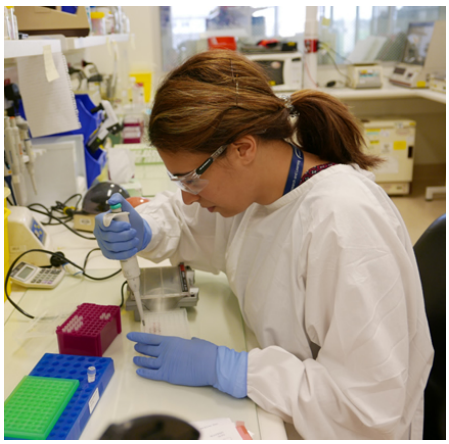
Highlights and developments 2018: *In vitro* studies have shown that nitazoxanide and oseltamivir have an additive to synergistic interaction. In a ferret model, combination treatment of the nitazoxanide and oseltamivir was more effective at preventing influenza virus infection and lower respiratory tract replication compared to oseltamivir treatment alone.

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 2018: *In vivo* studies are being conducted to determine if baloxavir treatment of ferrets at 24 or 48 hours post-infection is able to reduce viral replication in ferrets compared to either oseltamivir or placebo treatment, and whether baloxavir treatment reduces the transmission of viruses to co-housed naïve ferrets.



Research Students

PhD Candidates

Ms Rubaiyea Farrukee, a PhD candidate from the University of Melbourne, continued her PhD project titled: "Assessing replication, transmission and fitness of antiviral resistant influenza viruses", under the supervision for **Aeron Hurt** and **Patrick Reading**.

Ms Paulina Koszalka, a PhD candidate from Monash University, commenced her PhD project titled "Efficacy, resistance and drug interactions for influenza antivirals in clinical development", in March 2018 under the supervision of **Aeron Hurt** and Vijaykrishna Dhanasekaran (Monash University).

Ms Annika Suttie, a PhD candidate from Federation University, continued her PhD project titled "Molecular epidemiology of influenza virus in Cambodia", under the supervision of Andrew Greenhill (Federation University), **Yi-Mo Deng**, Jenny Mosse (Federation University)

MAE Candidate

Dr Ximena Tolosa, a Master of Philosophy in Applied Epidemiology (MAE) candidate from the Australian National University, completed her placement at the Centre, under the supervision of **Sheena Sullivan**.

Research Funding and Awards

Centre staff members are Chief Investigators in grants awarded in 2018 for the following projects due to commence in 2019:

National Health and Medical Research Council (NHMRC) Development Grant: "*Clamp stabilised vaccines to provide broad spectrum protection against influenza*".

$956,898 awarded for the period 1 January 2019 – 31 December 2021. (Chief investigators Paul Young, **Patrick Reading,** Keith Chappell and Daniel Watterson). The grant will be administered by the University of Queensland and the work will be undertaken at the University of Queensland.

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

$784,418 awarded for the period 1 January 2019 – 31 December 2019. (Chief investigators **Kanta Subbarao,** Brad Gilbertson, Anice Lowen and Vijaykrishna Dhanasekaran). The grant will be administered by the University of Melbourne and the work will be undertaken at the University of Melbourne.

APPRISE sub-grant: *"Influenza sero-surveillance at the animal-human interface: a feasibility study in high-risk groups"*

$20,000 awarded for the period 1 July 2018 – 30 June 2019 (Chief investigator: David Smith; Project Team: Paul Effler, Frank Wong, Marion Koopmans, **Ximena Tolosa**, **Kanta Subbarao**, **Sheena Sullivan**, Soren Alexanderson). The grant will be administered by PathWest Laboratory Medicine and the work will be undertaken at the PathWest Laboratory Medicine, the WA Department of Health, the Australian Animal Health Laboratory (AAHL), Erasmus Medical Centre, Geelong Centre for Emerging Infectious Diseases and the Centre.

Coalition for epidemic preparedness innovations (CEPI) project grant: *"Rapid Response Pipeline for Stabilised Subunit Vaccines"*

US $10.6 million (AUS $14.7 million) awarded for the period 1 July 2018 – 30 June 2021 (Chief investigators Paul Young, **Patrick Reading**, Keith Chappell, Glenn Marsh, George Lovrecz and Charani Ranasinghe). The grant will be administered by the University of Queensland and the work will be undertaken at the University of Queensland, CSIRO Australian Animal Health Laboratory, Australian National University and the Centre.

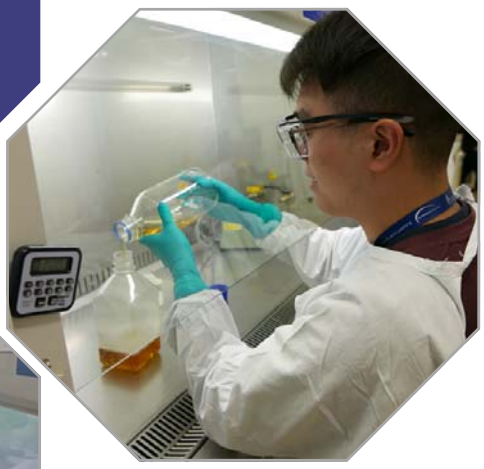
Australian Partnership for Preparedness Research on Infectious Disease Emergencies (APPRISE) sub-grant: *"Sampling, shipping and serology: a proof of concept study of influenza immunity".*

$20,000 awarded for the period 1 July 2018 – 30 June 2019 (Chief investigator: David Smith and Kristine Macartney; Project Team: **Ian Barr**, Kylie Carville, Mike Catton, Jen Kok, Jodie McVernon, David Price, **Sheena Sullivan**). The grant will be administered by PathWest Laboratory Medicine and the work will be undertaken at the Victorian Infectious Diseases Reference Laboratory (VIDRL), the Children's Hospital at Westmead, the Doherty Institute, PathWest Laboratory Medicine, Pathology West at Westmead Hospital and the Centre.

Centers of Excellence for Influenza Research and Surveillance (CEIRS) sub-grant: *"The effect of prior natural infection or vaccination on subsequent response to influenza vaccine in children"*

US$400,000 awarded for the period 1 August 2018 – 30 July 2019 (Chief investigator: **Kanta Subbarao**; Key personnel: Nigel Crawford, Kristine Macartney, Rajeev Rudraraju, Katherine Kedzierska, **Annette Fox**, **Sheena Sullivan**). The grant will be administered by the University of Melbourne and the work will be undertaken at the Murdoch Children's Research Institute, the Royal Children's Hospital, the Childrens' Hospital at Westmead, the University of Melbourne and the Centre.

Around the laboratories



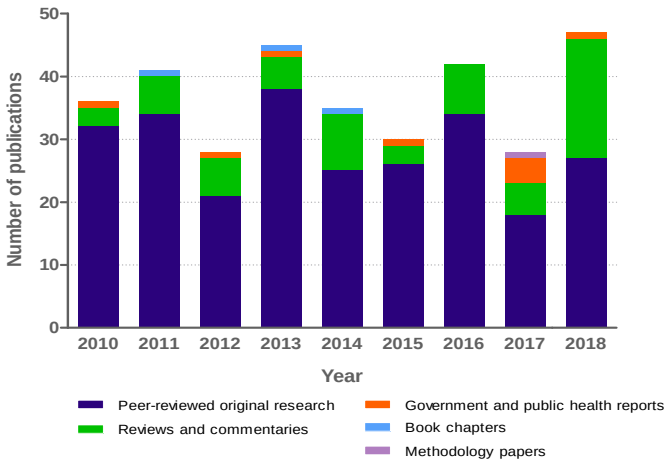
Communications and Advisory Activities

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 47 original research papers, reviews and reports in 2018 (Figure 21). The is the highest annual number of publications by Centre staff. Included in these publications were two papers published in the New England Journal of Medicine.

