Annual Report 2017

WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL

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. In 2017 the Centre's funding was renewed by the Department of Health for the period 2017-2021.

Contact information

WHO Collaborating Centre for Reference and Research on Influenza (VIDRL)
Peter Doherty Institute for Infection and Immunity
792 Elizabeth Street, Melbourne, VIC 3000, Australia
Phone: +613 9342 9300 Fax: +613 9342 9329
Email: whoflu@influenzacentre.org
Website: http://www.influenzacentre.org

Highlights of 2017

25 years
since the Centre was first designated as a Collaborating Centre by WHO.

5867
samples were received and processed at the Centre.

The Centre hosted the **WHO Consultation on the Composition of Influenza Virus Vaccines** for use in the 2018 Southern Hemisphere Influenza Season. *(pictured above)*

The first fully cell-based vaccine component was produced by Seqirus and distributed during the 2017-18 Northern Hemisphere season using an A(H3N2) virus first isolated at the Centre.

17 scientists from **13 countries** participated in a workshop on Viral Isolation and Characterisation. *(pictured below)*

A virus received from Singapore and first **isolated as a candidate vaccine virus in eggs** at the Centre was included in the WHO recommended vaccine strains for the Southern Hemipshere in 2018.

23 papers
published in peer-reviewed journals.

Approximately **200 people** attended the **12th Australian Influenza Symposium.**

Director's report

It is a pleasure to present the 2017 Annual Report of the WHO Collaborating Centre for Reference and Research on Influenza. This year is the 25th anniversary of the Centre's designation as a WHO Collaborating Centre. In September, we hosted the WHO Consultation on the Composition of Influenza Virus Vaccines for use in the 2018 Southern hemisphere influenza season. 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.

The number of notifications in the 2017 influenza season in Australia was much higher than average in all jurisdictions except WA. The season began earlier than usual and there were many outbreaks in residential care facilities. The Centre received and processed over 5800 influenza samples from 40 laboratories in Australia and 13 other countries in the region during 2017. The largest proportion of the samples analysed were A(H3N2) viruses and there was considerable genetic diversification of the H3 HA gene. As we noted in the past few years, influenza A(H3N2) viruses are difficult to characterise in the laboratory. We normally rely on the haemagglutination inhibition (HI) assay for antigenic analysis of influenza viruses but this is not possible with a large proportion of A(H3N2) viruses. About 50% of the A(H3N2) viruses that we received could not be tested in HI assays because they did not yield sufficiently high haemagglutination titres to be tested even when oseltamivir carboxylate was added to circumvent neuraminidase-mediated agglutination or the viruses could not be recovered. Therefore, the Centre relies more heavily on the Focus Reduction Assay for detection of antigenic changes in A(H3N2) viruses.

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. With the increasing difficulty in isolating influenza A(H3N2) viruses and to support Vaccine Effectiveness studies analysing viral subpopulations, we have turned to genetic characterisation by NGS. In 2017, the Centre sequenced 109 full genomes and 1346 partial genomes (HA and NA genes plus M gene for influenza A viruses) by NGS.

In conjunction with the WHO Western Pacific Regional Office and with participation from the WHO Collaborating Centre in Japan, the Centre hosted a very successful virus isolation and characterisation workshop that was attended by 17 scientists from 13 countries. Centre staff presented at several domestic and international conferences in 2017.

The first fully cell-based vaccine component using an A(H3N2) virus first isolated at the Centre was produced by Seqirus and distributed during the 2017-18 Northern Hemisphere season. During 2017 the Centre provided an egg-isolated A(H3N2) virus for vaccine production as listed in the WHO approved Candidate Vaccine Viruses for the Southern Hemisphere 2018 and Northern Hemisphere 2017-8 seasons. 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 contributed to a total of 28 original research papers, reviews and reports in 2017 and hosted the Australian Influenza Symposium that was attended by more than 200 people. A wide range of topics were covered, including the evolution and spread of zoonotic influenza viruses, influenza vaccines, epidemiology, new and emerging technologies, diagnostics and treatments, developments in understanding influenza biology and the immune system response and a roundtable discussion on ways to reduce the impact of seasonal influenza epidemics in Australia. The Symposium was also followed by a special joint session on Respiratory Syncytial Virus (RSV) with the Australian Respiratory Virology Meeting.

We are very grateful to Dr Mike Catton, Director of VIDRL, and many other members of VIDRL staff, especially Dr Bill Maskill, Jane Brewster, Anna Ayres and Dallas Wilson, for their support of the Centre's work at every level during 2017. 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 2017. It is a privilege to work with the Centre staff and I look forward to working with our partners in 2018 and onwards.

Dr Kanta Subbarao
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.

Receipt of Influenza Viruses

During 2017 the Centre received 5867 clinical specimens and/or virus isolates from 40 laboratories in 14 countries (Figures 1 and 2, Table 1). This is the highest number of samples received in a year since the 2009 pandemic.

A total of 5655 samples (96.4%) 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, 14.2% were identified as A(H1N1)pdm09, 52.4% were A(H3N2) viruses, 4.5% were B/Victoria and 27.2% were B/Yamagata viruses (Table 2). A total of 1148 samples came from Australian general practictioner based surveillance systems (Table 3).

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.

Figure 1. Samples received by the Centre, 2013-2017

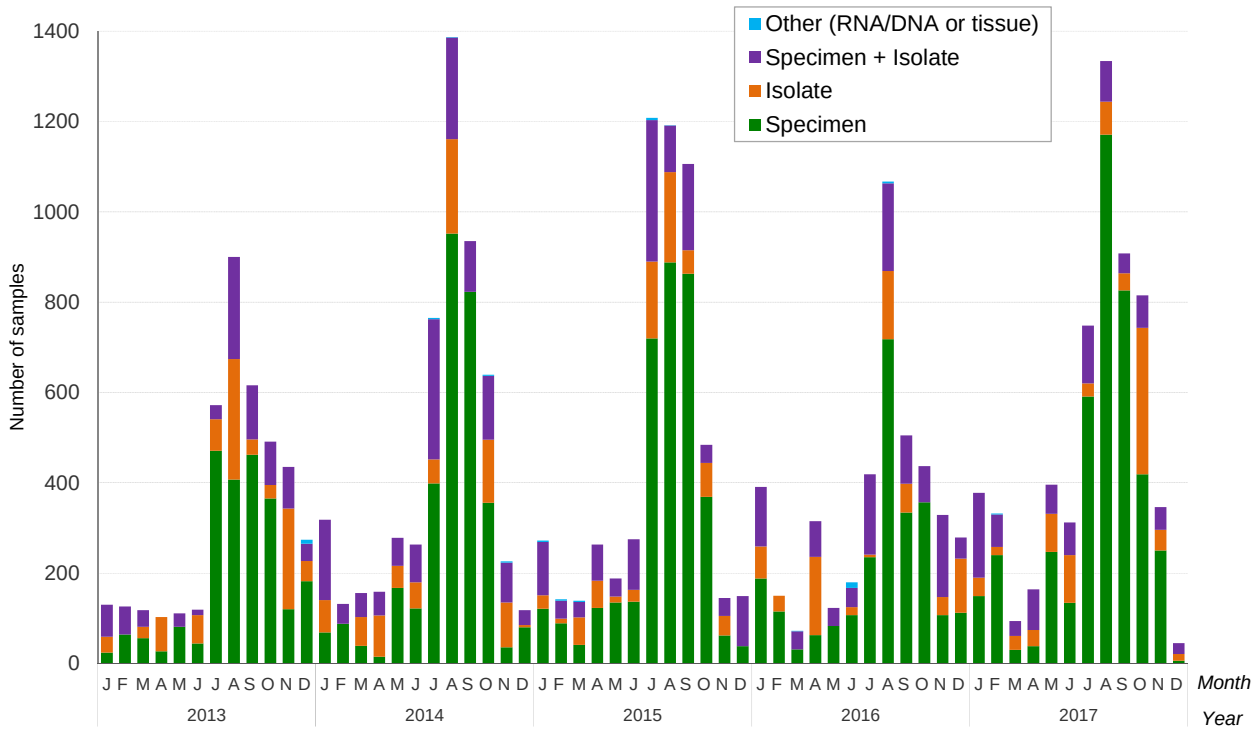


Figure 2. Geographic spread of influenza laboratories sending viruses to the Centre during 2017.

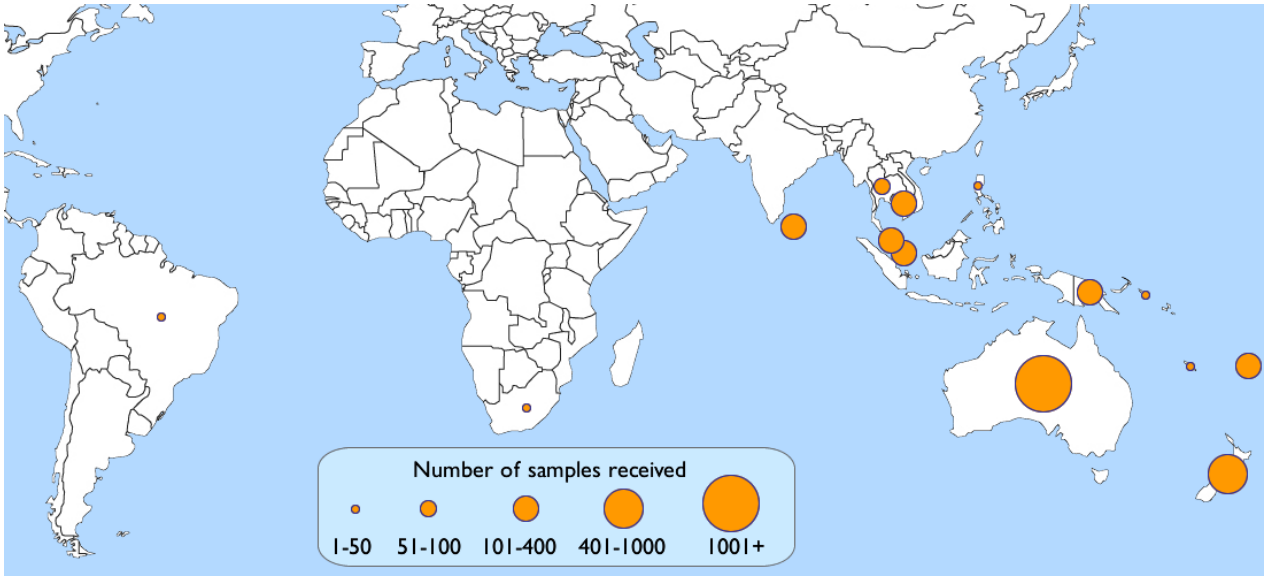


Table 1. Samples received by the Centre in 2017, by country.

Country	Samples received				% Samples tested
	Specimens	Isolates	Specimen + Isolate	Other (eg. RNA/ DNA/tissue)	
AUSTRALASIA					
Australia	3444	340	673	2	96%
New Zealand	120	288	44	0	100%
SOUTH PACIFIC					
Fiji	117	0	0	0	92%
New Caledonia	13	0	0	0	100%
Papua New Guinea	134	0	0	0	60%
Solomon Islands	10	0	0	0	100%
SOUTH EAST ASIA					
Cambodia	73	33	0	0	100%
Malaysia	0	116	9	0	100%
Philippines	19	0	31	0	100%
Singapore	0	0	158	0	100%
Thailand	10	59	0	0	100%
SOUTH ASIA					
Sri Lanka	128	0	0	0	66%
AFRICA					
South Africa	7	0	18	0	100%
SOUTH AMERICA					
Brazil	21	0	0	0	100%
TOTAL	**4096**	**836**	**933**	**2**	**93%**

Table 2. Samples successfully tested by cell culture and/or RT-PCR assay at the Centre in 2017, by country.

Country	Samples tested by HI and/or RT-PCR assay							
	A(H1N1)pdm09	A(H3N2)	A (unsubtyped)	B/Victoria	B/Yamagata	B lineage undetermined	Untyped	Mixed type
AUSTRALASIA								
Australia	415	2004	21	59	940	51	814	6
New Zealand	49	156	0	5	209	0	33	0
SOUTH PACIFIC								
Fiji	1	69	0	1	29	0	8	0
New Caledonia	0	3	0	2	8	0	0	0
Papua New Guinea	31	19	0	0	24	0	7	0
Solomon Islands	0	0	0	0	1	0	9	0
SOUTH EAST ASIA								
Cambodia	37	20	0	35	1	0	12	0
Malaysia	19	13	0	65	14	0	14	0
Philippines	9	12	0	5	8	0	16	0
Singapore	37	80	0	19	21	0	1	0
Thailand	15	23	0	15	11	0	5	0
SOUTH ASIA								
Sri Lanka	49	24	0	3	2	0	48	2
AFRICA								
South Africa	3	18	0	0	3	0	1	0
SOUTH AMERICA								
Brazil	0	7	0	0	2	0	12	0
TOTAL	**665**	**2448**	**21**	**209**	**1273**	**51**	**980**	**8**

Table 3. Samples received from general practitioner based surveillance systems in Australia, 2017

	No. samples received	No. isolates recovered*	Viruses analysed by HI assay
Australian Sentinel Practices Research Network *(ASPREN)*	898	226	134
Victorian Sentinel Practices Influenza Network *(VicSPIN)*	250	194	147

** 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.

Antigenic analyses 2017

A total of 5237 isolates that were received at the Centre in 2017 were cultured and isolated in MDCK cells, of which 3857 (73.6%) produced a positive result. The largest proportion of viruses were A(H3N2) (53.5%), followed by B/Yamagata lineage viruses (26.2%) (Figure 3). The relative proportions of different subtypes and lineages were similar throughout the different world regions for samples received and successfully analysed at the Centre (Figure 4). The exceptions to this were South East Asia and South Asia, where there were more B/Victoria lineage viruses than B/Yamagata lineage viruses.

Figure 3. Influenza sub/types and lineages of samples received in 2017 and characterised by antigenic analysis.

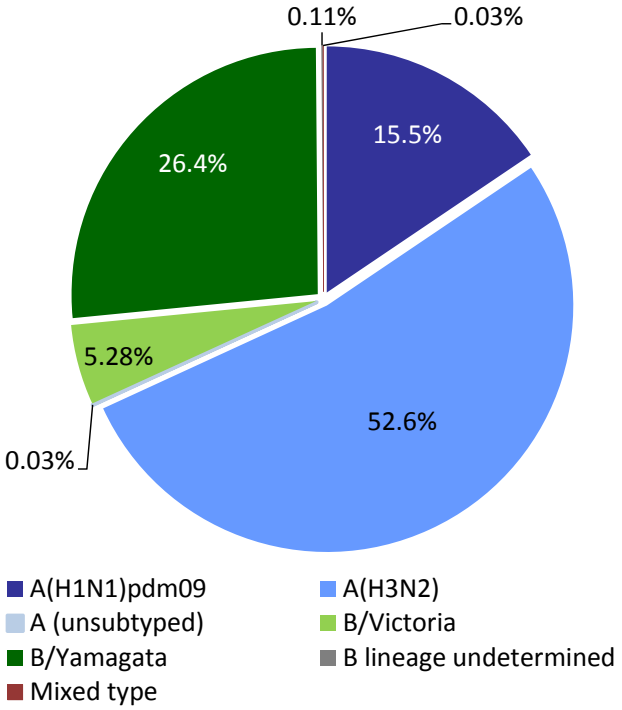
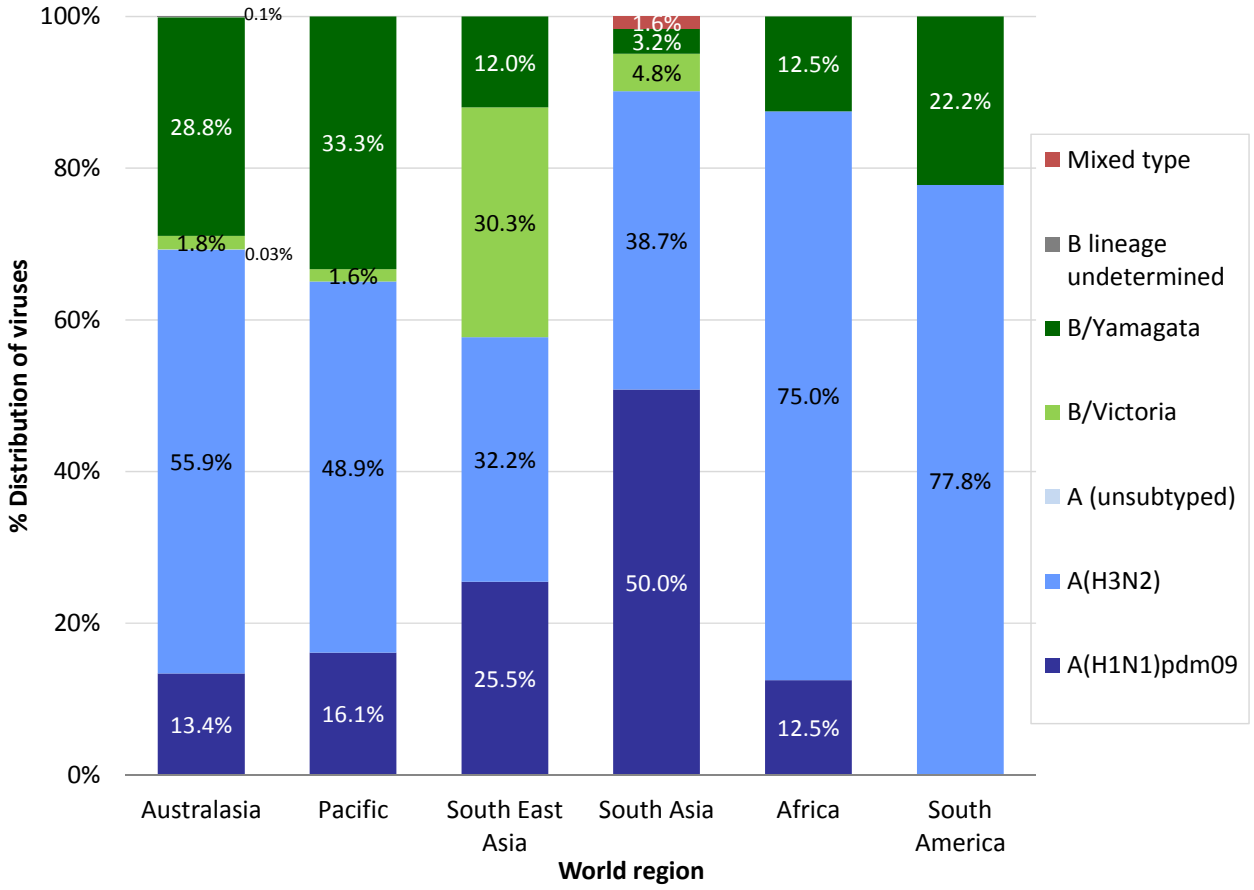


Figure 4. Influenza sub/types and lineages of isolates received from different world regions during 2017 as determined by antigenic analysis.



Genetic Analysis of Influenza Viruses

Background

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

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

Since the acquisition of an IonTorrent PGM™ system in 2014, 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 (Figures 6 and8).

Sequencing 2017

In 2017 502 HA, 363 NA, 198 MP and 94 NS genes from 502 human viruses received at the Centre were analysed by Sanger sequencing (Figure 5). In addition, the HA, NA and MP genes of 1271 influenza A and 75 influenza B (HA and NA only, 28 MP genes) viruses were sequenced by NGS techniques (Figures 5 and 6).

Full genome sequencing was performed on 109 viruses, using NGS techniques (Figures 7 and 8). Viruses were selected for these analyses because they were representative of the viruses received and/or because they displayed unusual properties during antigenic analysis. In 2017 for the first time all full genome sequencing was performed using NGS techniques (Figure 7).

Figure 5. Sanger and NGS sequence analysis of samples received at the Centre in 2017.

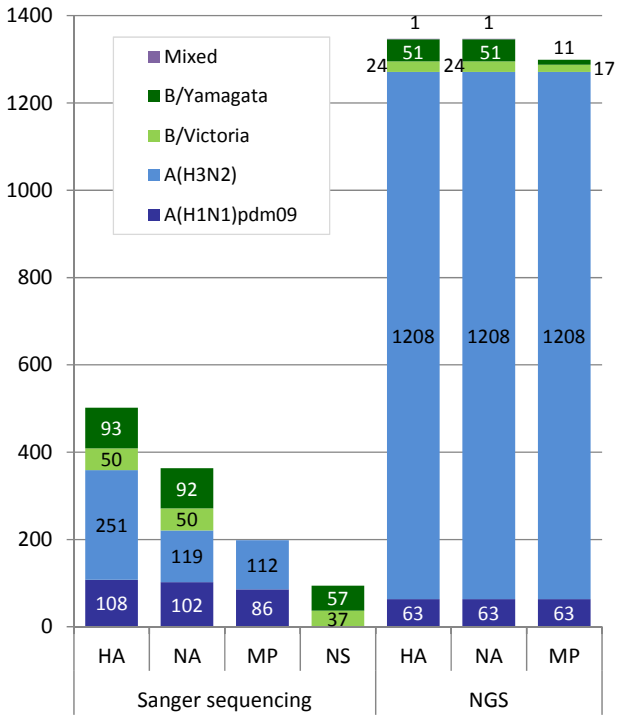


Figure 6. Geographic spread of submitting laboratories and numbers of viruses with HA, NA and MP (Influenza A only) genes sequenced using NGS at the Centre in 2017.

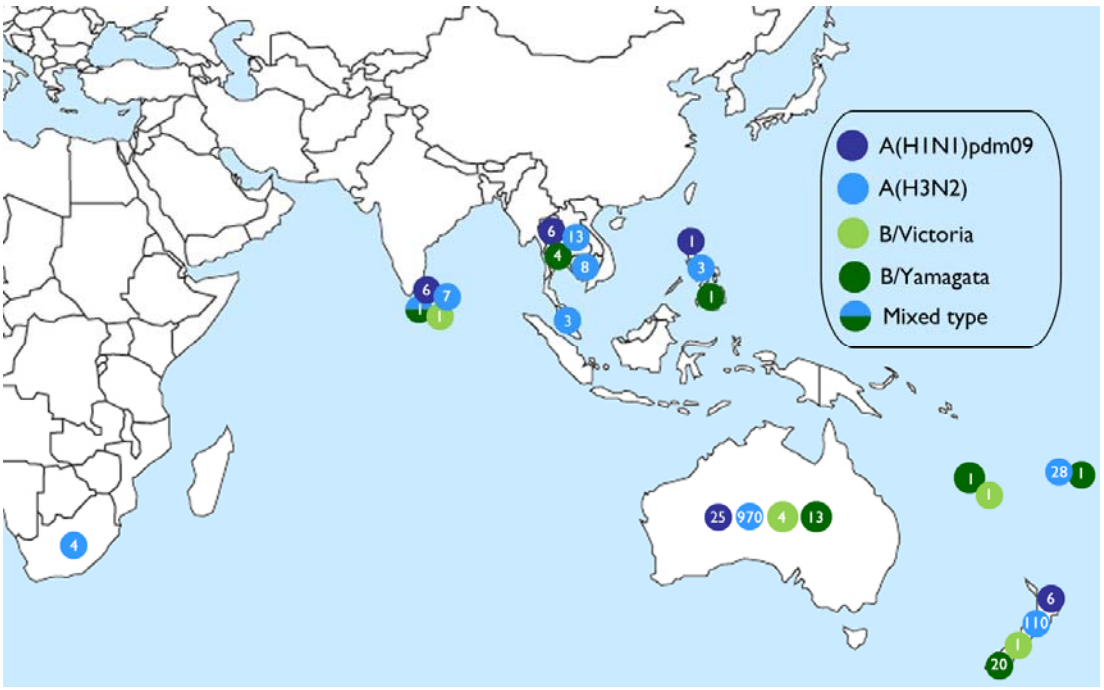


Figure 8. Number of viruses analysed by full genome sequencing 2010-2017 using Sanger sequencing and NGS techniques.

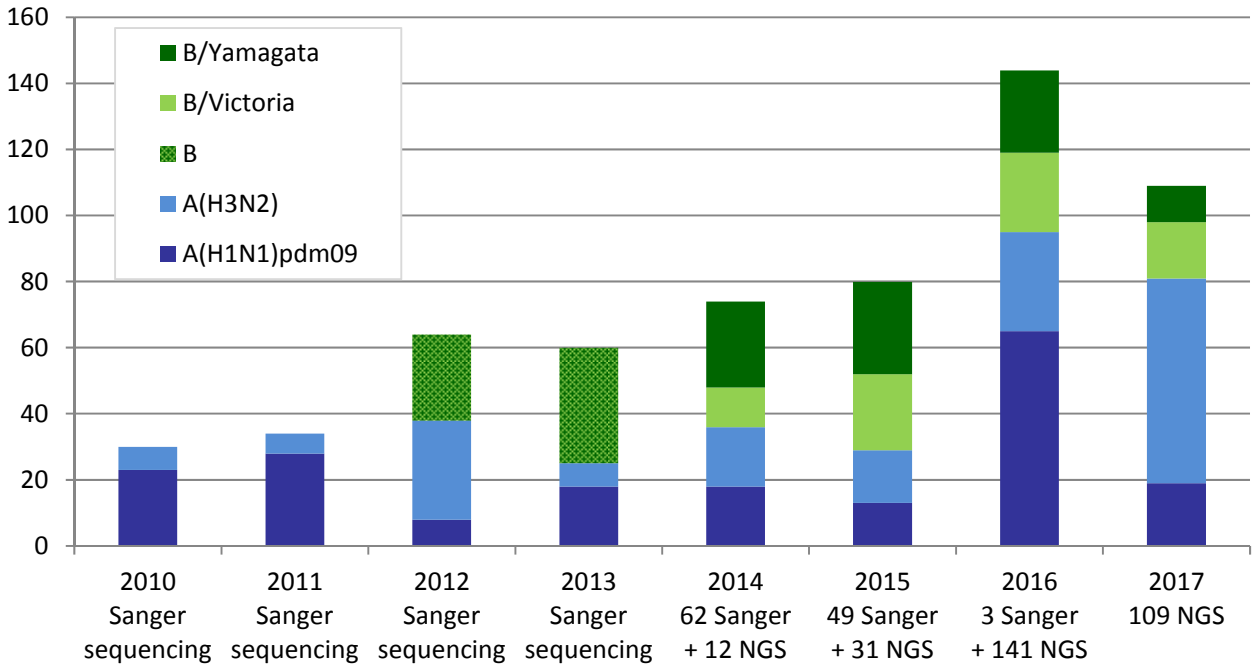
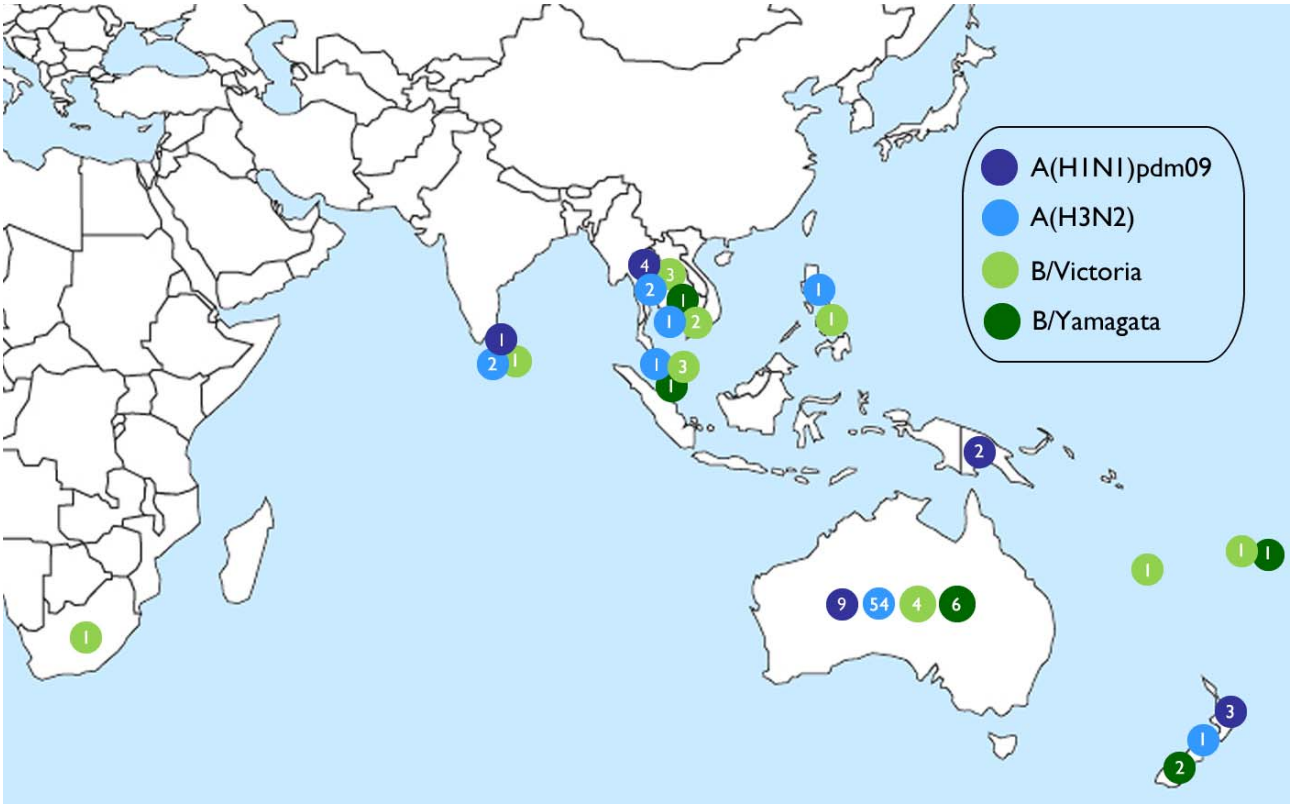


Figure 8. Geographic spread of submitting laboratories and numbers of viruses analysed by full genome sequencing using NGS techniques at the Centre in 2017.



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).

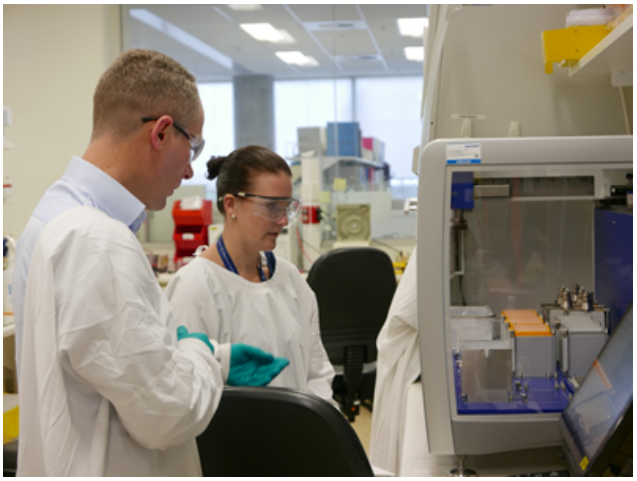
Sequences submitted in 2017

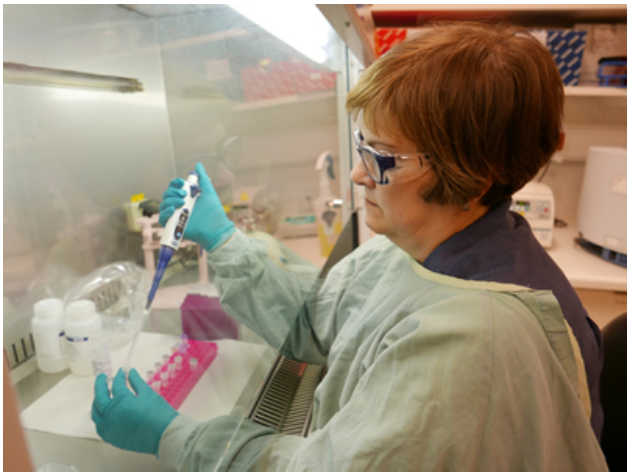
A total of 4877 gene sequences from 1590 viruses were deposited with GISAID in 2017 (Table 4). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 72 influenza viruses were also represented in the Centre's submissions (data not shown).

Table 4. Genetic sequences submitted to GISAID by the Centre in 2017.*

Gene / Type/ Subtype/	HA	NA	MP	NS	PB1	PB2	PA	NP	Total
A(H1N1)pdm09	174	170	138	39	37	32	38	39	**667**
A(H3N2)	1220	1153	1107	30	30	29	30	30	**3629**
B/Victoria	69	69	13	37	12	9	13	12	**234**
B/Yamagata	127	127	11	56	5	5	5	11	**347**
Total	**1590**	**1519**	**1269**	**162**	**84**	**75**	**86**	**92**	**4877**

** Counts include all sequences submitted to GISAID during 2017, which includes viruses received in previous years and viruses sequenced for research purposes.*





Surveillance Results by Influenza Subtype

Viruses were analysed by comparison with reference viruses recommended by WHO for the 2017 Southern Hemisphere and 2017-2018 Northern 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 555 A(H1N1)pdm09 isolates were analysed by HI assay in 2017. Almost all of these viruses (99.1%) displayed similar antigenic properties to the vaccine reference strain A/Michigan/45/2015 (Figure 9, Table 5).

Haemagglutinin gene sequencing

Sequencing was performed on a total of 171 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 9. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/Michigan/45/2015 reference virus.

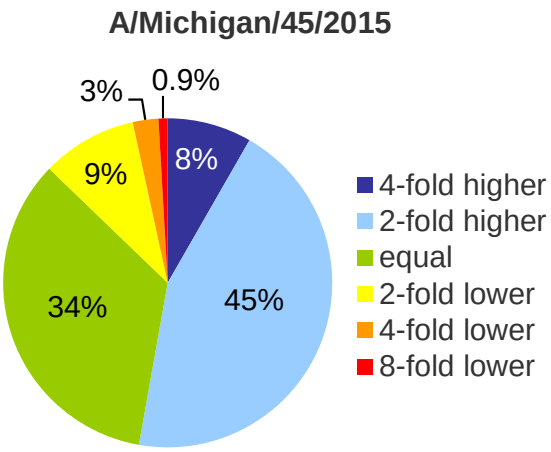


Table 5. Antigenic characterisation of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/Michigan/45/2015 reference virus.

A(H1N1)pdm09 reference strain: A/Michigan/45/2015		
Region	**Like**	**Low reactor (%)**
Australasia	396	2 (0.5%)
Pacific	30	0
South East Asia	114	3 (2.6%)
South Asia	7	0
Africa	3	0
South America	0	0
Total	**550**	**5 (0.9%)**

Figure 10. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2017.

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 Focus Reduction Assay (FRA), a form of virus neutralisation assay, are required to test the antigenic characteristics of these viruses. During 2017 FRAs were performed on a regular basis and continue to be integrated into the Centre's routine surveillance activities.

Of 933 A(H3N2) subtype isolates analysed by HI assay compared to the cell-grown reference strain A/Hong Kong/4801/2014 (Figure 11, Table 6), the majority were antigenically similar to the reference virus when using ferret antisera generated to cell grown A(H3N2) viruses. However, a non-negligible portion (almost 20%) of viruses were found to be low reactors to A/Hong Kong/4801/2014 - this proportion increased when ferret antisera to egg isolated viruses was used.

Haemagglutinin gene sequencing

A total of 1459 HA genes from A(H3N2) viruses were sequenced. Phylogenetic analysis indicate that most circulating viruses fell into clade 3C.2a, represented by the previous vaccine virus A/Hong Kong/4801/2014 or subclade 3C.2a1, represented by the new reference strain A/Singapore/INFIMH-16-0019/2016, which was recommended by WHO for inclusion in Southern Hemisphere vaccine in 2018 (Figure 12).

Figure 11. Summary of fold differences in HI titres of A(H3N2) viruses analysed at the Centre compared to the A/Hong Kong/4801/2014 reference virus.