Figure 21. Centre publications 2010–2018.



Centre Publications 2018

1. **Barr IG** and Cheng AC. Difficulties of predicting the timing, size and severity of influenza seasons. Respirology, 2018. 23(6): 562-563.

2. **Barr IG**, Donis RO, Katz JM, McCauley JW, Odagiri T, Trusheim H, Tsai TF and Wentworth DE. Cell culture-derived influenza vaccines in the severe 2017-2018 epidemic season: a step towards improved influenza vaccine effectiveness. NPJ Vaccines, 2018. 3: 44.

3. Belser JA, Barclay W, **Barr** I, Fouchier RAM, Matsuyama R, Nishiura H, Peiris M, Russell CJ, **Subbarao K**, Zhu H and Yen HL. Ferrets as models for influenza virus transmission studies and pandemic risk assessments. Emerg Infect Dis, 2018. 24(6): 965-971.

4. Chamings A, Nelson TM, Vibin J, **Wille M**, Klaassen M and Alexandersen S. Detection and characterisation of coronaviruses in migratory and non-migratory Australian wild birds. Sci Rep, 2018. 8(1): 5980.

5. **Chan KF**, **Carolan LA**, Druce J, Chappell K, Watterson D, Young P, Korenkov D, **Subbarao K**, **Barr IG**, **Laurie KL** and **Reading PC**. Pathogenesis, humoral immune responses and transmission between co-housed animals in a ferret model of human RSV infection. J Virol, 2018. 92(4): e01322-17.

6. **Chan KF**, **Carolan LA**, Korenkov D, Druce J, McCaw J, **Reading PC**, **Barr IG** and **Laurie KL**. Investigating viral interference between influenza A virus and human respiratory syncytial virus in a ferret model of infection. J Infect Dis, 2018. 218(3): 406-417.

7. Cheng AC and **Subbarao K**. Epidemiological data on the effectiveness of influenza vaccine - another piece of the puzzle. J Infect Dis, 2018. 218(2): 176-178.

8. Cowling BJ and **Sullivan SG**. A concern over terminology in vaccine effectiveness studies. Euro Surveill, 2018. 23(10).

9. de Boer PT, Kelso JK, Halder N, Nguyen TP, Moyes J, Cohen C, **Barr IG**, Postma MJ and Milne GJ. The cost-effectiveness of trivalent and quadrivalent influenza vaccination in communities in South Africa, Vietnam and Australia. Vaccine, 2018. 36(7): 997-1007.

10. Dendle C, Stuart RL, Mulley WR, Polkinghorne KR, Gan PY, Kanellis J, Ngui J, **Laurie K**, Thursky K, **Leung VK** and Holdsworth SR. Measurement of Humoral Immune Competence and the Risk of Sinopulmonary Infection in a Cohort of Kidney Transplant Recipients. Transplant Proc, 2018. 50(10): 3367-3370.

11. Feng S, Chiu SS, Chan ELY, Kwan MYW, Wong JSC, Leung CW, Chung Lau Y, **Sullivan SG**, Peiris JSM and Cowling BJ. Effectiveness of influenza vaccination on influenza-associated hospitalisations over time among children in Hong Kong: a test-negative case-control study. Lancet Respir Med, 2018. 6(12): 925-34.

Centre Publications (continued)

12. Feng S, Cowling BJ, Kelly H and **Sullivan SG**. Estimating influenza vaccine effectiveness with the test-negative design using alternative control groups: a systematic review and meta-analysis. Am J Epidemiol, 2018. 187(2): 389-397.

13. **Fox A**, Quinn KM and **Subbarao K**. Extending the breadth of influenza vaccines: status and prospects for a universal vaccine. Drugs, 2018. 78(13): 1297-1308.

14. **Fox A**, **Subbarao K** and **Reading P**. Infants harness the germline against RSV. Immunity, 2018. 48(2): 190-192.

15. Fuglsang E, Pizzolla A, Krych L, Nielsen DS, Brooks AG, Frokiaer H and **Reading PC**. Changes in gut microbiota prior to influenza A virus infection do not affect immune responses in pups or juvenile mice. Front Cell Infect Microbiol, 2018. 8: 319.

16. Geoghegan JL, Saavedra AF, Duchene S, **Sullivan S**, **Barr I** and Holmes EC. Continental synchronicity of human influenza virus epidemics despite climactic variation. PLoS Pathog, 2018. 14(1): e1006780.

17. Grant KA, Carville K, **Sullivan SG**, Strachan J, Druce J and Fielding J. A severe 2017 influenza season dominated by influenza A(H3N2), Victoria, Australia. Western Pac Surveill Response J, 2018. 9(Suppl 1): 1-9.

18. Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, **Hurt AC**, Ishida T, Sekino H, Yamada K, Portsmouth S, Kawaguchi K, Shishido T, Arai M, Tsuchiya K, Uehara T, Watanabe A and Baloxavir Marboxil Investigators G. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. N Engl J Med, 2018. 379(10): 913-923.

19. Ieng V, **Tolosa MX**, Tek B, Sar B, Sim K, Seng H, Thyl M, Dara C, Moniborin M, Stewart RJ, Bell LC, Theocharopolous G, Chin S, Chau D, Iuliano AD, Moen A, Tsuyuoka R, Dueger EL, **Sullivan SG** and Ly S. National burden of influenza-associated hospitalizations in Cambodia, 2015 and 2016. Western Pac Surveill Response J., 2018. 9(Suppl 1).

20. Jackson-Thompson BM, Kim SY, Jaiswal S, Scott JR, Jones SR, Morris CP, Fite JJ, **Laurie K**, Hoy AR, Dardzinski BJ and Mitre E. Brugia malayi infection in ferrets - a small mammal model of lymphatic filariasis. PLoS Negl Trop Dis, 2018. 12(3): e0006334.

21. Jennings L, Huang QS, **Barr I**, Lee PI, Kim WJ, Buchy P, Sanicas M, Mungall BA and Chen J. Literature review of the epidemiology of influenza B disease in 15 countries in the Asia-Pacific region. Influenza Other Respir Viruses, 2018. 12(3): 383-411.

22. Korenkov DA, **Laurie KL**, **Reading PC**, **Carolan LA**, **Chan KF**, Isakova S, II, Smolonogina TA, **Subbarao K**, **Barr IG**, Villanueva J, Shcherbik S, Bousse T and Rudenko LG. Safety, immunogenicity and protection of A (H3N2) live attenuated influenza vaccines containing wild-type nucleoprotein in a ferret model. Infect Genet Evol, 2018. 64: 95-104.

23. Koutsakos M, Wheatley AK, Loh L, Clemens EB, Sant S, Nussing S, Fox A, Chung AW, **Laurie KL**, **Hurt AC**, Rockman S, Lappas M, Loudovaris T, Mannering SI, Westall GP, Elliot M, Tangye SG, Wakim LM, Kent SJ, Nguyen THO and Kedzierska K. Circulating TFH cells, serological memory, and tissue compartmentalization shape human influenza-specific B cell immunity. Sci Transl Med, 2018. 10(428).

24. Lackenby A, Besselaar TG, Daniels RS, Fry A, Gregory V, Gubareva LV, Huang W, **Hurt AC**, **Leang SK**, Lee RTC, Lo J, Lollis L, Maurer-Stroh S, Odagiri T, Pereyaslov D, Takashita E, Wang D, Zhang W and Meijer A. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors and status of novel antivirals, 2016-2017. Antiviral Res, 2018. 157: 38-46.

25. **Laurie KL**, Horman W, **Carolan LA**, **Chan KF**, Layton D, Bean A, Vijaykrishna D, **Reading PC**, McCaw JM and **Barr IG**. Evidence for viral interference and cross-reactive protective immunity between influenza B virus lineages. J Infect Dis, 2018. 217(4): 548-559.

26. **Lee LYY**, **Izzard L** and **Hurt AC**. A review of DNA vaccines against influenza. Front Immunol, 2018. 9: 1568.

27. Li L, Wong JY, Wu P, Bond HS, Lau EHY, **Sullivan SG** and Cowling BJ. Heterogeneity in estimates of the impact of influenza on population mortality: a systematic review. Am J Epidemiol, 2018. 187(2): 378-388.

28. Matos AR, Resende PC, Miranda MD, Garcia CC, Caetano BC, Lopes JCO, Debur MC, Cury ALF, Vianna LA,

Centre Publications (continued)

29. **Mifsud EJ**, **Tai CM** and **Hurt AC**. Animal models used to assess influenza antivirals. Expert Opin Drug Discov, 2018. 13(12): 1131-1139.

30. Nüssing S, Sant S, Koutsakos M, **Subbarao K**, Nguyen THO and Kedzierska K. Innate and adaptive T cells in influenza disease. Front Med, 2018. 12(1): 34-47.

31. **Oh DY**, **Panozzo J**, **Vitesnik S**, **Farrukee R**, Piedrafita D, Mosse J and **Hurt AC**. Selection of multi-drug resistant influenza A and B viruses under zanamivir pressure and their replication fitness in ferrets. Antivir Ther, 2018. 23(4): 295-306.

32. Paules CI, **Sullivan SG**, **Subbarao K** and Fauci AS. Chasing seasonal influenza - the need for a universal influenza vaccine. N Engl J Med, 2018. 378(1): 7-9.

33. Regan AK, Moore HC and **Sullivan SG**. Does influenza vaccination during early pregnancy really increase the risk of miscarriage? Vaccine, 2018. 36(17): 2227-2228.

34. Rudraraju R and **Subbarao K**. Passive immunization with influenza haemagglutinin specific monoclonal antibodies. Hum Vaccin Immunother, 2018. 14(11): 2728-2736.

35. Sim SA, **Leung VKY**, Ritchie D, Slavin MA, **Sullivan SG** and Teh BW. Viral respiratory tract infections in allogeneic hematopoietic stem cell transplantation recipients in the era of molecular testing. Biol Blood Marrow Transplant, 2018. 24(7): 1490-1496.

36. Squires RC, **Reading PC**, **Sullivan SG**, **Barr IG** and Konings F. Influenza virus detection: driving change in public health laboratories in the Western Pacific Region. Western Pac Surveill Response J., 2018. 9(Suppl 1).

37. **Subbarao K**. Advances in influenza virus research: a personal perspective. Viruses, 2018. 10(12).

38. **Subbarao K**. Avian influenza H7N9 viruses: a rare second warning. Cell Res, 2018. 28(1): 1-2.

39. **Sullivan S**. Challenges in reducing influenza-associated mortality. Lancet, 2018. 391(10127): 1242-1244.

40. **Suttie A**, Karlsson EA, **Deng YM**, Horm SV, Yann S, Tok S, Sorn S, Holl D, Tum S, **Hurt AC**, Greenhill AR, **Barr IG**, Horwood PF and Dussart P. Influenza A(H5N1) viruses with A(H9N2) single gene (matrix or PB1) reassortment isolated from Cambodian live bird markets. Virology, 2018. 523: 22-26.

41. **Suttie A**, Yann S, Y P, Tum S, **Deng YM**, Hul V, Horm VS, **Barr I**, Greenhill A, Horwood PF, Osbjer K, Karlsson EA and Dussart P. Detection of low pathogenicity influenza A(H7N3) virus during duck mortality event, Cambodia, 2017. Emerg Infect Dis, 2018. 24(6): 1103-1107.

42. Tam YH, Valkenburg SA, Perera R, Wong JHF, Fang VJ, Ng TWY, Kwong ASK, Tsui WWS, Ip DKM, Poon LLM, Chau CKV, **Barr IG**, Peiris JSM and Cowling BJ. Immune responses to twice-annual influenza vaccination in older adults in Hong Kong. Clin Infect Dis, 2018. 66(6): 904-912.

43. **Tolosa MX**, **Leung VK**, **Buettner I**, **Todd A**, **Deng YM**, **Shaw R**, **Subbarao K**, **Barr IG**, Herring B, Barakat A, Palekar R, Zhang W, Fuster C, Samaanf MD and **Reading PC**. Isolation and identification of human influenza viruses in cell culture: summary analysis of the WHO external quality assessment programme for National Influenza Centres in the WHO regions of the Americas, Africa and Eastern Mediterranean, 2017. Weekly Epidemiological Record, 2018. 37(14): 480-488.

44. van Dijk JG, Verhagen JH, **Wille M** and Waldenstrom J. Host and virus ecology as determinants of influenza A virus transmission in wild birds. Curr Opin Virol, 2018. 28: 26-36.

45. Wei VWI, Wong JYT, Perera R, Kwok KO, Fang VJ, **Barr IG**, Peiris JSM, Riley S and Cowling BJ. Incidence of influenza A(H3N2) virus infections in Hong Kong in a longitudinal sero-epidemiological study, 2009-2015. PLoS One, 2018. 13(5): e0197504.

46. **Wille M**, Netter HJ, Littlejohn M, Yuen L, Shi M, Eden JS, Klaassen M, Holmes EC and **Hurt AC**. A divergent hepatitis D-like agent in birds. Viruses, 2018. 10(12).

47. Wong FYK, Donato C, **Deng YM**, Teng D, **Komadina N**, **Baas C**, Modak J, O'Dea M, Smith DW, Effler PV, Cooke J, Davies KR, **Hurt A**, Kung N, Levy A, Loh R, Shan S, Shinwari MW, Stevens V, Taylor J, Williams DT, Watson J, Eagles D, McCullough S, **Barr IG** and Dhanasekaran V. Divergent human-origin influenza viruses detected in Australian swine populations. J Virol, 2018. 92(16)

Presentations

Centre staff members presented talks and posters at numerous events during 2018, including national and international conferences, WHO meetings, educational lectures and research seminars.