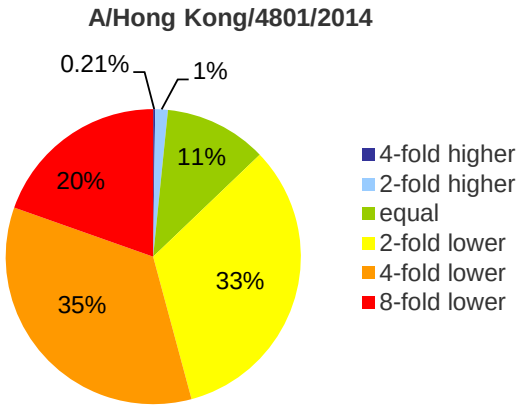
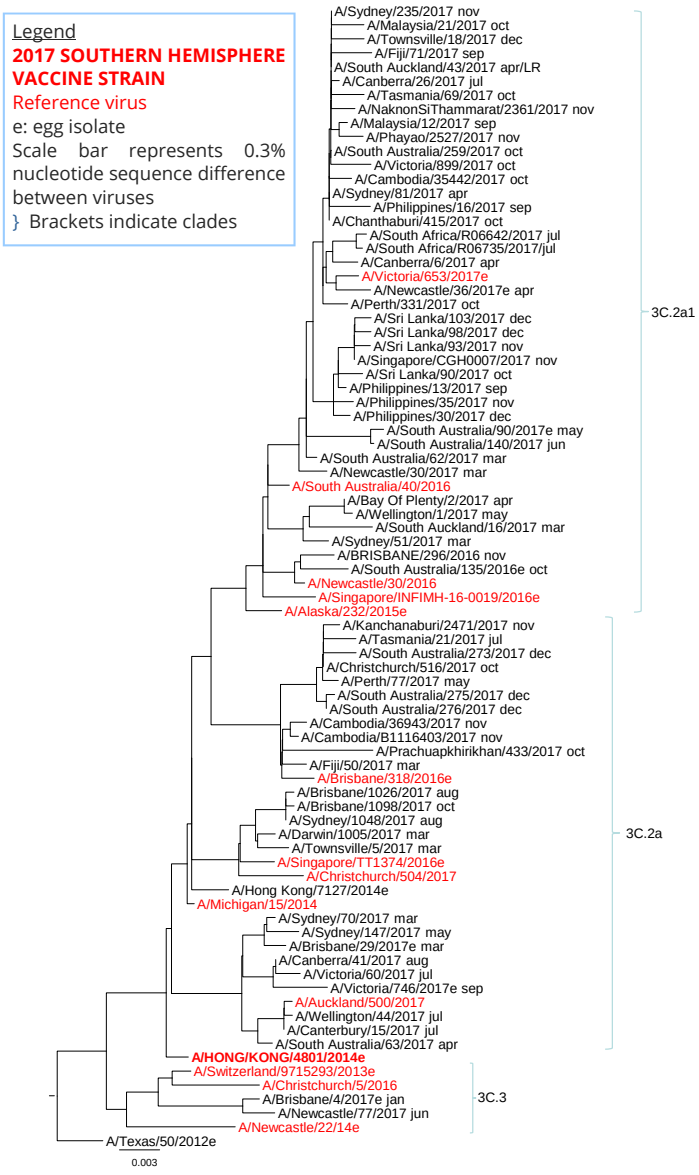


Table 6. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the A/Hong Kong/4801/2014 reference virus.

A(H3N2) reference strain: A/Hong Kong/4801/2014		
Region	**Like**	**Low reactor (%)**
Australasia	659	150 (18.5%)
Pacific	15	18 (54.5%)
South East Asia	57	12 (17.4%)
South Asia	7	0
Africa	10	2 (16.7%)
South America	3	0
Total	**751**	**182 (19.5%)**

Figure 12. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2017.



Influenza B

Antigenic analysis

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 2017 the Centre received many more B/Yamagata lineage viruses compared to B/Victoria lineage viruses. The vast majority of the 196 B/Victoria viruses that were analysed by HI assay were antigenically similar to B/Brisbane/60/2008 (Figure 13, Table 7). Similarly, all of the 1001 B/Yamagata viruses analysed by HI assay were antigenically similar to B/Phuket/3073/2013. (Figure 14, Table 7). With the growing predominance of the B/Yamagata lineage, the recommended vaccine strain for the 2018 Southern Hemipshere trivalent vaccine was changed to a B/Phuket/3073/2013– like virus.

Haemagglutinin gene sequencing

A total of 74 HA genes from B/Victoria and 144 B/Yamagata viruses were sequenced. All of the viruses of B/Victoria lineage belonged to the same genetic clade as the B/Brisbane/60/2008 reference virus (Figure 15). Almost all of the B/Yamagata lineage viruses belonged to the clade represented by B/Phuket/3073/2013 (Figure 16).

Figure 13. Summary of fold differences in HI titres of B/Victoria viruses analysed at the Centre compared to the B/Brisbane/60/2008 reference virus.

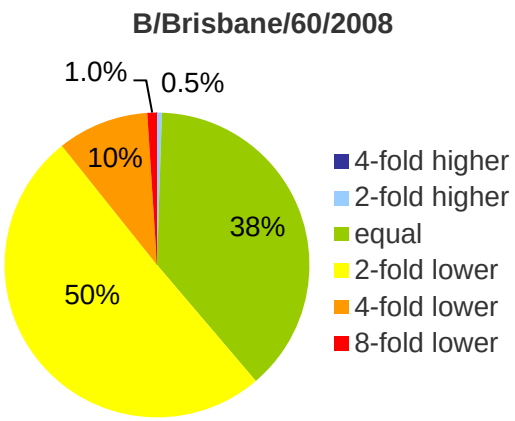


Figure 14. Summary of fold differences in HI titres of B/Yamagata viruses analysed at the Centre compared to the B/Phuket/3073/2013 reference virus.

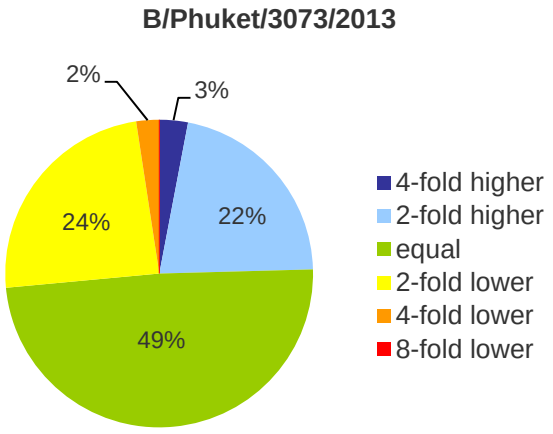
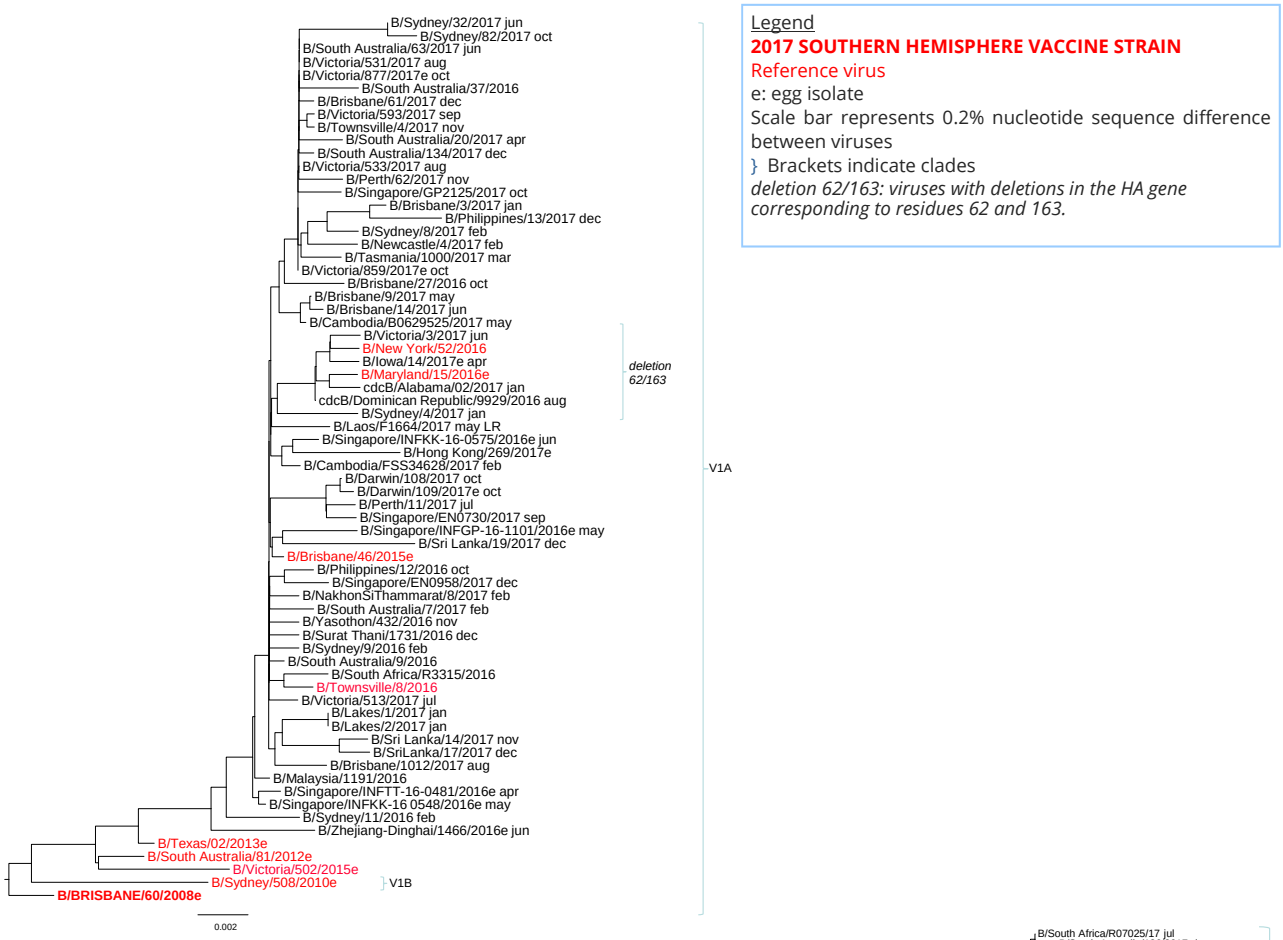


Table 7. Antigenic characterisation of B viruses received at the Centre during 2016 compared to the B/Brisbane/60/2008 and B/Phuket/3073/2013 reference viruses.

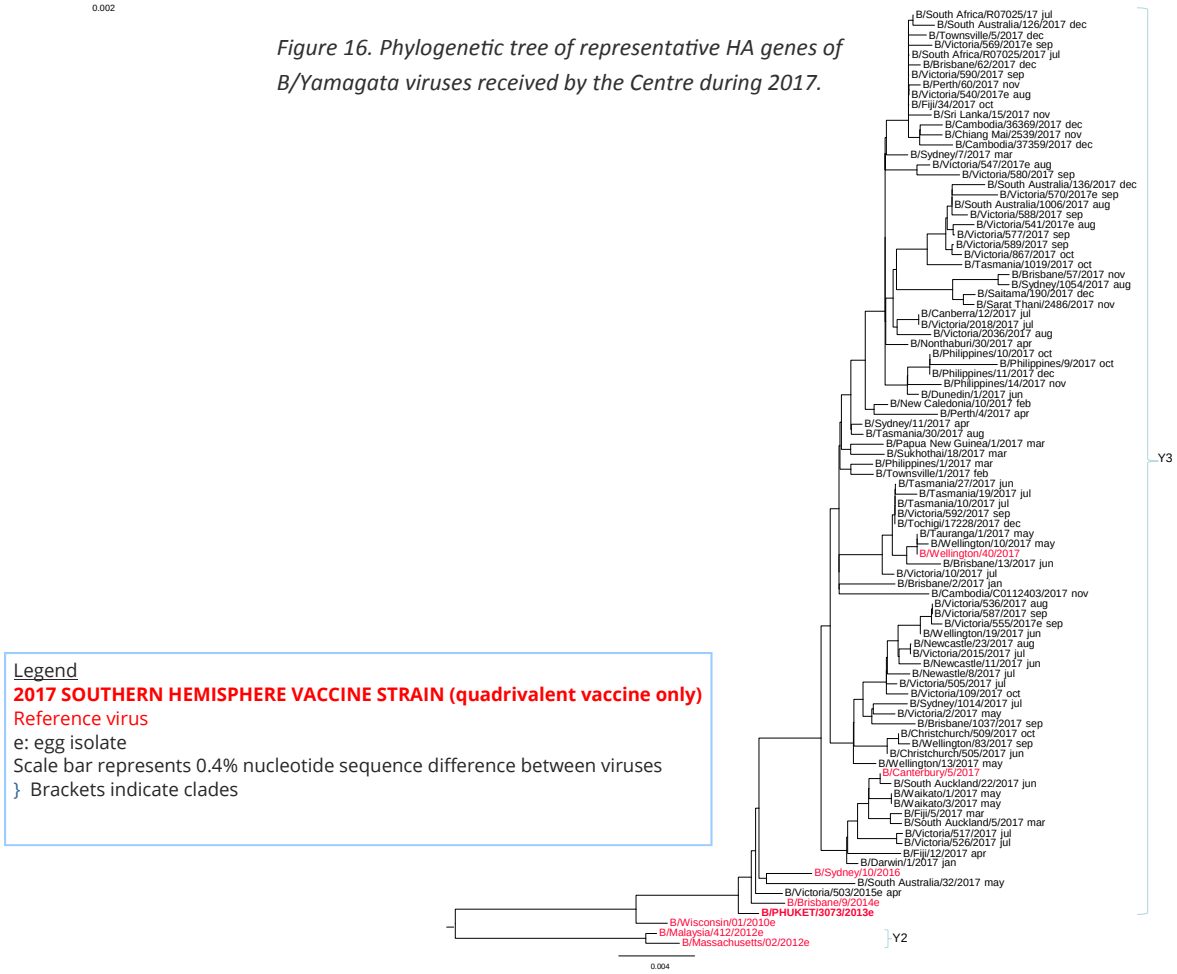
	B/Victoria reference strain: B/Brisbane/60/2008		B/Yamagata reference strain: B/Phuket/3073/2013	
Region	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**
Australasia	51	2 (3.8%)	877	0
Pacific	3	0	62	0
South East Asia	137	0	55	0
South Asia	3	0	2	0
Africa	0	0	3	0
South America	0	0	2	0
Total	**194**	**2 (1.0%)**	**1001**	**0**

Figure 15. Phylogenetic tree of representative HA genes of B/Victoria viruses received by the Centre during 2017.



Legend
2017 SOUTHERN HEMISPHERE VACCINE STRAIN
Reference virus
e: egg isolate
Scale bar represents 0.2% nucleotide sequence difference between viruses
} Brackets indicate clades
deletion 62/163: viruses with deletions in the HA gene corresponding to residues 62 and 163.

Figure 16. Phylogenetic tree of representative HA genes of B/Yamagata viruses received by the Centre during 2017.



Legend
2017 SOUTHERN HEMISPHERE VACCINE STRAIN (quadrivalent vaccine only)
Reference virus
e: egg isolate
Scale bar represents 0.4% nucleotide sequence difference between viruses
} Brackets indicate clades

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 are in use 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. The application of the Tecan EVO 200 liquid handling robot to NAI assays since 2014 has enabled routine automation of screening of all viruses.

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.

Antiviral resistance analyses 2017

NAI assays were used to analyse 3751 viruses for reduced inhibition by the NAIs (Tables 8 and 9). Viruses showing highly reduced inhibition to one or more NAIs underwent further analysis to determine the presence of amino acid substitutions in the NA protein associated with the reduction of inhibition by NAIs.

A total of 9 viruses (3 A(H1N1) pdm09, 1 A(H3N2), 3 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 10).

In addition, the neuraminidase gene of 4 A(H1N1)pdm09 viruses from Perth were analysed by pyrosequencing and found to contain the H275Y mutation, which reduce inhibition of these viruses by oseltamivir (data not shown).

Table 8. Viruses received by the Centre in 2017 and tested by NAI assay, by country.

Country \ Type/ subtype/ lineage	A(H1N1)pdm09	A(H3N2)	A(unsubtyped)	B/Victoria	B/Yamagata	Mixed type	TOTAL
Australasia							
Australia	349	1525	1	51	664		2590
New Zealand	49	155		5	209		418
South Pacific							
Fiji	1	69		1	30		101
New Caledonia		3		2	8		13
Papua New Guinea	29	19			25		73
Solomon Islands					1		1
South East Asia							
Cambodia	37	20		35	1		93
Malaysia	20	13		65	15		113
Philippines	9	12		5	8		34
Singapore	37	79		19	21		156
Thailand	15	23		15	11		64
South Asia							
Sri Lanka	31	24		3	2	2	62
Africa							
South Africa	3	18			3		24
South America							
Brazil		7			2		9
TOTAL	**580**	**1967**	**1**	**201**	**1000**	**2**	**3751**

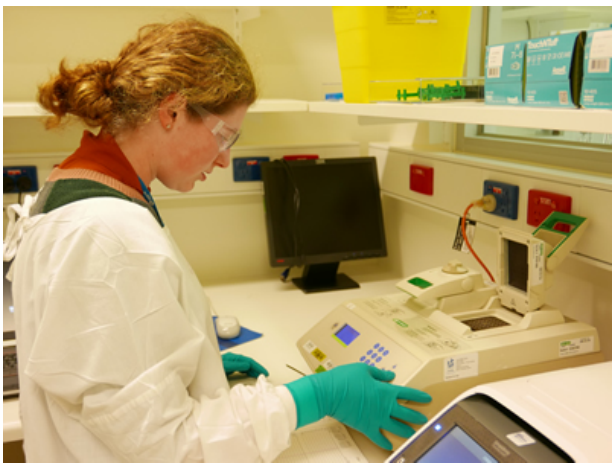
Table 9. Neuraminidase inhibitor sensitivity of viruses received by the Centre in 2017.*

Type/Subtype/ Lineage	No. tested	Oseltamivir		Peramivir		Laninamivir		Zanamivir	
		RI	HRI	RI	HRI	RI	HRI	RI	HRI
A(H1N1)pdm09	580		2 (0.3%)	2 (0.3%)	2 (0.3%)	1 (0.2%)		1 (0.2%)	1 (0.2%)
A(H3N2)	1967	1 (0.05%)	1 (0.05%)	2 (0.1%)					
A (unsubtyped)	1								
B/Victoria	201	2 (1.0%)		1 (0.5%)	3 (1.5%)			2 (1.0%)	
B/Yamagata	1000	2 (0.2%)		2 (0.2%)	2 (0.2%)				
Mixed type	2								
TOTAL	**3751**	**5 (0.13%)**	**3 (0.08%)**	**7 (0.2%)**	**7 (0.2%)**	**1 (0.03%)**	**0**	**3 (0.08%)**	**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 2016-2017. **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 10. Characteristics of viruses received by the Centre during 2017 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	Sydney	•	•			H275Y
	Singapore	•	•			H275Y
	Brisbane				•	Q136R
A(H3N2)	Sydney	•				R292K
B/Victoria	Malaysia		•			T146I
	Malaysia		•			E105K
	Malaysia		•			H273Y
B/Yamagata	Malaysia		•			T146K
	Brisbane		•			T146I



Resistance to Adamantanes

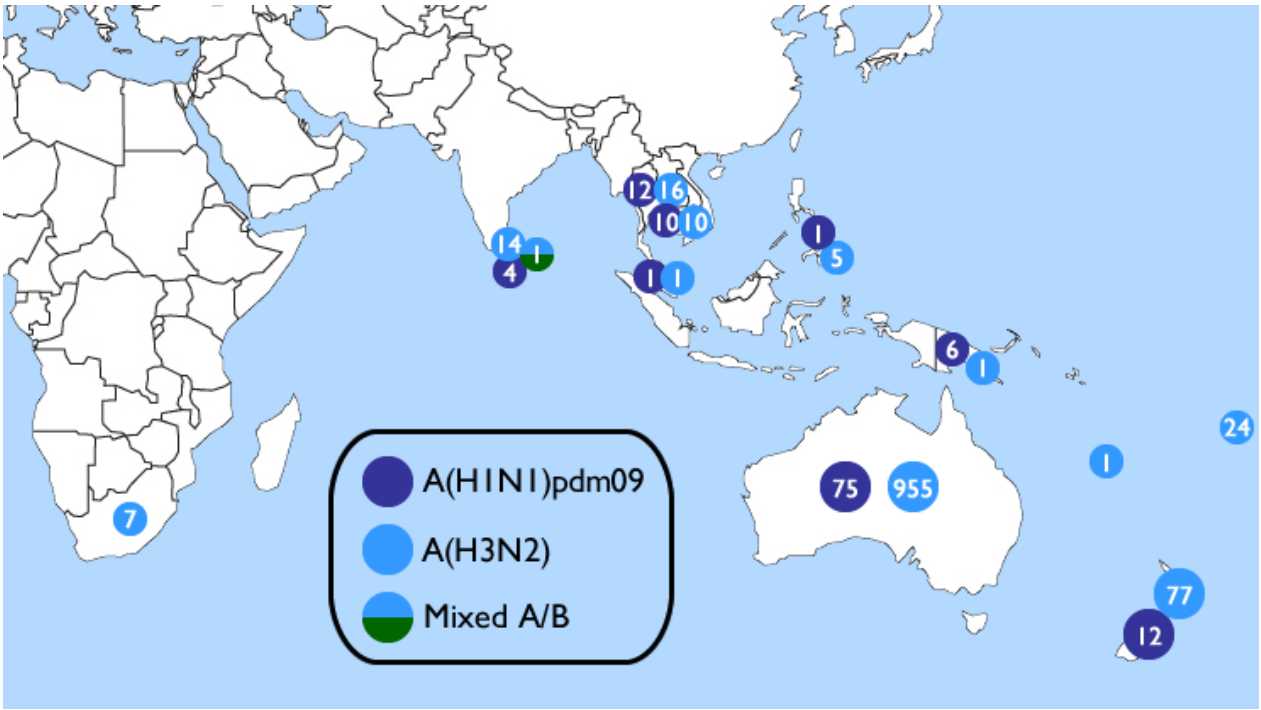
Background

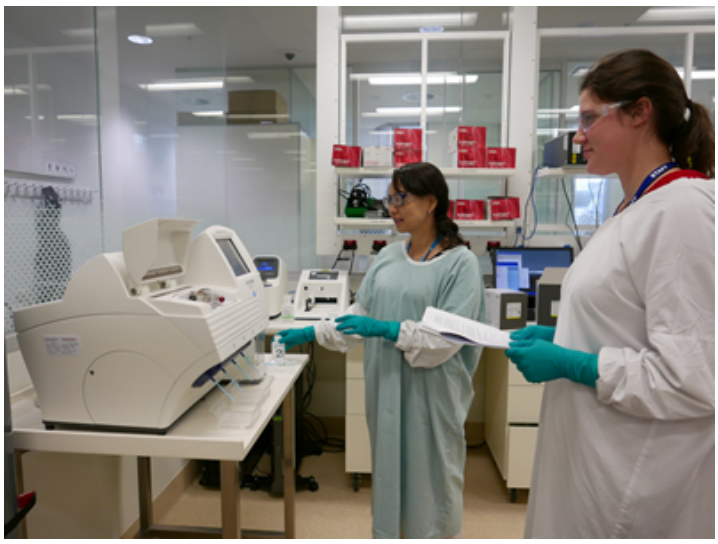
The adamantane class of antiviral drugs (amantadine and rimantadine) were previously used to treat cases of influenza A, but are no longer recommended due to the almost universal adamantane resistance amongst circulating influenza A strains in recent years. All five WHO Collaborating Centres continue 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 2017

Real-time PCR or sequencing was used to analyse 1233 influenza A viruses, which were representative of those submitted to the Centre during 2017 (Figure 17). Almost all of the tested influenza A viruses carried the S31N mutation, indicating that they would be resistant to adamantanes. A further five viruses from Australia were found to contain a S31D mutation in the matrix protein; these viruses remain resistant to adamantanes. However, 20 A(H3N2) viruses from Australia and one A(H3N2) virus from New Zealand were found to contain a serine residue at position 31 in the matrix protein rendering them susceptible to adamantanes. The observation of these adamantane-sensitive viruses was published in November 2016 (Hurt et al., Euro Surveill. 2017 Nov;22 (47).)

Figure 17. Geographic spread of viruses received at the Centre during 2017 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 2017

In 2017, the isolation of viruses in eggs focused heavily on A(H3N2) viruses, which have a lower success rate for isolation. In total. 44 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 46% (Tables 10 and 11).

Table 10. Virus isolation in eggs at the Centre in 2017.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	5	4	80%
A(H3N2)	80	30	38%
B/Victoria	5	4	80%
B/Yamagata	6	6	100%
Total	**96**	**44**	**46%**

Table 11. Potential candidate vaccine strains isolated in eggs at the Centre in 2017.

A(H1N1)pdm09	A(H3N2)	
A/Brisbane/81/2017	A/South Australia135/2016	A/Brisbane/4/2017
A/Newcastle/67/2017	A/Victoria/624/2016	A/Brisbane/27/2017
A/Newcastle/86/2017	A/Brisbane/299/2016	A/Brisbane/29/2017
A/Brisbane/70/2017	A/Brisbane/285/2016	A/Brisbane/32/2017
B/Victoria	A/Singapore/KK1100/2016	A/Sydney/103/2017
B/Victoria/877/2017	A/Brisbane/321/2016	A/Newcastle/35/2017
B/Victoria/859/2017	A/Singapore/TT1374/2016	A/Newcastle/36/2017
B/Darwin/109/2017	A/Singapore/GP2646/2016	A/Sydney/52/2017
B/Brisbane/46/2017	A/Brisbane/318/2016	A/South Australia/90/2017
B/Yamagata	A/Tasmania/219/2016	A/Tasmania/37/2017
B/Victoria/540/2017	A/Antananarivo/1067/2016	A/Tasmania/18/2017
B/Victoria/541/2017	A/Washington/106/2016	A/South Australia/209/2017
B/Victoria/547/2017	A/Delaware/32/2016	A/Victoria/624/2017
B/Victoria/555/2017	A/Idaho/37/2016	A/Victoria/653/2017
B/Victoria/569/2017	A/Brisbane/1/2017	A/Victoria/746/2017
B/Victoria/570/2017		

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 2017, 34 candidate vaccine viruses were received from other WHO Collaborating Centres and laboratories and then passaged in eggs at the Centre (Table 12).

Selected egg-isolated candidate vaccine strains are made available to the four laboratories that undertake virus reassortment for WHO — bioCSL (Australia), the National Institute for Biological Standards and Control (NIBSC, UK), New York Medical College (NYMC, USA) and the Center for Biologics Evaluation and Research (CBER, USA) — where they are reassorted with established egg-adapted strains to produce potential vaccine seed strains. The reassortant vaccine seed viruses are returned to the Centre, where they are analysed by HI assay and genetic sequencing to ensure that key antigenic and genetic properties of the vaccine virus have been retained.

The vaccine seed viruses are distributed to other WHO Collaborating Centres and vaccine manufacturers worldwide through Essential Regulatory Laboratories at the Therapeutic Goods Administration (Australia), NIBSC and the Centre for Biologics Evaluation and Research, Food and Drug Administration (USA).

Table 12. Potential candidate vaccine viruses received from other WHO Collaborating Centres during 2017.

A(H1N1)pdm09	A(H3N2)
NYMC X-291 (hy A/Slovenia/2903/2015)	A/Norway/3806/2016
NYMC X-291A (hy A/Slovenia/2903/2015)	A/Hong Kong/50/2016
A/Montana/50/2016	NYMC X-295 (hy A/Norway/3806/2016)
A/Shanghai-Huangpu/SWL13439/2016	NYMC X-297 (hy A/Hong Kong/50/2016)
NYMC X-299 (hy A/Montana/50/2016)	A/Greece/4/2017
IVR-180A (A/Singapore/GP1908/2015	A/Norway/4849/2016
B/Victoria	A/Norway/4465/2016
B/Pennsylvania/19/2016	A/Washington/16/2017
B/St Petersburg/293/2016	NIB-103 (A/Norway/3806/2016)
B/Maryland/15/2016	NIB-104 (A/Singapore/INFIMH-16-0019/2016)
B/Colorado/6/2017	A/Hong Kong/2286/2017
B/Iowa/14/2017	A/Hong Kong/2277/2017
B/Alabama/2/2017	A/Kalamata/540/2017
NYMC BX-69 (B/Maryland/15/2016)	**B/Yamagata**
NYMC BX-69A (B/Maryland/15/2016)	B/Texas/81/2016
B/Norway/2409/2017	B/New Hampshire/01/2016
B/Hong Kong/269/2017	B/Guangxi-Xixiangtang/11019/2016
	NYMC BX-63 (B/Arizona/10/2015)
	NYMC BX-63A (B/Arizona/10/2015)

Serological Analyses

Background

Antigenic changes in circulating influenza viruses are also monitored by the extent to which they are inhibited by antibodies produced by subjects who have been immunised with current inactivated seasonal influenza vaccines. Twice a year the WHO Collaborating Centres and Essential Regulatory Laboratories in the WHO surveillance network exchange panels of sera collected from subjects pre- and post-influenza vaccination. These panels are analysed using the HI assay against the current vaccine and representative influenza strains in preparation for the biannual WHO Consultations on the Composition of Influenza Vaccines (Table 13). Serum panels from children, younger adults (20-64 years old) and older adults (≥ 65 years old) are assessed.

Serum panel analyses in February 2017

In February the Centre analysed serum panels from recipients of seasonal trivalent influenza vaccines in Australia, China and Europe. 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 a minority of representative recent A(H1N1)pdm09 viruses were significantly lower compared to GMTs against the vaccine strain A/California/7/2009.

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 egg-propagated vaccine virus B/Brisbane/60/2008, but reductions were not as great when compared to vaccine virus grown in cells.

In studies using serum panels from individuals who had received quadrivalent vaccine, 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., although there some reductions compared to the egg-propagated vaccine virus.

Serum panel analyses in September 2017

In September, the Centre analysed serum panels from Australia and USA. The combined data from all ERLs and WHO Collaborating Centres showed that GMTs of antibodies against representative recent A(H1N1) pdm09 viruses were somewhat reduced compared to the A/Michigan/45/2015 vaccine virus.

GMTs of antibodies against representative recent A(H3N2) lineage viruses grown in cell culture were significantly reduced compared to titres against the A/Hong Kong/4801/2014 vaccine virus grown in eggs. Additionally, GMTs against some representative recent viruses were significantly reduced compared to cell culture-progagated vaccine virus. Microneutralisation assays using the same serum panels and viruses showed similar results.

Comparison of GMTs of antibodies against some representative recent B/Victoria/2/87 lineage viruses were similar compared titres against the cell-grown vaccine virus B/Brisbane/60/2008. Similarly, GMTs of antibodies against some representative recent B/Yamagata/16/88 lineage viruses were lower compared to titres against the egg-grown B/Phuket/3073/2013 quadrivalent vaccine virus.

Table 13. Representative and vaccine candidate strains used for serological analyses during 2017. All viruses are egg grown unless indicated otherwise.

FEBRUARY	SEPTEMBER
A(H1N1)pdm09	**A(H1N1)pdm09**
A/Michigan/45/2015*^ [E, C]	A/Michigan/45/2015*^ [E]
A/California/7/2009 [E]	A/South Auckland/2/2016 [E, C]
A/Sydney/344/2016 [C]	A/Newcastle/86/2017 [E, C]
A/Singapore/GP1908/2015 [C]	A/Perth/85/2017 [C]
A/Brisbane/294/2016 [C]	A/Townsville/9/2017 [C]
A(H3N2)	**A(H3N2)**
A/Singapore/INFTT-16-0612/2016 [E]	A/Hong Kong/4801/2014*^ [E, C]
A/Hong Kong/4801/2014*^ [E]	A/Sydney/142/2016 [E,C]
A/Norway/3806/2016 [E]	A/Michigan/15/2014 [C]
A/Michigan/15/2014 [C]	A/Singapore/GP2646/2016 [E, C]
A/Brisbane/296/2016 [C]	A/Brisbane/32/2017 [E,C]
A/Townsville/44/2016 [C]	A/Brisbane/321/2016 [E,C]
	A/Singapore/TT1374/2016 [E, C]
B/Victoria	**B/Victoria**
B/Florida/78/2015 [E]	B/Brisbane/60/2008*^ [E]
B/Singapore/INFKK-16-0575/2016 [E]	B/Singapore/INFKK-16-0575/2016 [E]
B/Brisbane/60/2008*^ [E]	B/Townsville/7/2016 [C]
B/Townsville/7/2016 [E]	B/South Australia/63/2017 [C]
	B/Maryland/15/2016 [E, C]
B/Yamagata	**B/Yamagata**
B/Singapore/INFTT-16-0610/2016 [E]	B/Phuket/3073/2013^ [E]
B/Phuket/3073/2013^ [E]	B/Singapore/INFTT-16-0610/2016 [E]
B/Arizona/10/2015 [E]	B/Sydney/5/2016 [C]
B/Newcastle/14/2016 [C]	B/Tasmania/27/2017 [C]
B/Sydney/45/2016 [C]	B/Victoria/505/2017 [C]
B/Sydney/5/2016 [C]	B/Dunedin/1/2017 [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 2017 WHO made the recommendations reported below.

In September 2017, the Centre hosted the WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2018 at the Peter Doherty Institute for Infection and Immunity.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2017–2018, Geneva, Switzerland, 27 February - 2 March 2017

It is recommended that vaccines for use in the 2017–2018 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/Brisbane/60/2008*-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013*-like virus.

WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2018, Melbourne, 25–27 September 2017

It is recommended that vaccines for use in the 2017 influenza season (southern hemisphere winter) contain the following:

- an A/Michigan/45/2015 (H1N1)-like virus;
- an A/Singapore/INFIMH-16-0019/2016* (H3N2)-like virus;
- a B/Phuket/3073/2013*-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008*-like virus.

* *These viruses were 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 2017 the following candidate vaccine viruses were listed by WHO as being suitable for vaccine use following the indicated meeting and originally isolated at the Centre, either in eggs or cells.

Type/Subtype/ Lineage	Egg-derived CVVs	Cell-derived CVVs
A(H1N1)pdm09	A/Singapore/GP1908/2015 (Feb, Sept)	
A(H3N2)	A/Victoria/673/2014 (Feb) A/New Caledonia/ 71/2014 (Feb)	A/Singapore/GP2050/2015 (Feb) A/Canberra/7/2016 (Sept)
B/Victoria	B/Brisbane/33/2008 (Feb, Sept) B/Brisbane/46/2015 (Feb, Sept)	B/Brisbane/63/2014 (Feb, Sept)
B/Yamagata	B/Brisbane/9/2014 (Feb, Sept)	B/Singapore/INFKK-16-0569/2016 (Sept) B/Brisbane/9/2014 (Feb, Sept)

WHO officials, advisors from the WHO Collaborating Centres for Influenza and Essential Regulatory Laboratories, and observers from other centres in WHO GISRS in attendance at the WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2018, held at the Peter Doherty Institute for Infection and Immunity.

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.

At its meeting on 11 October AIVC accepted the September WHO recommendation and decided that the Australian influenza vaccine for 2018 should contain the following:

- an A/Michigan/45/2015 (H1N1)-like virus;
- an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus;
- a B/Phuket/3073/2013*-like virus.

Quadrivalent vaccines should contain viruses listed above, plus the additional B virus: B/Brisbane/60/2008-like virus.

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 2017, 32 kits were sent to 15 laboratories in 11 countries. Each kit contained 10 mL each of the reference antigens A/Michigan/45/2015, A/Hong Kong /4801/2015, B/Brisbane/60/2008 and B/Phuket/3073/2013 and homologous antisera.

Recipients of the 2017 Kit

AUSTRALIA: Queensland Health Scientific Services, Brisbane, Queensland; Vaxxas, Brisbane, Queensland; Australian Institute for Bioengineering and Nanotechnology, Brisbane , Queensland; Westmead Hospital, Sydney, New South Wales

CAMBODIA: Institut Pasteur du Cambodge, Phnom Penh

HONG KONG SAR: University of Hong Kong

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

MACAU SAR: Public Health Laboratory

MALAYSIA: Institute for Medical Research, Kuala Lumpur;

NEW ZEALAND: 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

THAILAND: National Institute of Health, Bangkok

Virus Panels for Analysis of Resistance to Antiviral Drugs

The Centre produces and distributes a panel of reference viruses on request to laboratories conducting NAI assays on behalf of the International Society for Influenza and other Respiratory Virus Diseases (isirv) Antiviral Group. In 2017 panel kits were sent to the Naval Health Research Center (San Diego CA, USA) and Shionogi & Co., Ltd., (Osaka, Japan). Kits were composed of 2 vials (250 µL) of each of the reference viruses listed in the table below.