ORAL PRESENTATIONS

Event/Institute; Location, date	SPEAKER, Title(s)
Indian Academy of Sciences Public Lecture; Bangalore, India, 25 January	KANTA SUBBARAO: Seasonal and pandemic influenza.
International Congress of Cell Biology; Hyderabad, India, 27–31 January	KANTA SUBBARAO: Transport and packaging of influenza viral RNA.
University of Melbourne Animal Ethics Training Day 2018; Melbourne, 31 January	AERON HURT: How ferret studies contribute to the global fight against influenza.
Influenza Specialist Group Annual Scientific Meeting; Melbourne, 4–5 February	AERON HURT: Guidelines for clinical management of severe influenza infection. IAN BARR: Review of the 2017 influenza season in Australia and what to expect in 2018. KANTA SUBBARAO: Determinants of human adaptation and gain of pandemic potential; How prepared are we for the next pandemic?
Lorne Infection and Immunity Conference; Lorne, Victoria, 14–16 February	KANTA SUBBARAO: Pandemic influenza viruses.
Workshop on Influenza Epidemiology and Evolution in Vietnam; Hanoi, Vietnam, 4–6 March	KANTA SUBBARAO: The WHO Influenza Centres global network for influenza surveillance.
ISIRV 2nd International Meeting on Respiratory Pathogens; Singapore, 7–9 March	AERON HURT: Neuraminidase inhibitor resistance: detection and response. NAOMI KOMADINA: The GISAID Initiative: Real-Time Global Communication in Disease Prevention.; Introduction to GISAID EpiFlu Database.
Influenza in Residential Aged Care seminar; Melbourne, 27 March	SHEENA SULLIVAN: Influenza vaccination recommendations, evaluation and research.
RNA viruses: Immunology, pathogenesis and translational opportunities; New Delhi, India, 28–30 March	KANTA SUBBARAO: Pandemic influenza viruses: biology and transmission.
Victorian Comprehensive Cancer Centre Monday Lunch Live; Melbourne, 19 March	IAN BARR: Influenza then and now; reflections on past pandemics and annual epidemics.
TSANZSRS Annual Scientific Meeting; Adelaide, 23–27 March	AERON HURT: Nuances of vaccine matching and the potential of future vaccines.
MDU PHL-VIDRL Seminar; Melbourne, 28 March	IAN BARR: What's new for influenza vaccines in 2018?
10th International Symposium on Avian Influenza; Brighton, UK, 15–18 April	ANNIKA SUTTIE: Avian influenza surveillance in Cambodian live bird markets. MICHELLE WILLE: Serological analysis of migratory shorebirds to assess exposure risk and incursions of highly pathogenic avian influenza into Australia.
2018 FETP International Night, 67th Annual Epidemic Intelligence Service Conference; Atlanta GA, USA, 17–18 April	XIMENA TOLOSA: Influenza Vaccine Effectiveness in Australia, 2012-2017.

ORAL PRESENTATIONS (continued)

Event/Institute; Location, date	SPEAKER, Title(s)
Visit to University of California Los Angeles; Los Angeles CA, USA, 18–20 April	SHEENA SULLIVAN: Why is the influenza vaccine not 100% effective and what can epidemiology do to help?
2018 Annual Conference on Vaccinology Research; Bethesda MD, USA, 23–25 April	SHEENA SULLIVAN: Vaccine effectiveness studies using the test-negative design--Biases and Benefits.
Visit to Centers for Disease Control and Prevention; Atlanta GA, USA, 26 April	SHEENA SULLIVAN: Does repeated influenza vaccination constrain the immune response?
University of Newcastle; Newcastle, NSW, 27 April	PATRICK READING: Sensing and responding to respiratory virus infection.
Global health, security and sustainability; University of Melbourne, 16 May	AERON HURT: Influenza
Viruses in May; Katoomba, NSW, 17–19 May	KANTA SUBBARAO: Monitoring for influenza viruses? molecular and emerging techniques used in vaccine design. IAN BARR: Pandemic and other emerging threats from animal and human influenza
American Thoracic Society Annual Meeting; San Diego CA, USA, 18–23 May	KANTA SUBBARAO: A tickle at the back of your throat? The role of the soft palate in airborne transmission of influenza virus.
Annual Meeting of the Japanese Association for Infectious Diseases and the 66th Annual Meeting of the Japanese Society of Chemotherapy; Okayama City, Japan, 29 May – 6 June	KANTA SUBBARAO: Influenza vaccines and therapeutics
16th PHAA National Immunisation Conference; Adelaide, 5–7 June	HEIDI PECK: Cell-based human influenza vaccines may provide greater protection against A/H3N2 influenza viruses. OLIVIA PRICE: Assessing the effect of swabbing practices on estimates of influenza vaccine effectiveness. SHEENA SULLIVAN: Annual influenza vaccine effectiveness and antigenic distance: consequences of related vaccination. XIMENA TOLOSA: Reliability of interim estimates of influenza vaccine effectiveness, 2012-2017.
Negative Strand Viruses; Verona, Italy, 18–22 June	KANTA SUBBARAO: Heads win! Head-specific B cells and antibody dominate the immune response in a mismatched prime-boost vaccine strategy. PATRICK READING: Defining host restriction factors that modulate respiratory virus entry and exit from infected cells.
Melbourne Health Research Week; Melbourne, 21–28 June	KANTA SUBBARAO: What's new about the 2018 influenza vaccines, and who should get one?
I-MOVE; Veyrier du Lac, France, 25–29 June	SHEENA SULLIVAN: Does repeated influenza vaccination constrain the immune response?
12th Biregional Meeting of National Influenza Centres and Influenza Surveillance in the Western Pacific and South-East Asia Regions; Kathmandu, Nepal, 10–12 July	IAN BARR: Influenza activity in the Southern Hemisphere in 2018. NAOMI KOMADINA: How genetic sequence data informs us on influenza.
University of Canberra; Canberra, 13 July	KANTA SUBBARAO: What's new about the 2018 influenza vaccines, and who should get one?

ORAL PRESENTATIONS (continued)