Viruses in the 2017 NAI assay panel

Reference virus	**Inhibition by antiviral drugs *(Normal or Highly Reduced (HRI))***			
	Oseltamivir	**Laninamivir**	**Peramivir**	**Zanamivir**
(Former seasonal A(H1N1); A/New Caledonia/20/99-like)				
A/Mississippi/3/01 (H1N1) wild-type	Normal	Normal	Normal	Normal
A/Mississippi/3/01 (H1N1) variant **(H275Y)**	HRI	Normal	HRI	Normal
(A(H3N2); A/Fujian/411/2002-like)				
A/Fukui/20/04 (H3N2) wild-type	Normal	Normal	Normal	Normal
A/Fukui/45/04 (H3N2) variant **(E119V)**	HRI	Normal	Normal	Normal
(B; B/Sichuan/379/1999-like)				
B/Perth/211/2009 wild-type	Normal	Normal	Normal	Normal
B/Perth/211/2009 variant **(D197E)**	HRI	Normal	HRI	Normal
(A(H1N1)pdm09; A/California/7/2009-like)				
A/Perth/265/2009 (H1N1)pdm09 wild-type	Normal	Normal	Normal	Normal
A/Perth/261/2009 (H1N1)pdm09 variant **(H275Y)**	HRI	Normal	HRI	Normal

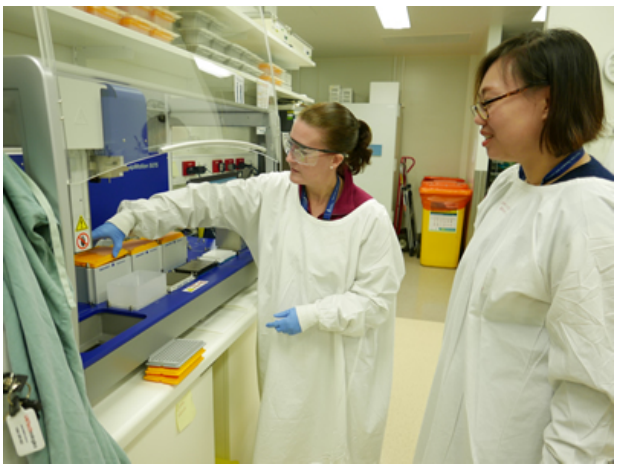
Training

Training and Support of National Influenza Centres

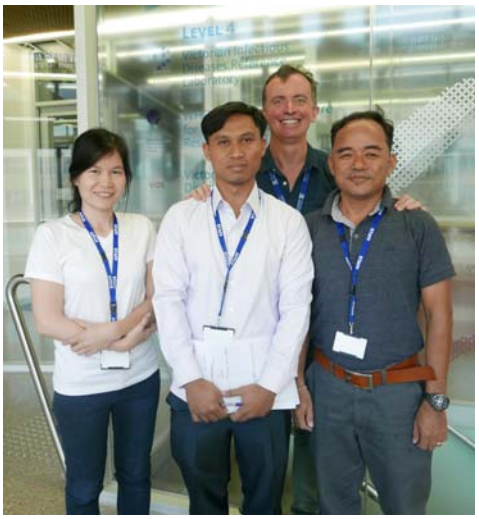
The Centre provides support in the form of training and advice to WHO National Influenza Centres (NICs) and other diagnostic laboratories, especially in the Asia-Pacific region. Strengthening technical capabilities and infrastructure for surveillance work in regional laboratories increases their capacity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

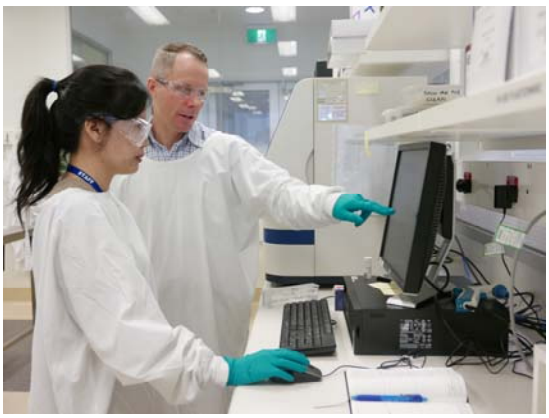
Ms Jiayu Wang from the Shanghai Center for Disease Control and Prevention (CDC) (Shanghai, China), visited the Centre on 12 July – 1 August to undertake training in genetic analysis techniques.



Ms Phalla Y and Mr Songha Tok from Institut Pasteur du Cambodge (Phnom Penh, Cambodia), and Mr Siyeatra Sok (National Public Health Laboratory, Phnom Penh, Cambodia), visited the Centre 20 November – 1 December. Mr Tok and Mr Sok undertook training in surveillance techniques including serological analysis and genetic analysis, while Ms Y was trained in antiviral resistance testing techniques.



L to R: Ms Phalla Y, Mr Songha Tok and Mr Siyeatra Sok, with Centre Educator Patrick Reading (at rear)



Training Programs and Visits to Regional Laboratories

Naomi Komadina ran the Sequencing and the GISAID EpiFlu™ Database workshop in Kuala Lumpur, Malaysia on 26 April *(pictured below)*. The workshop was attended by approximately 20 people.

Patrick Reading visited the Research Institute of Tropical Medicine (RITM), in Muntinlupa City, Philippines on 14–16 August. He visited the Institute to provide training to new staff regarding cell culture and isolation of influenza viruses, as well as to advise on different tests that could be implemented at RITM to test for the sensitivity of influenza viruses to currently antiviral drugs.

Ximena Tolosa worked with WHO Cambodia country office staff to deliver a Hospital Admission Review data analysis training course in Phnom Penh, Cambodia on 22–23 May *(pictured below)*. This training course was attended by 15 participants who conduct influenza surveillance throughout Cambodia. Participants from the Cambodian Ministry of Health Department of Communicable Disease Control, Provincial Health Department, and National Institute of Public Health were trained in Hospital Admission Review data collection and data analysis.

Patrick Reading attended the WHO Global Outbreak and Response Network (GOARN) Outbreak Response Training held in Manila and Antipolo, Philippines, on 28 September – 7 October. The GOARN outbreak response training brings together participants from GOARN partner institutions throughout the world. Over 20 participants (including clinicians, nurses, veterinarians, laboratory scientists and epidemiologists from different countries throughout the world) were trained using the developing outbreak scenario, which incorporates intense group work, practical exercises and role play. Patrick attended as a faculty member and laboratory expert. He played a major role in guiding the laboratory diagnoses associated with the outbreak scenario.

External Quality Assurance Project for Virus Isolation

In 2016 the Centre developed and coordinated an external quality assurance project (EQAP) to test the proficiency of virus isolation techniques in National Influenza Centres (NICs) in the WHO Western Pacific Region (WPR) and South-East Asia Region (SEAR). Results of this EQAP were published during 2017: https://www.ncbi.nlm.nih.gov/pubmed/29127947

Following the success of the EQAP in 2016, in 2017 the Centre conducted a similar EQAP for NICs in the WHO Regions of Africa (AFRO), the Americas (AMRO) and the Eastern Mediterranean (EMRO). Patrick Reading coordinated the EQAP, which involved a total of 27 NICs — 12 in AFRO, 5 in AMRO and 10 in EMRO. Test panels each containing 16 test samples were sent to the laboratories in November and December, and it is anticipated that results will be received from all participating NICs in early 2018.

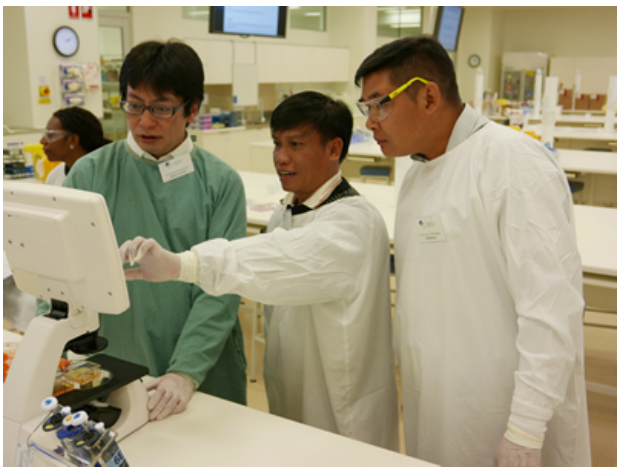
Workshop on Virus Isolation and Characterisation for National Influenza Centre Staff in the Western Pacific Region

The Centre organised and hosted a week-long workshop on viral isolation and characterisation of influenza viruses on 29 May – 2 June 2017. A total of 17 scientists from National Influenza Centres in the WHO Western Pacific Region (Australia, Cambodia, China, Fiji, Lao PDR, Malaysia, Mongolia, New Caledonia, New Zealand, Papua New Guinea, The Philippines, Singapore and Vietnam) attended the workshop, which was held at the Doherty Institute. Staff from the Centre, Dr Kazuya Nakamura from the WHO Collaborating Centre for Reference and Research on Influenza in Japan and Dr Frank Konings from the WHO Office for the Western Pacific Region (WPRO) presented lectures and led laboratory practical sessions in techniques on cell culture and isolation of influenza viruses.

The workshop was a success on multiple fronts. Participants were tested on their theoretical and practical knowledge of cell culture and virus isolation prior to and following the workshop, and every participant improved their score after completing the workshop. Feedback from the participants was overwhelmingly positive, with many reporting an increased understanding of cell culture and different methods for identifying and characterising influenza viruses, as well as influenza vaccine development in general. All participants indicated that their learnings from the workshop would be useful and applicable in their work upon returning to their

"I had a really great time. I learned a lot and hope to improve my contribution to the global surveillance"
– Workshop participant

"All the culture/lab work was useful as I have got ideas to take back and try plus shared other ideas which WHOCC staff might try."
– Workshop participant



Research

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

Antivirals and Viral Fitness

Centre staff and students

Aeron Hurt, Danielle Tilmanis, Edin Mifsud, Sook Kwan Leah Brown, Celeste Tai, Merryn Roe, Rubaiyea Farrukee

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.

Collaborators

James McCaw and Alex Zarebski (University of Melbourne); Jessie Bloom (Fred Hutchinson Cancer Research Centre, USA); Jean-Francois Rossignol (Romark Laboratories, USA); Peter Jenkins (Aus Bio Ltd., Victoria)

Highlights and developments 2017

In 2017 we assessed the fitness cost of two amino acid substitutions, D197N and H273Y, in the neuraminidase of contemporary influenza B viruses. These influenza B variants are of particular interest as they have been recently detected in community settings and have been associated with resistance to neuraminidase inhibitors, the current antiviral drug of choice against influenza infections. We used a combination of *in vitro* techniques, ferret infection studies and mathematical modelling to perform a comparative analysis between wild-type influenza B viruses and the variants. Our results showed that while the fitness cost of the H273Y substitution was significant, the D197N substitution had a relatively mild effect on fitness, suggesting that this variant may be a potential risk for community spread.

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 nitzoxanide 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.

In 2017 a CRADA with Aus Bio Ltd. was initiated to investigate the *in vivo* effectiveness of a newly designed influenza antiviral using both prophylaxis and therapeutic regimens in the ferret model. The novel influenza antivirals were more effective at reducing clinical signs in ferrets associated with influenza infection when compared to currently available antiviral compounds oseltamivir and zanamivir. Further studies are being carried out to investigate if these compounds can reduce viral replication in the lower respiratory tract.

Evolution, Modelling and Serological Responses to Influenza Viruses

Centre staff

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

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 project working with Jemma Geohagan and Eddie Holmes (University of Sydney, NSW) assessed the synchronicity of influenza outbreaks in Australia from 2007-2016. Contrary to previous beliefs, our study showed that over this period of time that influenza outbreaks occurred at very similar time frames regardless of location within Australia. A follow up study is planned for the 2017 season to see if this persisted in a record year for influenza cases in Australia.

Other work has continued with Vijaykrishna Dhanasekaran (Monash University) and the J. Craig Venter Institute to analyse 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. These data, together with previous sequence data from our earlier studies, will be analysed to determine evolutionary patterns in these viruses as they circulated in this region during these periods.

A project funded by the US Department of Health and Human services via the Biomedical Advanced Research and Development Authority (BARDA) with collaborators at Cambridge University, UK and other experts is also continuing. This five-year program aims to develop and clinically test novel vaccines for current and potentially future A(H5N1) viruses, based on antigenic mapping and predictive algorithms for the evolution of viruses. The same group of collaborators are participating in another project funded by the US based CEIRS (Centers of Excellence for Influenza Research and Surveillance) 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 also begun on the CEIRS project with antigenic testing (both HI and virus microneutralisation) of several panels of mutated viruses generated by human serum escape mutants and reverse engineered viruses containing selected mutations.

Serological responses to influenza infection and vaccination have been conducted using a cohort in North Vietnam in collaboration with Annette Fox (University of Melbourne). This work has been funded by the National Health and Medical Research Council (NHMRC) for the period 2016 to 2019 and the Centre's participation in this project began in 2017 with preparing antigens and helping perform HI assays on cohort sera. Other serology projects with collaborators in Hong Kong and Singapore were completed and published in 2017.

Highlights and developments 2017

A paper describing the synchronicity of influenza outbreaks study was accepted for publication in the high ranking journal PLoS Pathogens. Several other papers based on serological work performed by Centre staff were published in 2017.

A manuscript on the study of influenza B Yamagata-lineage viruses has been prepared for publication.

Collaborators

Annette Fox (University of Melbourne); 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); Ed 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 Ben Cowling (University of Hong Kong, Hong Kong); Mark Chen (Tan Tock Seng Hospital, Singapore); Julie McAuley (University of Melbourne); Steven Kent (University of Melbourne)

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.

Highlights and developments 2017

In 2017, we collected and screened 1176 samples from wild Anseriiformes (ducks) and Charadriiformes (shorebirds and terns) in Victoria and Tasmania, with 61 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 2017 blood samples were collected from the long distant migrant Red-necked Stint (n=100) and Ruddy Turnstones (n=328). These samples, combined with >1000 samples collected since 2012 are further being assayed for antibodies against H5 antibodies, to which they may have been exposed on their migrations to the northern hemisphere. The project has recently been funded by a small grant 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. To date, we have sequenced the virome of ducks (Grey Teal, Pacific Black Duck) and shorebirds (Ruddy Turnstones) which are known reservoirs of avian influenza, in addition to Australian Shelduck, Red-necked Avocet (Recurvirostrida novaehollandiae), and Gentoo Penguins (Pygoscelis papua) which may be spill over hosts for avian influenza in Australia and Antarctica. This project will continue in 2018, with specific focus on wild bird species in the orders Anseriiformes and Charadriiformes given their role as reservoir hosts of influenza A virus.

Collaborators

Marcel Klaassen (Deakin University, Victoria), Bethany Hoye (University of Wollongong, Victoria); Simone Warner (Department of Primary Industries, Victoria); Eddie Holmes (University of Sydney, New South Wales); Daniel González (Acuña (University of Concepción, Chile); Frank Wong, Australian Animal Health Labs; Andrew Breed, Department of Agriculture.

Samples collected from wild birds in 2017					
Avian order	**Species**	**Sampling date**	**Location**	**Samples collected**	**Influenza-positive samples**
Anseriiformes	Australian shelduck (*Tadorna tadornoides*)	January-June	Port Philip Bay	48	0
	Chestnut teal (*Anas castanea*)	January-June	Port Philip Bay	8	2
	Grey teal (*Anas gracillis*)	January-June	Port Philip Bay	101	12
	Hardhead (*Aythya australis*)	January-June	Port Philip Bay	1	0
	Pacific black duck (*Anas superciliosa*)	January-June	Port Philip Bay	51	6
	Pink-eared duck (*Malacorhynchus membranaceus*)	January-June	Port Philip Bay	57	12
	Wood duck (*Chenonetta jubata*)	January-June	Port Philip Bay	43	0
Charadriiformes	Curlew sandpiper (*Calidris ferruginea*)	July-December	Port Philip Bay	20	0
	Red-necked stint (*Calidris ruficolis*)	January-June	Western Port Bay	463	20
	Red-necked stint	July-December	Port Philip Bay	95	6
	Ruddy turnstone (*Arenaria interpres*)	January-June	King Island	213	8
	Ruddy turnstone	July-December	King Island	115	11
	Sharp-tailed sandpiper (*Calidris acuminata*)	July-December	Port Philip Bay	24	0
	Crested tern (*Thalasseus bergii*)	July-December	King Island	70	1
	Whiskered tern (*Chlidonias hybridus*)	July-December	Port Philip Bay	23	0
Gruiformes	Dusky moorhen (*Gallinula tenebrosa*)	January-March	Port Philip Bay	5	0

Epidemiology

Centre staff and student

Sheena Sullivan, Vivian Leung, Ximena Tolosa

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), the Victorian General Practice Sentinel Surveillance (VicSPIN) network, and the Influenza Complications Alert Network (FluCAN) to estimate influenza vaccine effectiveness in the community. We are evaluating the validity of the studies used to estimate vaccine effectiveness and working with colleagues at the University of Hong Kong (Ben Cowling) to understand bias in vaccine effectiveness studies and improve the utility of these estimates for influenza vaccine strain selection.

Vaccine effectiveness estimates are extremely useful for supporting the use of influenza vaccines, which are the best means available for reducing the considerable burden of influenza. The quantification of this burden was another key area of research in 2017.

Collaborators

Nigel Stocks, Monique Chilver (University of Adelaide); James Fielding, Kylie Carville and Kristina Grant (VIDRL); Ben Cowling and Jessica Wong (University of Hong Kong); Hannah Moore and Tom Snelling (Telethon Kids Institute); George Milne and Joel Kelso (University of Western Australia); Annette Regan (Curtin University), Ben Teh and Monica Slavin (Peter MacCallum Cancer Centre); Dave Burgner (Murdoch Children's Research Institute)

Highlights and developments 2017

In 2017, Australia experienced a severe influenza season and for the first time since the 2009 pandemic, we published interim vaccine effectiveness estimates for Australia, which garnered considerable interest. We also continued to publish studies evaluating the reliability of influenza vaccine effectiveness studies.

We were awarded a government tender to work on a project that uses use mathematical modelling to inform vaccination policy. This has been a collaborative effort with colleagues at the Telethon Kids Institute, the University of Western Australia and the University of Hong Kong. The Centre's epidemiology team are leading 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 severe 2017 season prompted instigation of some of the vaccination scenarios modelled prior to completion of the project. However, the study will provide valuable additional information to support these policies.

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. This work is driven by the pandemic influenza preparedness framework, for which there was a goal to calculate a global burden estimate in late 2017.

We were also involved in projects to quantify the burden of influenza and other respiratory viruses in special risk groups including pregnant women, allogeneic stem cell transplant patients , and in young children.

Interactions between Immune Response and Respiratory Viruses

Centre staff

Karen Laurie, Kok Fei (Jimmy) Chan, Louise Carolan, Patrick Reading

Research overview

We have been using the ferret model to investigate the phenomenon of viral interference, whereby a primary virus infection of the host will lower the host's susceptibility to subsequent infection by another virus. We have also investigated the utility of the ferret model to study pathogenesis, immunity and transmission of human respiratory syncytial virus (RSV). Finally, in collaborative studies with Dr Daniil Korenkov and Professor Larisa Rudenko from the Institute of Experimental Medicine, Saint Petersburg, Russia, we have assessed the efficacy of six new live attenuated influenza vaccine (LAIV) strains in conferring protection to ferrets from influenza virus infections.

Highlights and developments 2017

In a previous study, we established evidence for viral interference between antigenically related and unrelated influenza A viruses. In 2017, we have investigated viral interference between different influenza B lineages, finding that interference occurred at both short (day 3-10) and longer (day 28) challenge intervals, suggesting that both innate and adaptive immune mechanisms can contribute to viral interference between influenza B lineages. A manuscript documenting these findings was accepted for publication in The Journal of Infectious Diseases in 2017.

In an independent study, we compared the pathogenesis, humoral immune responses and transmission of two strains of human RSV in the ferret model. These studies provide important information regarding the utility of the ferret model for future studies examining novel antiviral drugs and/or vaccination strategies designed to limit RSV infections. Our findings from these studies were published in The Journal of Virology in 2017. Furthermore, studies are currently underway to determine if virus interference can be detected between influenza A viruses

Collaborators

Daniil Korenkov, Larisa Rudenko (Institute of Experimental Medicine, Saint Petersburg, Russia); Daniel Layton, Andrew Bean (Australian Animal Health Laboratory, CSIRO, Victoria); Vijay Dhanasekaran (Department of Microbiology, Monash University, Victoria); James McCaw (Melbourne School of Population and Global Health, The University of Melbourne); Lorena Brown, Katherine Kedzierska, Oanh Nguyen (Department of Microbiology and Immunology, The University of Melbourne)

Novel Inhalation Delivery of a DNA-Based Influenza Vaccine

Centre staff and student

Aeron Hurt, Leonard Izzard, Leo Lee

Research overview

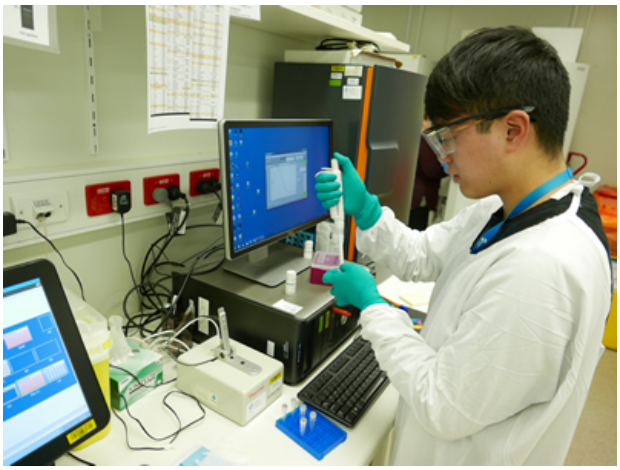
Our research, funded by an NHMRC development grant, investigates the feasibility of using a novel ultrasonic nebuliser device to deliver DNA vaccines in an *in vivo* model. To this end we use an influenza A model of infection in ferrets. Historically vaccines consist of either inactivated or live attenuated viruses. The presence of these foreign proteins stimulate the host's immune system to mount an immune response against the virus and help to protect it against a viral challenge. Our model differs in that we are delivering DNA plasmids that use the host's own cells to produce the foreign viral proteins. The route of administration is via the respiratory tract, which is facilitated by nebulisation of the plasmid mix using a novel ultrasonic nebuliser. This system will result in efficient delivery of the plasmid deep into the lungs including alveoli, allowing the production of viral proteins in this clinically relevant location. This influx of foreign viral proteins is designed to 'kick start' the immune response in a more efficient way than traditional vaccines.

Highlights and developments 2017

Expression vectors have been designed and optimised to encode the HA protein of influenza A(H1N1)pdm09 to raise a protective antibody response. These plasmids were able to produce functional HA protein in cell culture, but could not induce the production of HA-specific antibodies in ferrets following vaccination by nebuliser or the intranasal route. The nebuliser has since be redesigned to improve aerosol delivery, while cell entry reagents and novel adjuvants are being investigated to boost the immunogenicity of the vaccine antigen.

Collaborators

Leslie Yeo (RMIT University) and David Piedrafita (Federation University)



Early Recognition and Response to Influenza Infection

Centre staff

Patrick Reading

Research overview

Our research, which is undertaken at the Centre and at the University of Melbourne, investigates how the body first recognises and responds to infections with influenza and other respiratory viruses. We employ i*n vitro* studies using human proteins and cells, as well as i*n vivo* studies using mouse and ferret models of infection. Our current studies are focused on (i) identification of cell-surface receptors used by influenza and other respiratory viruses to gain entry into host cells, (ii) how different cell types in the respiratory tract sense and respond to influenza virus infection, and (iii) 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.

Collaborators

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

Highlights and developments 2017

During 2017, 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 not in epithelial cells. 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 9 peer-reviewed publications during 2017, in journals such as The Journal of Virology, Science Immunology and Viruses. Dr Reading presented several research talks at conferences and institutes during the year and was an organizer of the 2nd Australian Respiratory Virology Meeting, which was held at the Peter Doherty Institute for Infection and Immunity in Melbourne. In addition, he was awarded an NHMRC Project Grant entitled 'Identification of host restriction factors that block respiratory virus infection' to fund his research for the next 4 years. In 2017, his research group consisted of one post-doctoral scientist, two PhD students and one Master of Biomedical Science student. Dr Reading is co-supervisor of an additional three PhD students enrolled at the University of Melbourne.

Research Funding and Awards

Centre staff members are Chief Investigators in grants awarded in 2017 for the following projects due to commence in 2018:

National Health and Medical Research Council (NHMRC) Development Grant: *"Identification of host restriction factors that block respiratory virus infection."* $956,898 awarded for the period 1 January 2018 – 31 December 2020. (Chief investigators **Patrick Reading** and Sarah Londrigan). The grant will be administered by The University of Melbourne.

Royal Melbourne Hospital Home Lottery Grant in Aid: *Evaluating the impact of the GeneXpert rapid influenza diagnostic in an emergency department on patient outcome and hospital work flow" .*
$25,000 awarded for the period 1 February 2018 – 31 January 2019 (Chief investigators **Aeron Hurt**). The grant will be administered by the Royal Melbourne Hospital and and the work will be undertaken at the Centre .

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 by the Australian Government 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) (2016-2017)

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 2017: A total of 44 egg isolates were obtained from 96 inoculations with original clinical specimens from various geographical locations. Isolation rates varied from 38% to 100% according to virus type/subtype and lineage. Suitable isolates were made available to other laboratories and industry for reassortment and assessment as vaccine candidates. The candidate vaccine virus (A/Singapore/INFIMH-16-0019/2016), which was originally submitted to the Centre by the National Public Health Laboratory in Singapore and subsequently isolated in eggs at the Centre was included as the A(H3N2) component in the WHO recommended influenza vaccine for the Southern Hemisphere in 2018.

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

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

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 2017: During 2017, 113 clinical specimens were cultured in MDCK 33016PF cells, of which 96 (85%) 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.

In 2017 Seqirus produced the first fully cell-based influenza vaccine component (A(H3N2) component) to be incorporated into an influenza vaccine, for distribution in the USA during the 2017–2018 influenza season. The virus used for this A(H3N2) vaccine component was originally isolated at the Centre from a clinical sample submitted by the National Public Health Laboratory in Singapore (A/Singapore/GP2050/2015).

In addition, two B/Yamagata lineage isolates, B/Singapore/INFTT-16-0610/2016 and B/Singapore/INFKK-16-0569/2016 are entering the final stages of pre-production testing, with one strain to replace the egg-based B/Yamagata strain in the 2018-2019 Northern Hemisphere vaccine. Again, these strains were isolated and characterised at the Centre after receiving clinical samples from the National Public Health Laboratory in Singapore.

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

Centre staff: Edin Mifsud, Ding Yuan Thomas Oh, 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.

Agreement with AusBio Ltd: *In vivo* studies of a novel influenza antiviral (2017)

Centre staff: Celeste Tai, Aeron Hurt

Overview: The Centre is investigating the effectiveness of a newly designed influenza antiviral *in vivo* using both prophylaxis and therapeutic regimens in the ferret model.

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 Annika Suttie, a PhD candidate from Federation University, commenced 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) and Paul Horwood (James Cook University).

MAE Candidate

Dr Ximena Tolosa, a Master of Philosophy in Applied Epidemiology (MAE) candidate from the Australian National University, commenced her placement at the Centre, under the supervision of **Sheena Sullivan**. As part of her placement, Ximena has completed her first project "Burden of influenza estimation in Cambodia" and commenced her second project, "Influenza vaccine effectiveness estimates in Australia, 2012-2017".

Honours students

Mr Leo Lee, a BSc(Honours) student enrolled through the University of Melbourne, completed his Honours project under the supervision of **Leonard Izzard** and **Aeron Hurt**. His project was titled "Using molecular adjuvants to improve an influenza DNA vaccine". In his project, Leo constructed two DNA vaccines that each co-expressed an influenza A virus along with one of two molecular adjuvants. These DNA vaccines were first expressed and validated in mammalian cells, and then tested in the ferret model. The DNA vaccines were successfully administered via intranasal delivery to ferrets which were then with infected with influenza A. However, these vaccines failed to induce seroconversion and did not affect viral shedding or clinical symptoms during infection. Leo was awarded First-Class Honours.

Ms Merryn Roe, a BSc (Honours) student enrolled through the University of Melbourne, completed her Honours project under the supervision of **Leonard Izzard, Ian Barr and Aeron Hurt**. Her project was titled "Investigating egg adaptive mutations of A(H3N2) influenza viruses and their effect on antigenicity". Merryn used reverse genetics to introduce mutations to the haemagglutinin (HA) gene of an A(H3N2) virus with the aim of introducing egg-adaptive mutations that would enable the virus to grow in eggs without altering antigenicity. One mutant virus successfully grew in eggs and showed similar antigenic behaviour to the wildtype virus, however additional mutations that arose during further propagation in eggs resulted in changes in antigenicity of the virus. Merryn was awarded First-Class Honours.

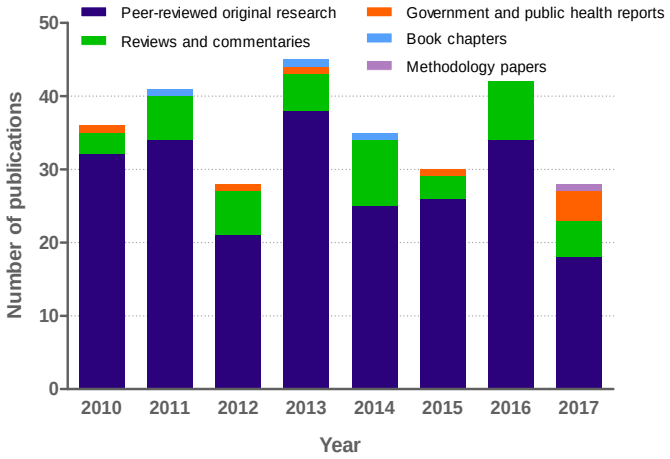
Communications and Advisory Activities

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. The Centre also organises and hosts the Australian Influenza Symposium.

Publications and Reports

The Centre continued to build its research and surveillance profile with the publication of 23 original research papers, reviews and reports in 2017 (Figure 18).

Figure 18. Centre publications 2010–2017



Centre Publications 2017

1. Allen RJ, Koutsakos M, **Hurt AC** and Kedzierska K. Uncomplicated cystitis in an adult male following influenza B virus infection. Am J Case Rep, 2017. 18: 190-193.

2. Ana-Sosa-Batiz F, Johnston APR, Hogarth PM, Wines BD, **Barr I**, Wheatley AK and Kent SJ. Antibody-dependent phagocytosis (ADP) responses following trivalent inactivated influenza vaccination of younger and older adults. *Vaccine*, 2017. 35(47): 6451-6458.

3. Arnott A, Carville K, Franklin L and **Sullivan SG**. Consecutive influenza infections in both adults and children. J Infect Dis, 2017. 215(4): 658-659.

4. **Barr IG**. Assessing the potential pandemic risk of recent avian influenza viruses. Eur Respir J, 2017. 49(3).

5. Douglas AP, Trubiano JA, **Barr I**, **Leung V**, Slavin MA and Tam CS. Ibrutinib may impair serological responses to influenza vaccination. Haematologica, 2017. 102(10): e397-e399.

6. Gavin K, Owen R and **Barr IG**. Annual report of the National Influenza Surveillance Scheme, 2010. Commun Dis Intell Q Rep, 2017. 41(4): E348-E368.

7. Goh EH, Jiang L, Hsu JP, Tan LWL, Lim WY, Phoon MC, Leo YS, **Barr IG**, Chow VTK, Lee VJ, Lin C, Lin R, Sadarangani SP, Young B and Chen MI. Epidemiology and Relative Severity of Influenza Subtypes in Singapore in the Post-Pandemic Period from 2009 to 2010. *Clin Infect Dis*, 2017. 65(11): 1905-1913.

8. Gubareva LV, Besselaar TG, Daniels RS, Fry A, Gregory V, Huang W, **Hurt AC,** Jorquera PA, Lackenby A, **Leang SK**, Lo J, Pereyaslov D, Rebelo-de-Andrade H, Siqueira MM, Takashita E, Odagiri T, Wang D, Zhang W and Meijer A. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2015-2016. Antiviral Res, 2017. 146: 12-20.

9. Hampson A, **Barr I**, Cox N, Donis RO, Siddhivinayak H, Jernigan D, Katz J, McCauley J, Motta F, Odagiri T, Tam JS, Waddell A, Webby R, Ziegler T and Zhang W. Improving the selection and development of influenza vaccine viruses - Report of a WHO informal consultation on improving influenza vaccine virus selection, Hong Kong SAR, China, 18-20 November 2015. Vaccine, 2017. 35(8): 1104-1109.

10. Horby PW, **Laurie KL**, Cowling BJ, Engelhardt OG, Sturm-Ramirez K, Sanchez JL, Katz JM, Uyeki TM, Wood J, Van Kerkhove MD and Committee CS. CONSISE statement on the reporting of Seroepidemiologic Studies for influenza (ROSES-I statement): an extension of the STROBE statement. Influenza Other Respir Viruses, 2017. 11(1): 2-14.

Centre Publications (continued)

11. **Hurt A**, **Komadina N**, **Deng YM**, **Kaye M**, **Sullivan S**, **Subbarao K** and **Barr I**. Detection of adamantane-sensitive influenza A(H3N2) viruses in Australia, 2017: a cause for hope? Euro Surveill, 2017. 22(47).

12. **Hurt AC** and **Subbarao K**. New options to treat influenza B. Nat Microbiol, 2017. 2(10): 1342-1343.

13. Kwok KO, Riley S, Perera R, Wei VWI, Wu P, Wei L, Chu DKW, **Barr IG**, Malik Peiris JS and Cowling BJ. Relative incidence and individual-level severity of seasonal influenza A H3N2 compared with 2009 pandemic H1N1. BMC Infect Dis, 2017. 17(1): 337.

14. **Leang SK** and **Hurt AC**. Fluorescence-based neuraminidase inhibition assay to assess the susceptibility of influenza viruses to the neuraminidase inhibitor class of antivirals. J Vis Exp, 2017(122).

15. **Leung VK**, **Carolan LA**, Worth LJ, Harper SA, **Peck H**, **Tilmanis D**, **Laurie KL**, Slavin MA and **Sullivan SG**. Influenza vaccination responses: Evaluating impact of repeat vaccination among health care workers. Vaccine, 2017. 35(19): 2558-2568.

16. **Leung VK**, **Spirason N**, **Lau H**, **Buettner I**, **Leang SK** and **Chow MK**. Influenza viruses received and tested by the Melbourne WHO Collaborating Centre for Reference and Research on Influenza annual report, 2015. Commun Dis Intell Q Rep, 2017. 41(2): E150-E160.

17. McAuley J, **Deng YM**, Gilbertson B, Mackenzie-Kludas C, **Barr I** and Brown L. Rapid evolution of the PB1-F2 virulence protein expressed by human seasonal H3N2 influenza viruses reduces inflammatory responses to infection. Virol J, 2017. 14(1): 162.

18. Pizzolla A, Nguyen THO, Smith JM, Brooks AG, Kedzieska K, Heath WR, **Reading PC** and Wakim LM. Resident memory CD8+ T cells in the upper respiratory tract prevent pulmonary influenza virus infection. Sci Immunol, 2017. 2(12).

19. Pizzolla A, Smith JM, Brooks AG and **Reading PC**. Pattern recognition receptor immunomodulation of innate immunity as a strategy to limit the impact of influenza virus. J Leukoc Biol, 2017. 101(4): 851-861.

20. Pizzolla A, Wang Z, Groom JR, Kedzierska K, Brooks AG, **Reading PC** and Wakim LM. Nasal-associated lymphoid tissues (NALTs) support the recall but not priming of influenza virus-specific cytotoxic T cells. Proc Natl Acad Sci U S A, 2017. 114(20): 5225-5230.

21. **Reading PC**, **Leung VK**, **Buettner I**, **Gillespie L**, **Deng YM**, **Shaw R**, **Spirason N**, **Todd A**, Shah AS, Konings F and **Barr IG**. The first external quality assessment of isolation and identification of influenza viruses in cell culture in the Asia Pacific region, 2016. J Clin Virol, 2017. 97: 54-58.

22. Regan AK, Moore HC, **Sullivan SG**, De Klerk Nand Effler PV. Epidemiology of seasonal influenza infection in pregnant women and its impact on birth outcomes. Epidemiol Infect, 2017. 145(14): 2930-2939.

23. Rondy M, El Omeiri N, Thompson MG, Leveque A, Moren A and **Sullivan SG**. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. J Infect, 2017. 75(5): 381-394.

24. **Sullivan SG**, Chilver MB, Carville KS, **Deng YM**, Grant KA, Higgins G, **Komadina N**, **Leung VK**, Minney-Smith CA, Teng D, Tran T, Stocks N and Fielding JE. Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017. Euro Surveill, 2017. 22(43).

25. **Tilmanis D**, van Baalen C, **Oh DY**, Rossignol JF and **Hurt AC**. The susceptibility of circulating human influenza viruses to tizoxanide, the active metabolite of nitazoxanide. Antiviral Res, 2017. 147: 142-148.

26. Villalon-Letelier F, Brooks AG, Saunders PM, Londrigan SL and **Reading PC**. Host cell restriction factors that limit influenza A infection. Viruses, 2017. 9(12).