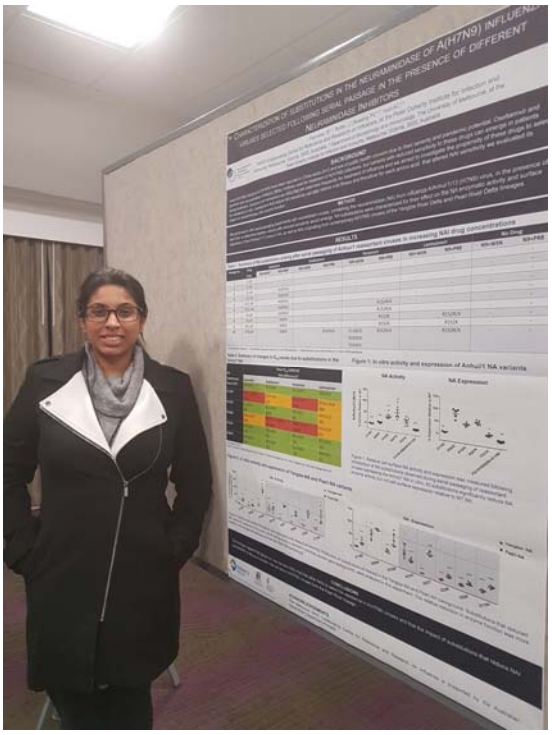
Event/Institute; Location, date	SPEAKER, Title(s)
West Gippsland Hospital; Warragul, Vic, 27 July	KANTA SUBBARAO: What's new about the 2018 influenza vaccines, and who should get one?
University of Melbourne Three Minute Thesis Competition (3MT); Melbourne, 31 July	RUBAIYEA FARRUKEE: Avian flu: the road to resistance.
Doherty Institute Public Health Night; Melbourne, 1 August	KANTA SUBBARAO: What's new with influenza vaccines in 2018?
University of Melbourne 1st year undergraduate subject "Our Planet, Our Health"; Melbourne, 6 August	MICHELLE WILLE: Influenza A viruses at the animal-human interface.
Training workshop to strengthen influenza-like illness (ILI) and severe acute respiratory infections (SARI) surveillance; Suva, Fiji, 6–10 August	PATRICK READING: Global influenza situation; Influenza vaccines; GISRS and reference laboratories servicing the Pacific Islands; Influenza tests in Pacific Island Countries and Territories; Sample collection, transport and testing.
Workshop: Optimization of animal models to better predict influenza vaccine efficacy; Rockville MD, USA,7–8 August	KANTA SUBBARAO: Animal models for evaluation of influenza vaccines and biologicals.
7th Meeting of the WHO Working Group on Surveillance of Antiviral Susceptibility of Influenza Viruses for GISRS; St Petersburg, Russia, 23–24 August	AERON HURT: Overview of global seasonal influenza NAI susceptibility.; Overview of resistance to baloxavir marboxil observed in clinical trials.
8th Orthomyxovirus Research Conference; Hanoi, Vietnam, 12–14 September	EDIN MIFSUD: Two is better than one: oseltamivir and nitazoxanide combination therapy. MICHELLE WILLE: Serological analysis of migratory shorebirds to assess exposure risk and incursions of highly pathogenic avian influenza into Australia.; Influenza A virus infection in wildlife birds is indicative of RNA virus diversity.
Centenary of the 1918 Pandemic: Advances in Diagnosis and Control of Influenza and Respiratory Viruses Symposium; Sydney, 14 September	IAN BARR: Lessons learnt from national and international surveillance for seasonal and pandemic influenza.
RNA viruses at the host interface – novel aspects of viral replication, antiviral immunity, and mechanisms of tissue damage and repair; Marburg, Germany, 19–21 September	KANTA SUBBARAO: Seasonal and pandemic influenza.
UCLA Department of Epidemiology Seminar Series; Los Angeles CA, USA, 1 October	SHEENA SULLIVAN: Trouble with flu vaccines.
Workshop to Strengthen Influenza-like Illness & Severe Acute Respiratory Infections (SARI) Surveillance in Solomon Islands; Honiara, Solomon Islands, 2–4 October	PATRICK READING: Global influenza situation; Influenza vaccines; Laboratory testing to detect influenza virus in clinical specimens.
ID Week; San Francisco, 3–7 October 2018	AERON HURT: New players in influenza antivirals: new mechanisms of action and resistance. KANTA SUBBARAO: Emerging novel influenza viruses with pandemic potential.
35th NRL Workshop on Infectious Diseases; Melbourne, 17–18 October 2018	KANTA SUBBARAO: What's new about influenza viruses and who should get one.

ORAL PRESENTATIONS (continued)

Event/Institute; Location, date	SPEAKER, Title(s)
VIIN Young Investigator Symposium; Melbourne, 18 October	RUBAIYEA FARRUKEE: Assessing the replication, transmission and fitness of antiviral resistant influenza B viruses.
Presentation at the Lyceum Club; Melbourne, 22 October	KANTA SUBBARAO: 1918 to 2018: a hundred years of influenza pandemics.
The Annual Scientific Meeting of the Australasian Epidemiological Association; Fremantle, WA, 22–24 October	SHEENA SULLIVAN: Appropriate use of the test-negative design for administrative data.
WHO Meeting of final review of the RSV surveillance pilot based on the Global Influenza Surveillance and Response System; Bangkok, Thailand, 23–25 October	ANGELA TODD: Roles and expectations of RSV reference laboratories. IAN BARR: Role of RSV reference laboratories with regards to EQAP.
National Avian Influenza in Wildbirds Meeting; Melbourne, 23–24 October	MICHELLE WILLE: Serological analysis of migratory shorebirds to assess exposure risk and incursions of highly pathogenic avian influenza into Australia.
Doherty Institute Respiratory Research Seminar; Melbourne, 29 October	ANNETTE FOX: Effects of repeated vaccination on antibody responses to influenza A/H3N2 virus.
Asian-Pacific Centenary Spanish 1918-Flu Symposium; Shenzhen, China, 1–2 November	IAN BARR: Pandemics and epidemics in Australia.
9th TEPHINET Bi-Regional Scientific Conference; Vientiane, Lao PDR, 5–9 November	XIMENA TOLOSA: Establishing basic public health capacity in the context of a large-scale acute refugee crisis.
100 Years Since The 1918 Spanish Influenza: are we prepared against the next emerging pathogen pandemic?; Santiago, Chile, 12 November	KANTA SUBBARAO: Assessment of pandemic potential of novel influenza viruses.
XXIV Latin American Congress of Microbiology; Santiago, Chile, 13–16 November	KANTA SUBBARAO: Pandemic influenza vaccines.
6th ISIRV-AVG Conference: Advances in Respiratory Virus Therapeutics; Washington DC, USA, 13–15 November	AERON HURT: Antiviral resistance monitoring strategies. RUBAIYEA FARRUKEE: Oseltamivir resistance: correlating *in vitro* IC_{50} with *in vivo* clinical effectiveness using a ferret model. (*Recipient of an ArkBiosciences award*)
Infectious Diseases: Past, Present, Future; Heidelberg, Germany, 15–16 November	KANTA SUBBARAO: 1918 to 2018: A hundred years of flu pandemics.
NHMRC "Limiting the Impact of Influenza" Program retreat; Melbourne, 10–11 December	ANNETTE FOX: Effects of influenza exposure history on influenza vaccine antibody responses. RUBAIYEA FARRUKEE: Oseltamivir resistance: Correlating *in vitro* IC_{50} with *in vivo* clinical effectiveness using a ferret model. PAULINA KOSZALKA: Influenza polymerase inhibitors: efficacy and resistance.
10th HKU Pasteur Immunology Course, Anniversary Symposium; Hong Kong SAR, 14 December	KANTA SUBBARAO: Broad protection against influenza viruses by active and passive immunization.

POSTER PRESENTATIONS

Event; Location, date	Title and authors *(Centre authors are marked in bold, presenting author is underlined)*
7th Australasian Vaccines & Immunotherapeutics Development Meeting; Melbourne, 16–18 May	Neuraminidase inhibiting antibody responses to the A(H3N2) component of influenza vaccine are attenuated in highly vaccinated health care workers. **Carolan L**, **Leung V**, **Aban M**, **Laurie K**, Marshall C, **Fox A** and **Sullivan S** Investigating cytokine molecular adjuvants for DNA vaccines against influenza in the ferret model. **Lee L**, **Izzard L**, McDonnell A, Piedrafita D, Yeo L and **Hurt A**
Doherty Institute Research Day; Melbourne, 20 September	Combination therapy of nitazoxanide and oseltamivir reduces the impact of influenza virus infection in ferrets. **Oh DY**, **Tai CM**, **Tilmanis D**, **Mifsud EJ**, Rossignol JF and **Hurt AC** Neuraminidase inhibiting antibody responses to the A(H3N2) component of influenza vaccine are attenuated in highly vaccinated health care workers. **Carolan L**, **Leung V**, **Aban M**, **Laurie L**, Marshall C, **Fox A** and **Sullivan S**
9th TEPHINET Bi-Regional Scientific Conference; Vientiane, Lao PDR, 5–9 November	Burden of influenza-associated hospitalisations, Cambodia, 2016. **Tolosa MX**, Ieng V, Thyl M, Dara C, Moniborin M, Sar B, Seng H, Ly S, Stewart RJ, Dueger EL and **Sullivan S**
6th ISIRV-AVG Conference: Advances in Respiratory Virus Therapeutics; Washington DC, USA, 13–15 November	Combination therapy of nitazoxanide and oseltamivir reduces the impact of influenza virus infection in ferrets. **Mifsud EJ**, **Tilmanis D**, **Oh DY** , **Tai CM**, Rossignol JF and **Hurt AC** Combination therapy of a second generation thiazolide and oseltamivir reduces viral burden and clinical signs in mice. **Mifsud EJ**, Nuessing S, **Tilmanis D**, **Oh DY** , Hensen L, Mercuri F, **Tai CM**, Rossignol JF, Kedzierska K and **Hurt AC** Characterisation of substitutions in the neuraminidase of A(H7N9) influenza viruses selected following serial passage in the presence of different neuraminidase inhibitors. **Farrukee R**, **Butler J**, **Reading PC** and **Hurt AC**
Third Regional Forum of WHO Collaborating Centres in the Western Pacific; Ho Chi Minh City, Vietnam, 22–23 November	WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia.



Rubaiyea Farrukee at the 6th ISIRV-AVG Conference: Advances in Respiratory Virus Therapeutics

Engagement in WHO Activities

Event; Location, Date	Centre staff involved
WHO's Global Outbreak Alert and Response Network (GOARN) and Bangladesh Ministry of Health and Family Welfare (MHFW): Diphtheria outbreak in Cox's Bazar Mission; Cox's Bazar, 10 January – 6 February	Ximena Tolosa participated in the mission which was co-ordinated in response to a complex large-scale humanitarian emergency involving the displaced Rohingya population.
WHO Consultation on the Composition of Influenza Vaccines for the northern hemisphere 2018–2019; Geneva, Switzerland, 19–21 February	Kanta Subbarao and Ian Barr participated, Aeron Hurt attended.
Special Advisory Group of Experts (SAGE) for Influenza; Reykjavik, 5–6 July	Sheena Sullivan participated.
12th Biregional Meeting of National Influenza Centres and Influenza Surveillance in the Western Pacific and South-East Asia Regions; Kathmandu, Nepal, 10–12 July	Patrick Reading, Yi-Mo Deng and Naomi Komadina attended. Ian Barr was a session facilitator and chaired a roundtable discussion.
WHO Working Group Meeting for the Molecular Detection and Subtyping of Influenza Viruses and the use of Next Generation Sequencing (NGS) in GISRS; St Petersburg, Russia, 21–22 August	Yi-Mo Deng attended.
7th Meeting of the WHO Working Group on Surveillance of Antiviral Susceptibility of Influenza Viruses for GISRS; St Petersburg, Russia, 23–24 August	Aeron Hurt was meeting chair.
WHO Consultation on the Composition of Influenza Vaccines for the southern hemisphere 2019; Atlanta GA, USA, 24–28 September	Ian Barr and Kanta Subbarao participated. Sheena Sullivan presented the Global Influenza Vaccine Effectiveness report.
WHO Meeting of final review of the RSV surveillance pilot based on the Global Influenza Surveillance and Response System; Bangkok, Thailand, 23–25 October	Angela Todd and Ian Barr attended.
Third Regional Forum of WHO Collaborating Centres in the Western Pacific; Ho Chi Minh City, Vietnam, 22–23 November	Ian Barr attended.

Centre staff in attendance at the 12th Biregional Meeting of National Influenza Centres and Influenza Surveillance in the Western Pacific and South-East Asia Regions. Photos courtesy of SEARO.

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
Influenza Specialist Group Annual Scientific Meeting; Melbourne, 4–5 February	Sheena Sullivan attended.
ISIRV 4th International Neglected Influenza Viruses Symposium; Brighton, UK, 18–20 April	Annika Suttie attended.
BioMedVic Communications Professionals Forum; Melbourne, 24 April	Michelle Chow attended.
7th Australasian Vaccines & Immunotherapeutics Development Meeting; Melbourne, 16–18 May	Ian Barr was part of the organising committee.
CEIRS meeting; Memphis TN, USA, 4–6 June	Ian Barr attended.
GI-CoRE; Sapporo, Japan, 17–20 July	Edin Mifsud attended.
National Avian Influenza in Wildbirds Meeting; Melbourne, 23–24 October	Aeron Hurt attended.
NHMRC "Limiting the Impact of Influenza" Program retreat; Melbourne, 10–11 December	Aeron Hurt, Edin Mifsud, Ian Barr, Kanta Subbarao, Naomi Komadina, Sheena Sullivan and Patrick Reading attended.

Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2018.

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 Judes Children's Research Hospital, Scientific Advisory Committee
Doherty Institute, Shared PC3 Laboratory Advisory Committee, Member
Doherty Institute Operational Management Committee, Member
Influenza Research and Treatment, Editorial Board
Influenza and other respiratory viruses, Editorial Board
Public Health Laboratory Network (Department of Health)

Michelle Chow
Doherty Institute Communications Working Group, Member

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

Chris Durrant
Victorian Infectious Diseases Reference Laboratory, Safety Committee

Committees and Advisory Groups (continued)

Aeron Hurt
Antiviral Research, Editorial Board
Avian Influenza in Wild Birds, Australian Wildlife Health Network, Steering Committee
Doherty Institute Safety Committee, Member
Frontiers in Microbiology, Associate editor
Infection, Ecology and Epidemiology – The One Health Journal, Editorial Advisory Board
Influenza Specialist Group, Scientific Committee
International Society for Influenza and other Respiratory Virus Diseases, Board of Trustees
Neuraminidase Inhibitor Susceptibility Network Meeting/Committee of Antiviral Special Interest Group of the International Society for Influenza and other Respiratory Virus Diseases, Committee member
Victorian Infection and Immunity Network, Executive Committee member
WHO Working Group for influenza antiviral resistance, Committee member

Matthew Kaye
Doherty Institute, Shared PC3 Laboratory Advisory Committee
Victorian Infectious Diseases Reference Laboratory, Chemical Safety Officer
Victorian Infectious Diseases Reference Laboratory Safety Committee, Member