27. Yan AW, Cao P, Heffernan JM, McVernon J, Quinn KM, La Gruta NL, **Laurie KL** and McCaw JM. Modelling cross-reactivity and memory in the cellular adaptive immune response to influenza infection in the host. J Theor Biol, 2017. 413: 34-49.

28. Zhou B, **Deng YM**, Barnes JR, Sessions OM, Chou TW, Wilson M, Stark TJ, Volk M, **Spirason N**, Halpin RA, Kamaraj US, Ding T, Stockwell TB, Salvatore M, Ghedin E, **Barr IG** and Wentworth DE. Multiplex reverse transcription-PCR for simultaneous surveillance of influenza A and B viruses. J Clin Microbiol, 2017. 55(12): 3492-3501.

Australian Influenza Symposium

The 12th Australian Influenza Symposium was held at the Peter Doherty Institute for Infection and Immunity, Melbourne on 1–2 November 2017 and was attended by approximately 200 delegates from Australia and other countries including the United States, China, Taiwan and the United Kingdom, including five invited international speakers:

Ben Cowling, The University of Hong Kong, Hong Kong
Anice Lowen, Emory University, Atlanta, GA, USA
Saad Omer, Emory University, Atlanta, GA, USA
Malik Peiris, The University of Hong Kong, Hong Kong
Yuelong Shu, Sun Yat-Sen University, Guangzhou, China

A broad range of topics were presented and discussed at the Symposium, including the evolution and spread of zoonotic influenza viruses; Influenza vaccinations for maternal, juvenile and elderly populations; attitudes towards influenza vaccination; epidemiological studies of influenza; new and emerging technologies in influenza vaccines, diagnostics and treatments; recent research developments in understanding influenza biology and the immune system response; and a roundtable discussion on ways to reduce the impact of seasonal influenza epidemics in Australia. The Symposium was also followed by a special joint session on Respiratory Syncytial Virus (RSV) with the Australian Respiratory Virology Meeting.

The organising committee for the Symposium was Ian Barr and Jayde Simpson. Almost all staff members from the Centre attended the symposium. Kanta Subbarao presented a talk and chaired a plenary session, and Sheena Sullivan chaired a workshop. Most staff members from the Centre attended the Symposium.

Presentations

Centre staff members presented talks and posters at numerous events during 2017, including national and international conferences, WHO meetings, educational lectures and research seminars.

ORAL PRESENTATIONS

Event/Institute; Location, date	Speaker, *Title(s)*
National University of Singapore Department of Microbiology & Immunology Programme Seminar Series; Singapore, 24 January 2017	Ding Yuan Thomas Oh: *Ferret as an animal model for investigating influenza antiviral: How far are we?*
Influenza Specialist Group Annual Scientific Meeting; Melbourne, 5–6 February 2017	Ian Barr: *An update on the 2016 and 2016-7 influenza seasons.* Aeron Hurt: *Debate regarding oseltamivir use for seasonal and pandemic influenza.* Kanta Subbarao: *Live attenuated influenza vaccines: potential role in an influenza pandemic.* Sheena Sullivan: *Vaccine effectiveness: variations by subtype and lineage.*
Australian Animal Health Laboratory; Geelong, Victoria, 23 February 2017	Kanta Subbarao: *Pandemic Influenza Viruses: Biology, Transmission and Vaccines*
Capital Health Network Immunisation Seminar; Canberra, 15 March 2017	Ian Barr: *Influenza and the influenza vaccine.*
WHO Antivirals Working Group meeting Hong Kong SAR, China, 12–13 April 2017	Aeron Hurt: *Update of influenza antivirals in late-phase clinical trial* Aeron Hurt: *A focus reduction assay for assessing susceptibility to nitazoxanide* Aeron Hurt: *BD iART rapid test (CDC experience)*
WHO PCR Working Group meeting Hong Kong SAR, China, 12–13 April 2017	Yi-Mo Deng: *Update of molecular surveillance activites at the Centre* Yi-Mo Deng: *Overview of the emerging NGS technology development.* Yi-Mo Deng: *NGS work at the WHO CC Melbourne.*
11th Bi-Regional Meeting of WHO NICs from WPRO and SEARO; Kuala Lumpur, Malaysia, 25 –27 April 2017	Kanta Subbarao: *Influenza vaccines: Present and Future.*
MDU PHL-VIDRL Public Health Seminar; Melbourne, 26 April 2017	Aeron Hurt: *What we do and what's new at the Influenza Centre*
Hospital Admission Review of Severe Acute Respiratory Infection (SARI); Siem Reap, 23 May 2017	Ximena Tolosa: *End of Mission Report, Hospital Admission Review, Siem Reap, 1–23 May, 2017.*
Visit to Telethon Kids Institute; Perth, 8 May 2017	Sheena Sullivan: *Methodological Issues in studies to estimate vaccine effectiveness.*
Optimising the use of administrative data for acute respiratory infection research Symposium; Perth, 9 May 2017	Sheena Sullivan: *Flu research in Victoria.*
2017 Viruses and Cells Gordon Research Conference; Barga, Italy, 14–19 May 2017	Kanta Subbarao: *Viral and host determinants of influenza virus transmission.*

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	Speaker, *Title(s)*
Lecture to 3rd year students, University Breadth Subject "Global health, security and sustainability", University of Melbourne; Melbourne, 17 May 2017	Aeron Hurt: *Influenza.*
University of Cambridge; Cambridge UK, 22 May 2017	Sheena Sullivan: *Methodological issues in studies to estimate vaccine effectiveness.*
I-MOVE (Influenza Monitoring Vaccine Effectiveness) meeting; Veyrier du Lac, France, 22–25 May 2017	Sheena Sullivan: *A prospective serosurvey to investigate antibody responses and risk of infection after influenza vaccination in multiply vaccinated healthcare workers.*
Workshop on conducting a Hospital Admission Review to estimate the burden of influenza; Phnom Penh, 22–23 May 2017	Ximena Tolosa: *Hospital Admission Review Data Analysis Training Part 1. Obtaining a numerator for influenza BOD estimation.* *Ximena Tolosa: Hospital Admission Review Data Analysis Training Part 2. Obtaining a denominator for influenza BOD estimation.*
Royal Melbourne Hospital Essential ID Seminar; Melbourne, 25 May 2017	Aeron Hurt: *Influenza.*
Gene Technology Access Centre (GTAC) 13th Annual Teacher Symposium: "One Health: new perspectives on managing disease"; Melbourne, 14 June 2017	Kanta Subbarao: *Birds, pigs, camels and bats: responding to global outbreaks of novel respiratory viruses.*
5th ISIRV-AVG conference; Shanghai, China, 14 –16 June 2017	Naomi Komadina: *The EpiFlu™ Database.* Ding Yuan Thomas Oh: *Evaluation of the effectiveness of oseltamivir against influenza variants with the H275Y neuraminidase mutation in ferrets.*
Australian Animal Health Laboratory; Geelong, Victoria, 16 June 2017	Sheena Sullivan: *Methodological issues in studies to estimate vaccine effectiveness.*
Symposium on seasonal influenza treatment and vaccination policy development and implementation; Beijing, China, 17–18 June 2017	Aeron Hurt: *Antiviral resistance surveillance and treatment protocol development.* Kanta Subbarao: *Country report: seasonal influenza vaccination and coverage in Australia.*
Transmission of respiratory viruses: from basic science to evidence based options for control; Hong Kong SAR, China, 19–22 June 2017	Kanta Subbarao: *Seasonal, pandemic, and emerging influenza viruses transmit with similar efficiency over sequential rounds of airborne contact in ferrets.* Kanta Subbarao: *Insights into influenza virus biology, host-pathogen interactions and interventions from airborne transmission studies in ferrets.*
Communicable Diseases Control Conference; Melbourne, 26–28 June 2017	Vivian Leung: *Antibody response and influenza-like illness among healthcare workers after influenza vaccination.*
Presentation to students visiting the Doherty Institute from Tsinghua University; Melbourne, 28 June 2017	Aeron Hurt: *Influenza pandemics.*
The 24th NIBSC influenza meeting; London, UK, 13–14 July 2017	Ian Barr*: Overview of the 2017 Southern hemisphere influenza season so far……*

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	Speaker, *Title(s)*
WHO Meeting of National Influenza Centres; Geneva, Switzerland, 17–19 July 2017	Ian Barr*: An overview of laboratory assays – challenges and solutions.*
Seminar at Department of Biochemistry, University of Oxford; Oxford, UK, 21 July 2017	Patrick Reading*: Sensing and responding to respiratory virus infections.*
Postgraduate Association for Students of Immunology and Microbiology (SPASIM) 10th Biennial Scientific Conference; Melbourne, 21 July 2017	Rubaiyea Farrukee*: Characterization of influenza B variants with D197N and H273Y neuraminidase mutations.*
Seminar at the Institute of Clinical Chemistry and Clinical Pharmacology, Bonn University; Bonn, Germany, 25 July 2017	Patrick Reading*: Sensing and responding to respiratory virus infections.*
Seminar at National Heart & Lung Institute (NHLI), Imperial College London; London, UK, 27 July 2017	Patrick Reading*: Sensing and responding to respiratory virus infections.*
Department of Medicine seminar series, Deakin University; Geelong, Victoria, 8 August 2017	Aeron Hurt: *What's new with influenza?*
Doherty Seminar Series; Melbourne, 10 August 2017	Kanta Subbarao*: Developing pandemic influenza vaccines: business as usual versus a paradigm shift.*
Visit to Research Institute of Tropical Medicine (RITM), the National Influenza Centre; Muntinlupa City, Philippines, 14–16 August 2017	Patrick Reading*: What we do at the WHO Collaborating Centre for Reference and Research on Influenza (WHOCCRRI) in Melbourne.* Patrick Reading*: Setting up and maintaining cell culture and virus isolation in your laboratory.* Patrick Reading*: Laboratory tests to detect and characterise influenza virus in clinical specimens and isolates.* Patrick Reading*: Testing influenza viruses for sensitivity to antiviral drugs - why we do it.* Patrick Reading*: Practical considerations for setting up antiviral testing for influenza viruses in your laboratory.*
Expert consultation on new laboratory technologies for the detection and characterisation of emerging infectious diseases; Manila, Philippines, 17–18 August 2017	Patrick Reading*: Implementing new technologies into Pacific Island Countries and Territories.*
Singapore International Infectious Disease Conference; Singapore, 24–26 August 2017	Kanta Subbarao*: Influenza vaccines and therapeutics.*
Master of Philosophy in Applied Epidemiology (MAE): Tales from the Field seminar; ANU Research School of Population Health; Canberra, 5 September 2017	Ximena Tolosa*: Burden of influenza-associated hospitalisations in Cambodian children.*
Lecture to 3rd year Medical and Applied Immunolog students at the University of Melbourne; Melbourne, 15 September 2017	Patrick Reading*: Influenza virus- pandemics, epidemics and the continuing threat of novel viruses entering the human population.*
Doherty Institute Post Doctoral Seminar Series; Melbourne, 26 September 2017	Michelle Wille*: Viruses on the wing.*

ORAL PRESENTATIONS (continued)	
Event/Institute; Location, date	Speaker, *Title(s)*
Early Career Research Network in the Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne 'Alternative Careers in Science' night; Melbourne, 26 September 2017	Patrick Reading*: A career that combines research and public health interests – a balancing act.*
Visit to New York University; New York City NY, USA, 8 October 2017	Yi-Mo Deng*: Influenza surveillance work at the WHO CC Melbourne.*
Victorian Infectious Diseases Service (VIDS) seminar; Melbourne, 9 October 2017	Kanta Subbarao*: The 2017 influenza season and recommended composition for the 2018 vaccine.*
VIIN Young Investigator Symposium; Melbourne, 16 October 2017	Kanta Subbarao*: Building blocks of a research career: opportunities, initiative and.....luck.*
Queensland Influenza Summit; Brisbane, 18 October 2017	Kanta Subbarao*: The annual cycle: From virus typing to vaccine development and summary of the 2017 Australian influenza season.*
Australian Influenza Symposium; Melbourne, 1 –2 November 2017	Kanta Subbarao*: The role of monoclonal antibodies against the influenza virus haemagglutinin in prophylaxis and treatment of infection.*
Fudan University International Symposium on Infectology; Shanghai, China, 2–5 November 2017	Kanta Subbarao*: Prevention and control of pandemic influenza.*
2nd Australian Respiratory Virology Meeting; Melbourne, 2–3 November 2017	Louise Carolan*: Pathogenesis, humoral immune responses and transmission between co-housed animals in a ferret model of human RSV infection.*
Australian Orthinology Conference; Geelong, Victoria, 8–10 November 2017	Michelle Wille*: Serological analysis of migratory shorebirds to assess exposure risk and incursions of highly pathogenic avian influenza into Australia.*
Seminar at Burnet Institute; Melbourne, 14 November 2017	Kanta Subbarao*: Pandemic influenza vaccines.*
Guideline Development Committee Meeting - Updating the WHO standard guidance for the clinical management of influenza infections; Geneva, Switzerland, 14–16 November 2017	Aeron Hurt: *A review of novel and traditional rapid tests for influenza virus detection.*
NHMRC "Limiting the Impact of Influenza" Program retreat; Melbourne, 22–23 November 2017	Kanta Subbarao*: The challenge of seasonal influenza viruses.* Rubaiyea Farrukee*: Assessing the replication, transmission and fitness of antiviral resistant influenza viruses.* Sheena Sullivan*: Effectiveness of annual influenza vaccination.*
The University of Queensland Diamantina Institute; Brisbane, 23 November 2017	Patrick Reading*: Sensing and responding to respiratory virus infections.*
Faculty of Health Seminar at University of Tasmania; Hobart, 24 November 2017	Kanta Subbarao*: Seasonal and pandemic influenza.*
9th Australasian Virology Society Meeting; Adelaide, 5–8 December 2017	Kanta Subbarao*: Prevention and control of pandemic influenza viruses.* Patrick Reading*: Identification of host antiviral agents against respiratory viruses.*
2017 Scientific Conference of Research for Public Health; Ho Chi Minh City, Vietnam, 8 December 2017	Sheena Sullivan*: Translating influenza surveillance into policy in the Asia-Pacific.*

POSTER PRESENTATIONS

Event; Location, date	Title and authors *(Centre authors are marked in bold, presenting author is underlined)*
5th ISIRV-AVG conference; Shanghai, China, 14–16 June 2017	Nitazoxanide susceptibility of recently circulating human influenza viruses. **Tilmanis D**, van Baalen C, **Oh DY**, Rossignol JF and **Hurt AC** Evaluation of the effectiveness of nitazoxanide in a ferret model of influenza A(H1N1)pdm09 infection. **Oh DY**, **Tai CM**, **Tilmanis D**, Rossignol JF and **Hurt AC**
Melbourne Health Research Week; Melbourne, 22–29 June 2017	Viral respiratory tract infections in allogeneic haematopoietic stem cell transplant recipients. **Sim SA**, **Leung V**, Ritchie D, Teh BW and **Sullivan S** Antibody response and influenza-like illness among healthcare workers after influenza vaccination. **Leung VK**, **Aban M**, **Carolan LA**, **Laurie K**, Druce J, Slavin MA, Marshall C and **Sullivan SG**
Communicable Diseases Control Conference; Melbourne, 26–28 June 2017	Overcoming bias in the estimation of antibody titres. McLean A, **Leung V** and **Sullivan S**
The Sixth ESWI Influenza Conference; Riga, Latvia, 10–13 September 2017	Serial passage of influenza viruses under nitazoxanide selective pressure to investigate the likelihood for antiviral resistance. **Tilmanis D**, **Koszalka P**, **Oh DY**, Rossignol JF and **Hurt AC** Development of an antiviral focus reduction assay to determine the netazoxanide susceptibility of recently circulating human influenza virus. **Tilmanis D**, van Baalen C, **Oh DY**, Rossignol JF and **Hurt AC**
Global Virus Network Meeting; Melbourne, 25–27 September 2017	Serological analysis of migratory shorebirds to assess exposure risk and incursions of highly pathogenic avian influenza in Australia. **Wille M**, Lisovski S, Klaassen M and **Hurt AC** Characterization of influenza B virus variants with reduced neuraminidase inhibitor susceptibility. **Farrukee RF**, **Reading PC** and **Hurt AC** Leveraging surveillance data for influenza pandemic preparedness: a Cambodian example. **Tolosa MX**, Ieng V, Tek B, Sar B, Theocharopoulos G, Kheng S, Seng H, Ly S, **Leung VK** and **Sullivan SG**
2nd ASM Conference on Rapid Applied Microbial Next -Generation Sequencing and Bioinformatic Pipelines; Washington DC, USA, 8–11 October 2017	A fully integrated workflow for influenza virus surveillance using next generation sequencing. **Deng YM**, **Kaye M**, **Spirason N**, Kamaraj U, **Lau H**, **Iannello P**, **Todd A**, Sessions O, **Subbarao K** and **Barr I**
Doherty Research Day; Melbourne, 17 December 2017	Characterization of influenza B virus variants with reduced neuraminidase inhibitor susceptibility. **Farrukee RF**, **Reading PC** and **Hurt AC** A fully integrated workflow for influenza virus surveillance using next generation sequencing. **Deng YM**, **Kaye M**, **Spirason N**, Kamaraj U, **Lau H**, **Iannello P**, **Todd A**, Sessions O, **Subbarao K** and **Barr I** Leveraging surveillance data for influenza pandemic preparedness: a Cambodian example. **Tolosa MX**, Ieng V, Tek B, Sar B, Theocharopoulos G, Kheng S, Seng H, Ly S, **Leung VK** and **Sullivan SG**
9th Australasian Virology Society Meeting; Adelaide, 5–8 December 2017	Rapid molecular differentiation by pyrosequencing of the new B/Victoria-lineage deletion variants from other circulating human influenza B viruses. **Lau H**, Xu X, **Barr I** and **Deng YM** Use of the Focus Reduction Assay (FRA) to antigenically analyse circulating human Influenza A(H3N2) viruses. **Peck H**, **Gillespie L** and **Barr I** Influenza virus susceptibility and likelihood of resistance to the antiviral drug Nitazoxanide. **Koszalka P**, **Tilmanis D**, Rossignol JF and **Hurt AC** Characterization of influenza B virus variants with reduced neuraminidase inhibitor susceptibility. **Farrukee R**, **Reading PC** and **Hurt AC**

Engagement in WHO Activities

Event; Location, Date	Centre staff involved
WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for Use in the 2017-2018 Northern Hemisphere Influenza Season; Geneva, Switzerland, 27 February – 2 March 2017	Kanta Subbaro and Ian Barr participated, Aeron Hurt attended.
Informal consultation of experts of Public Health Laboratories in the South East Asian Region; Pune, India, 21–22 March 2017	Kanta Subbarao presented a talk. Patrick Reading attended.
WHO Meeting on Influenza Pandemic Preparedness: Launch of the Pandemic Influenza Severity Assessment (PISA) Framework and Update of the Guidance for Surveillance during an Influenza Pandemic; Geneva, Switzerland, 22–24 March 2017	Ian Barr attended.
WHO Antivirals Working Group meeting; Hong Kong SAR, China, 12–13 April 2017	Aeron Hurt was meeting chair and presented three talks.
WHO PCR Working Group meeting; Hong Kong SAR, China, 12–13 April 2017	Yi-Mo Deng presented three talks.
11th Bi-Regional Meeting of WHO NICs from WPRO and SEARO; Kuala Lumpur, Malaysia, 25–27 April 2017	Ian Barr, Patrick Reading, Sheena Sullivan and Yi-Mo Deng attended. Kanta Subbarao presented a talk. Naomi Komadina ran a workshop on "Sequencing & the GISAID EpiFLu™".
WHO Third informal consultation on influenza vaccine response during the start of a pandemic; Geneva, Switzerland, 7–9 June 2017	Ian Barr attended.
Informal meeting with other WHO Collaborating Centres; Geneva, Switzerland, 6 June 2017	Ian Barr attended.
WHO Meeting of National Influenza Centres; Geneva, Switzerland, 17–19 July 2017	Sheena Sullivan attended. Ian Barr presented a talk. Aeron Hurt and Patrick Reading each manned an information desk for a poster session.
WHO Meetings on PIP Partnership Contribution Implementation; Geneva, Switzerland, 20–21 July 2017	Ian Barr attended.
Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) Global Conference; Chiang Mai, Thailand, 7–11 August 2017	Kanta Subbarao was a panel member for the session "A spotlight on history: 70 years of global influenza control"
Expert consultation on new laboratory technologies for the detection and characterisation of emerging infectious diseases; Manila, Philippines, 17–18 August 2017	Patrick Reading attended and presented a talk.
WHO Consultation on the Composition of Influenza Vaccines for the southern hemisphere 2018; Melbourne, 25–27 September 2017	Kanta Subbarao and Ian Barr participated. Aeron Hurt attended. Sheena Sullivan presented the Global Influenza Vaccine Effectiveness report.
WHO PIP Partnership Contribution Independent Technical Expert Mechanism (PCITEM) meeting; Geneva, Switzerland, 26–27 October 2017	Kanta Subbarao participated.
Guideline Development Committee Meeting - updating the WHO standard guidance for the clinical management of influenza infections; Geneva, Switzerland, 14–16 November 2017	Aeron Hurt participated and presented a talk.

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
Viruses in May Katoomba, New South Wales, 11–13 May 2017	Malet Aban and Louise Carolan attended.
5th ISIRV-AVG conference; Shanghai, China, 14–16 June 2017	Aeron Hurt co-chaired two sessions.
Transmission of respiratory viruses: from basic science to evidence based options for control; Hong Kong SAR, China, 19–22 June 2017	Ian Barr and Aeron Hurt attended. Kanta Subbarao co-moderated a session.
NIAID/NIH sponsored workshop on Pathway to a Universal Influenza Vaccine; Bethesda MD, USA, 28–29 June 2017	Kanta Subbarao was rapporteur for discussions on Animal Models in Influenza Research
The Sixth ESWI Influenza Conference; Riga, Latvia, 10–13 September 2017	Ian Barr attended
2nd Australian Respiratory Virology Meeting; Melbourne, 2–3 November 2017	Angela Todd, Danielle Tilmanis, Leah Gillespie, Malet Aban and Sheena Sullivan attended. Patrick Reading was a co-organiser and session chair. Jayde Simpson was part of the organising committee.
Doherty Research Day; Melbourne, 17 November 2017	Patrick Reading was a co-organiser.
Brisbane Life Science ECR Symposium (BLiSS) for early career researchers; Brisbane, 23–24 November 2017	Patrick Reading was a presenter and panelist in the 'Careers outside academia' panel session.
Australian Society for Immunology; Brisbane, 27 November – 1 December 2017	Ian Barr attended.
2017 Scientific Conference of Research for Public Health; Ho Chi Minh City, Vietnam, 8 December 2017	Sheena Sullivan chaired a session.

Image courtesy of WPRO

Community Engagement

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

Ian Barr

- Participated in an interview for the show 'Ask the Doctor" on ABC TV on 24 May 2017. http://iview.abc.net.au/programs/ask-the-doctor/DO1625V010S00
- Participated in an interview with Australian Associated Press for articles "A better flu vaccine needed, says expert" (News.com.au) and "Experts to scrutinise the 2017 flu vaccine (SBS news), published 4 September 2017
  http://www.sbs.com.au/news/article/2017/09/04/experts-scrutinise-2017-flu-vaccine
  http://www.news.com.au/national/breaking-news/experts-to-scrutinise-the-2017-flu-vaccine/news-story/013a11f21f76e3136f42bd1394d1a791
- Provided comment for an article in The Australian, "For an instant man-flu diagnosis on your phone, just swab right, published 1 November 2017: http://www.theaustralian.com.au/news/health-science/for-an-instant-manflu-diagnosis-on-your-phone-just-swab-right/news-story/7c36a26c75823dea0ed90aa64f100038

Aeron Hurt

- Participated in radio interviews to provide commentary on a research publication in Science Immunology (http://immunology.sciencemag.org/content/2/12/eaam6970) on 6 June 2017.
  - "Breakfast with Peter Bell", ABC Radio Perth:
    http://www.abc.net.au/radio/perth/programs/breakfast/breakfast/8574356
  - "Mitchell's Front Page" on The Pulse Radio Geelong: http://mitchellsfrontpage.com/
  - "Breakfast with Paul Culliver" on ABC Radio North and West SA
- Participated in an interview with The Sydney Morning Herald for the article "Why didn't my flu jab keep influenza at bay this year?", published 26 September 2017: http://www.smh.com.au/national/health/why-didnt-my-flu-jab-keep-influenza-at-bay-this-year-20170926-gyou1x.html

Kanta Subbarao

- Participated in an interview for Channel 7¹s Weekend Sunrise program, 15 April 2017
- Participated in an interview with the University of Melbourne news site Pursuit for article "The Flu-Hunters", published 8 May 2017. https://pursuit.unimelb.edu.au/articles/the-flu-hunters
- Participated in an interview for the show 'Ask the Doctor" on ABC TV on 24 May 2017. http://iview.abc.net.au/programs/ask-the-doctor/DO1625V010S00
- Participated in Victoria's Gene Technology Access Centre (GTAC) 13th annual Teacher's Symposium on One Health: new perspectives on managing disease. Presented on 'Birds, pigs, camels and bats: responding to global outbreaks of novel respiratory viruses, 14 June 2017.
- Participated in an interview with The Age for the article "I didn't get the flu shot. Does that make me an anti-vaxxer?", published 8 September 2017. http://www.theage.com.au/comment/i-didnt-get-the-flu-shot-does-that-make-me-an-antivaxxer-20170908-gydm89.html
- Participated in an interview with Brisbane Times for the article "Do you use your hands to cover a cough or sneeze? You're doing it all wrong, published 8 September 2017. https://www.brisbanetimes.com.au/healthcare/do-you-use-your-hands-to-cover-a-cough-or-sneeze-youre-doing-it-all-wrong-20170908-gydem6.html
- Participated in an interview with the Herald Sun for the article "Deaths double as deadly flu strain hits aged-care homes, published 8 September 2017. http://www.heraldsun.com.au/news/victoria/deaths-double-as-deadly-flu-strain-hits-agedcare-homes/news-story/0978ebb30dabbd19cc7d554a525af8f4
- Participated in an interview with The Australian for the article "After deadly flu season, WHO calls for change to jab, published 28 September 2017. http://www.theaustralian.com.au/national-affairs/health/after-deadly-flu-season-who-calls-for-change-to-jab/news-story/11d93087d35be4f2520c2c9e8ecd9c1a
- Participated in an interview with The Sydney Morning Herald for the article "Death of three-year-old Vanika Idnani with influenza A stark warning to parents", published 8 October 2017. http://www.smh.com.au/national/health/death-of-threeyearold-vanika-idnani-with-influenza-a-stark-warning-to-parents-20171003-gytusa.html
- Participated in an interview with STAT for the article "Flu experts see potential for a nasty winter season", published 16 October 2017. https://www.statnews.com/2017/10/16/flu-virus-severity/
- Provided comment for an article in STAT, "How the incredible, edible egg may actually be hampering your flu vaccine", published 7 November 2017. https://www.statnews.com/2017/11/07/flu-vaccine-egg-production/

Sheena Sullivan

- provided comment for the article titled "Repeat influenza vaccination yields reduced antibody response" on the website Infectious Disease Advisor, published 6 June 2017: http://www.infectiousdiseaseadvisor.com/influenza/antiviral-serologic-response-not-improved-by-repeat-flu-vaccine/article/665956/

Ximena Tolosa

- wrote an article "Understanding the impact of influenza virus infections in Cambodia" for The Graduate Union Newsletter (published by The University of Melbourne Graduate Union)published August 2017 https://issuu.com/graduatehouse/docs/augustnewsletter_2017_web

Publications authored by staff were also featured in the following articles:

- Scientific American: Flu vaccine "factories" create errors that reduce protection: https://www.scientificamerican.com/article/flu-vaccine-ldquo-factories-rdquo-create-errors-that-reduce-protection/ (cites Sullivan et al. Eurosurveillance, 2017: http://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.43.17-00707)
- Medscape: Experts warn of severe influenza, low vaccine efficacy (Kanta Subbarao and Sheena Sullivan), published 4 December 2017: https://www.medscape.com/viewarticle/889563
- Medscape: Seasonal flu deaths more common worldwide than expected (Sheena Sullivan), published 13 December 2017: https://www.medscape.com/viewarticle/890082
- CIDRAP: New estimate shows higher global rate of deaths from flu (Sheena Sullivan), published 14 December 2017: http://www.cidrap.umn.edu/news-perspective/2017/12/new-estimate-shows-higher-global-rate-deaths-flu

Website

The Centre website was maintained and updated throughout the year. During 2017, the website was viewed by 8,725 unique users from 138 different countries. The majority of visits to the website came from Australia, followed by the USA.

Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2017.

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, Operational Management Committee*
- Influenza Research and Treatment, *Editorial Board*
- Public Health Laboratory Network (Department of Health)

Michelle Chow

- Doherty Institute, *Communications Working Group*

Yi-Mo Deng

- WHO Working Group for GISRS PCR detection for influenza surveillance

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*
- 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*

Naomi Komadina

- Global Initiative on Sharing All Influenza Data (GISAID), *Database Technical Committee (Chair)*

Katie Milne

- Medical Laboratory Quality Network
- Victorian Infectious Disease Reference Laboratory, *NATA Action Group*

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, Operational Management Committee*
- Universal Influenza Vaccine Project at Mount Sinai School of Medicine, New York City NY, USA, *Scientific Advisory Board*
- FLUCOP consortium, *External 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*
- Australasian Epidemiology Association*, Secretary*
- WHO Advisory Group on Observational Influenza Vaccine Effectiveness Reporting Standards

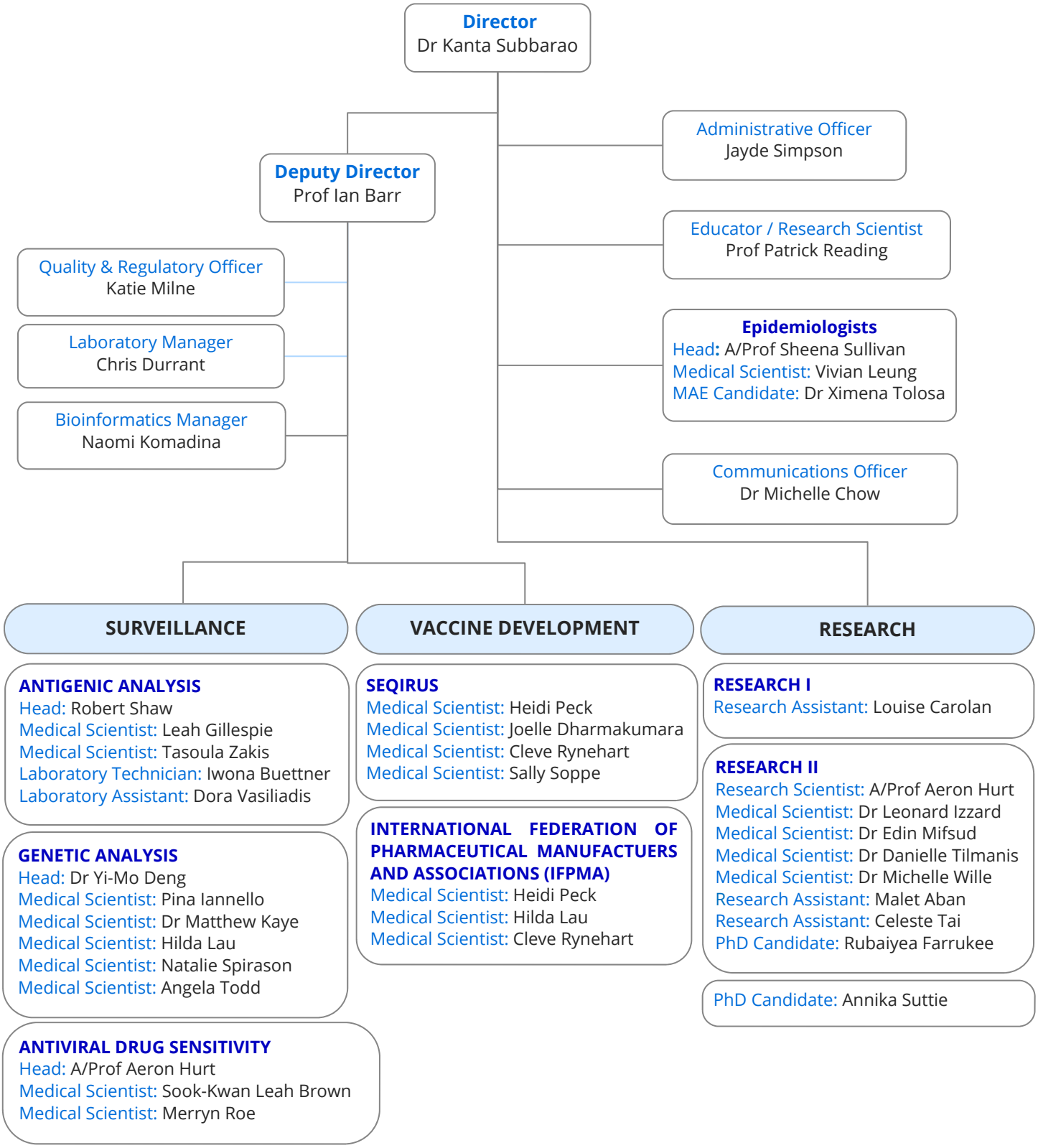
Visitors to the Centre

The Centre was pleased to host the following visitors during 2017.

Date	Visitor and affiliation
7 February	Dr Jackie Katz, Director, Atlanta World Health Organization (WHO) Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Atlanta GA, USA Dr Dan Jernigan, Director, Influenza Division in the National Center for Immunization and Respiratory Diseases, CDC, Atlanta GA, USA
8 March	Dr Philippe Dussart, Head, Virology Group, Institut Pasteur du Cambodge, Phnom Penh, Cambodia; Dr Paul Horwood, Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Queensland; Dr Andrew Greenhill, Federation University, Churchill, Victoria. *Research collaborators*
10 March	Prof Brendan Murphy, Chief Medical Officer, Australian Government Department of Health, Canberra
1 – 12 May	Dr Samuel Wilks, Research assistant, WHO Collaborating Centre for Modelling, Evolution and Control of Emerging Infectious Diseases, Department of Zoology, University of Cambridge, Cambridge, UK *Research collaborator.*
27 June – 21 July	Dr Jessica Wong, The University of Hong Kong, Hong Kong SAR, China. *Research collaborator*
29 June – 7 July	Dr Rosanne Barnes, Telethon Kids Institute, Perth. *Research collaborator*
30 June	Ms Cara Minney-Smith; PathWest Laboratory, Perth; *Visiting scientist, Learned about NGS and serology techniques at the Centre*
12 July	Master of Veterinary Public Health (Emergency Animal Diseases) students, accompanied by Dr Simon Firestone; The University of Melbourne, Melbourne; *Visiting students, toured Centre facilities*
19 July	Ms Maria Auladell Bernat; Department of Microbiology and Immunology, University of Melbourne, Melbourne; *Visiting scientist, undertook training in HI assays*
1 August	Mr Luca Hensen; Department of Microbiology and Immunology, University of Melbourne, Melbourne; *Visiting scientist, undertook training in HI assays*
24 October – 16 November	Dr Jessica Wong; The University of Hong Kong, Hong Kong SAR, China; *Research collaborator*
30 – 31 October	Ms Huiying Chua; The University of Hong Kong, Hong Kong SAR, China; *Visiting student*
30 October – 10 November	Dr Rosanne Barnes; Telethon Kids Institute, Perth; *Research collaborator*
31 October	Mrs Michelle Clarke; Women's and Children's Hospital, Adelaide; *Research collaborator*
31 October	Prof Ben Cowling; The University of Hong Kong, Hong Kong SAR, China; *Research collaborator*
20 – 24 November	Delegation from Tan Tock Seng Hospital (Dr Barnaby Young, Ms Rachel Lim, Ms Jung Pu Hsu, Ms Yazid Nurhidayah); Tan Tock Seng Hospital, Singapore; *Research collaborators, conducted HI assays and serological analyses*

Dr Jackie Katz (front, 2nd from right) and Dr Dan Jernigan (back, 2nd from right) meeting with Centre staff.

Management and staff



Staff Changes 2017

Ms Celeste Tai joined the Centre as a research assistant in February.

Dr Edin Mifsud joined the Centre as a post-doctoral researcher in August.

Ms Angela Todd joined the Centre in April in the Genetic Analysis group.

Ms Sally Soppe joined the Centre in July as a scientist on the Seqirus project.

Ms Merryn Roe joined the Centre in October in the Antiviral Drug Sensitivity group.