Naomi Komadina
Global Initiative on Sharing All Influenza Data (GISAID), GISAID Database Technical Committee (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
FLUCOP consortium, External Advisory Board,
Gates Center for Structure Guided Design of Next Generation Vaccine Immunogens at The Scripps Research Institute, La Jolla, CA, USA. Scientific Advisory Board
PLoS Pathogens, Associate Editor
mBio, Editorial board

Sheena Sullivan
National Influenza Surveillance Committee (Department of Health), Observer
Doherty Institute, Equity and Diversity in Science Committee, Member
Australasian Epidemiology Association, Secretary
WHO SAGE Working Group on Influenza Vaccines, Member

Angela Todd
Victorian Infectious Diseases Reference Laboratory, Safety Committee, Member

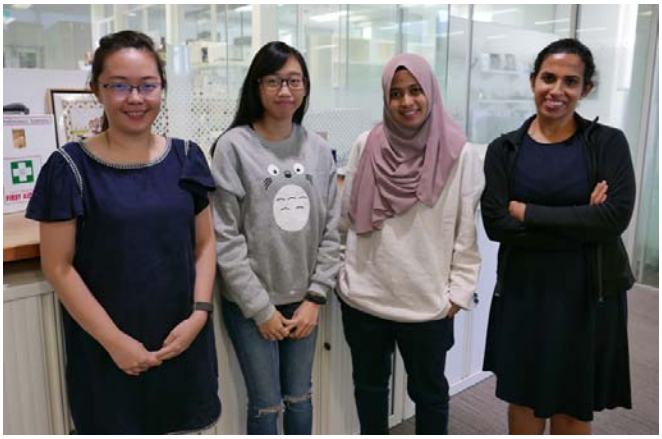
Visitors to the Centre

The Centre was pleased to host the following visitors during 2018.

Date	VISITOR and affiliation
8 February	PROF MALIK PEIRIS; The University of Hong Kong, Hong Kong SAR, China; Visiting scientist, Part of Doherty Institute Scientific Advisory Board
8 February	PROF FRANÇOISE BARRÉ-SINOUSSI; Institut Pasteur, Paris, France; Visiting scientist, Part of Doherty Institute Scientific Advisory Board
5–9 March	DELEGATION FROM TAN TOCK SENG HOSPITAL (DR SAPNA SADARANGANI, MS RACHEL LIM, MS CHERYL CHUAH, MS YAZID NURHIDAYAH); Tan Tock Seng Hospital, Singapore; Collaborator, Performing HI assays and serological analyses
13 March	PROF ARNOLD MONTO; University of Michigan, Ann Arbor, MI, USA; Visiting scientist
19 April	DR NITEEN WAIRAGKAR; Global Health Program, Bill and Melinda Gates Foundation, Seattle WA, USA; Visiting scientist
19 April	DR ANNE VON GOTTENBURG; National Institute for Communicable Diseases, Johannesburg, South Africa; Visiting scientist
23 April	DR JEAN-FRANCOIS ROSSIGNOL; Romark Laboratories, Tampa FL, USA; Collaborator
23-24 April	DR CHRIS GULLY AND DR AVISHEK NANDI; Seqirus, Holly Springs NC, USA; Collaborator
18–19 June	DR UMA KAMARAJ; Duke-NUS University, Singapore; Collaborator
9 August	DR MATTHEW SCOTCH; The Biodesign Institute, Arizona State University, Tempe AZ, USA; Visiting scientist.
14 August	PROF MARK LIPSITCH; Harvard University, Cambridge MA, USA; Visiting scientist.
16–17 August	A/PROF ADAM KUCHARSKI; London School of Hygiene and Tropical Medicine, London, UK; Visiting scientist.

L to R: Kanta Subbarao, Annette Fox, Ian Barr, Aeron Hurt, Arnold Monto (University of Michigan), Sheena Sullivan

Mark Lipsitch (right, Harvard University), with Sheena Sullivan



L to R: Rachel Lim, Cheryl Chuah, Yazid Nurhidayah, Sapna Sadarangani (Delegation from Tan Tock Seng Hospital, Singapore)

Community Engagement

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

Kanta Subbarao

- participated in an interview on ABC Drive with Steve Martin, published 11 January 2018
- participated in an interview for the Nature Microbiology Community online channel on the Centenary of the 1918 influenza pandemic, published 15 January 2018; https://naturemicrobiologycommunity.nature.com/channels/1469-centenary-of-1918-influenza-pandemic/posts/29277-snapshot-kanta-subbarao
- participated in an interview with BBC Radio 4, published 15 January 2018
- participated in an interview with The Smithsonian Magazine for the article "The pandemic everyone fears is flu in the wrong place at the wrong time", published 30 January 2018; https://www.smithsonianmag.com/innovation/pandemic-everyone-fears-is-flu-in-wrong-place-at-wrong-time-180967984
- publication quoted in the Helio article "Flu exposure may reduce vaccine effectiveness for some", published 3 February 2018; https://www.healio.com/infectious-disease/influenza/news/in-the-journals/%7Bb4287e94-a6b3-49d7-ab33-2e8c518245c1%7D/flu-exposure-may-reduce-vaccine-effectiveness-for-some
- participated in an interview with the ABC Radio National program Health Report for the segment "The Spanish flu: Understanding a devastating pandemic", published 9 April 2018; http://www.abc.net.au/radionational/programs/healthreport/the-spanish-flu-understanding-a-devastating-pandemic/9632956
- participated in an interview with ABC News for the article "Touching, talking, or sneezing: How the flu virus is transmitted between people", published 10 April 2018; http://www.abc.net.au/news/health/2018-04-10/how-flu-is-transmitted-people/9633660
- participated in an interview with ABC News for the article "Your flu questions answered: Face masks, garlic remedies and pet health", published 12 April 2018; http://www.abc.net.au/news/health/2018-04-12/flu-influenza-questions-answered-remedies-face-masks-pet-health/9641796
- wrote an article "Explainer: what?s new about the 2018 flu vaccines, and who should get one?" for The Conversation, published 18 April 2018; http://theconversation.com/explainer-whats-new-about-the-2018-flu-vaccines-and-who-should-get-one-94514
- participated in an interview for the Good Weekend magazine article "A century after the Spanish flu, are we ready for another pandemic?", published 21 April 2018; https://www.smh.com.au/national/a-century-after-the-spanish-flu-are-we-ready-for-another-pandemic-20180417-p4za2u.html
- participated in a podcast about influenza on the Better Health Channel (Victorian Government), published August 2018; https://www.betterhealth.vic.gov.au/health/podcasts/influenza
- participated in an interview with MJA InSight for the article "Under the microscope: enhanced flu vax for elders", published 16 July 2018; https://www.doctorportal.com.au/mjainsight/2018/27/enhanced-flu-vaccines-for-elders-under-the-microscope/
- participated in an interview with AARP for the article "What Australia's flu season tells us about our own", published 14 August 2018; https://www.aarp.org/health/conditions-treatments/info-2018/australia-flu-season-predictions.html
- participated in the panel discussion for “This is Not a Drill: A Hypothetical Pandemic”, held on 6 September 2018; https://www.wheelercentre.com/events/this-is-not-a-drill-a-hypothetical-pandemic;
- participated in an interview with Stuff.co.nz for the article "Flu pandemic that killed thousands of New Zealanders could happen again", published 14 October 2018; https://www.stuff.co.nz/national/107573793/Flu-pandemic-that-killed-thousands-of-New-Zealanders-could-happen-again

Ian Barr

- participated in an interview with New Scientist for the article "Jab in the dark: Why we don't have a universal flu vaccine", published 2 January 2018 https://www.newscientist.com/article/2156915-jab-in-the-dark-why-we-don't-have-a-universal-flu-vaccine/
- participated in an interview with CNN for the article "'Australian flu': It's not from Australia", published 3 February 2018 https://edition.cnn.com/2018/02/02/health/australian-flu-became-global/index.html
- participated in an interview with The Herald Sun for the article "Free turbocharged flu jab for three million older Australians", published 18 February 2018 http://www.heraldsun.com.au/news/free-turbocharged-flu-jab-for-three-million-older-australians/news-story/4da5f6954ebe82611ca9e85d3e8137da?csp=fd87c6a4b08ec608d0b8e8e2d1575058
- participated in an interview with The Sydney Morning Herald for the article "New 'super vaccines' for flu season as docs hope to cut deaths", published 17 April 2018 https://www.smh.com.au/national/new-super-vaccines-for-flu-season-as-docs-hope-to-cut-deaths-20180417-p4za1v.html

Aeron Hurt

- participated in an interview with Bloomberg for the article "New drugs are coming to fight nasty flu seasons", published 9 February 2018 https://www.bloomberg.com/news/articles/2018-02-08/flu-relief-is-coming-as-successors-to-aging-tamiflu-near-market
- participated in an interview with The Age for the article "Victoria's horror flu statistics revealed as stronger vaccine on way", published 25 January 2018 http://www.theage.com.au/victoria/victoria-s-horror-flu-statistics-revealed-as-stronger-vaccine-on-way-20180125-p4yywa.html?csp=68ae10b71c762d83659898077a76d975
- participated in an interview with news.com.au for the article "Everything you need to know about the flu vaccine in 2018", published 17 May 2018 https://www.news.com.au/lifestyle/health/health-problems/everything-you-need-to-know-about-the-flu-vaccine-in-2018/news-story/fd84ed85629a006507c5b8184855b434

Sheena Sullivan

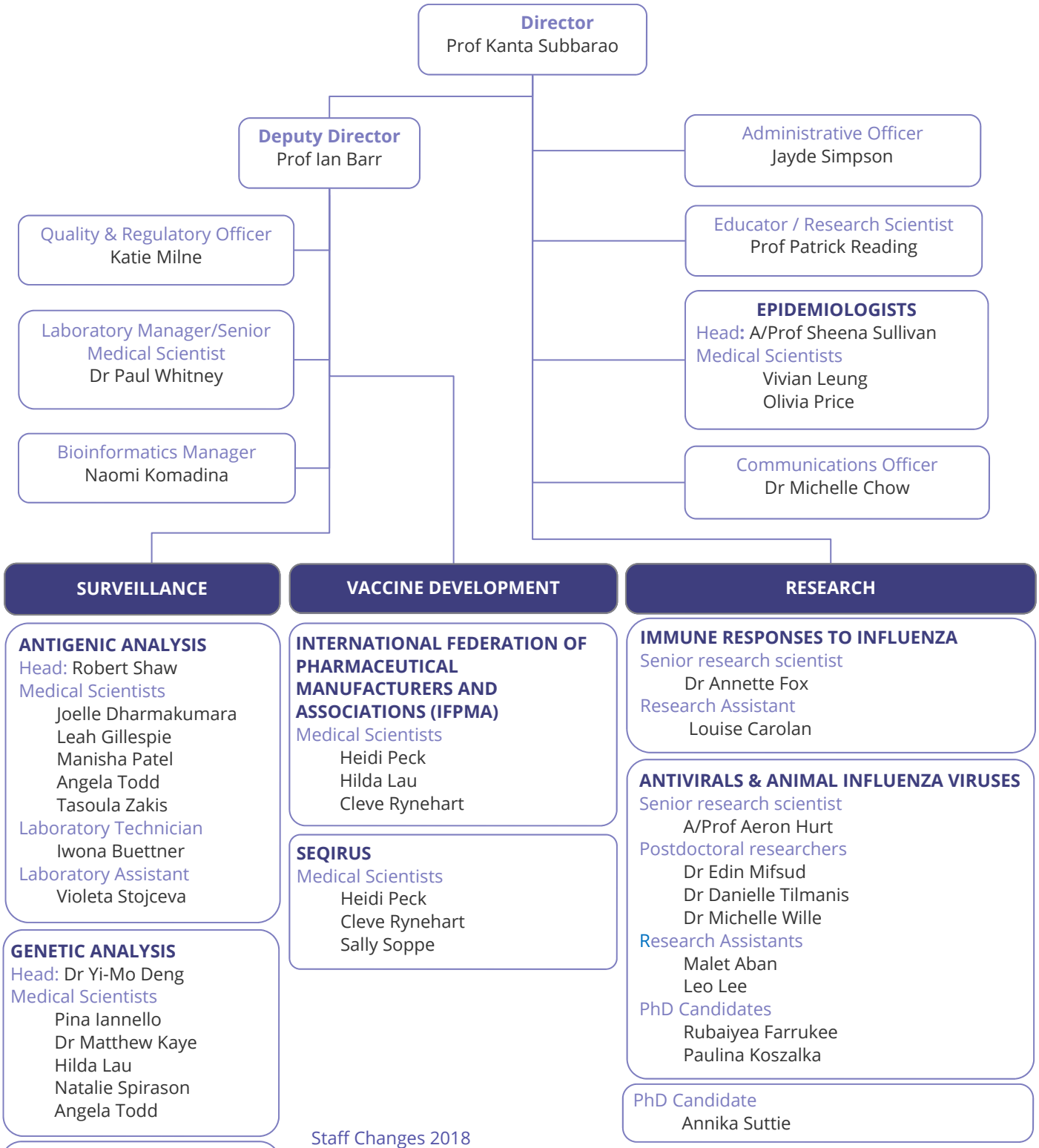
- participated in an interview with CNN for the article "'Australian flu': It's not from Australia ", published 3 February 2018; https://edition.cnn.com/2018/02/02/health/australian-flu-became-global/index.html
- presented an overview of influenza vaccines for the elderly to Soroptomist International, Perth, 22 October 2018.

Website and social media

The Centre website was maintained and updated throughout the year. During 2018, the website was viewed by 7,937 unique users from 143 different countries. The majority of visits to the website came from Australia, followed by the USA.

The Centre opened a Twitter account in August 2018. By the 31 December 2018, the Centre's Twitter profile had 113 followers.

Management and staff



Staff Changes 2018

Dr Annette Fox took up her position as senior research scientist in January.

Mr Leo Lee joined the Centre as a research assistant in January.

Ms Olivia Price joined the Epidemiology group in January.

Ms Violeta Stojceva joined the Center as laboratory assistant in June.

Ms Manisha Patel joined the Antigenic Analysis group as a scientist in June.

Dr Paul Whitney joined the Centre as laboratory manager and senior medical scientist in September.

Mr Chris Durrant retired from his position as laboratory manager in June after 51 years' continuous service at the Centre and its predecessor at the Commonwealth Serum Laboratories (CSL).