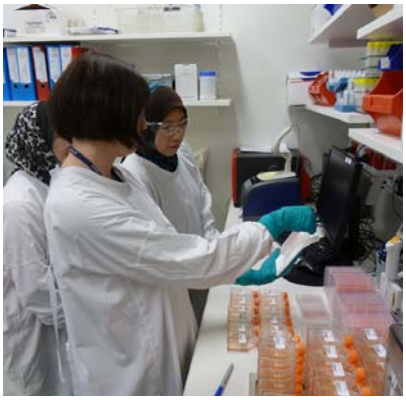

2014 Annual Report

WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL

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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 2011-2015) are:

i. 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;

ii. 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;

iii. to assist WHO in developing recommendations on viruses to be included in influenza vaccines;

iv. 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;

v. to collect epidemiological information on the prevalence of influenza, especially in countries and areas in the Region;

vi. to undertake research to improve the detection, prevention and treatment of influenza; and

vii. to assist WHO and national health authorities in developing and implementing plans for responding to pandemic influenza.

Governance

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

Contact information

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Highlights of 2014

Surveillance

The Centre received 5374 samples during 2014, the highest number since the pandemic in 2009. Of the samples tested, the highest proportion were A(H1N1) pdm09 viruses (40.5%).

Publications

Centre staff were authors on a total of 35 original research papers, reviews, reports and book chapters, including a paper in *Science*.

Research

The Centre continued to expand and develop its research interests during 2014, including phylodynamics of B influenza viruses, characterization of localised immune responses, and developing animal models for viral fitness.

Moving to the Doherty Institute

A new chapter in the history of the Centre opened in April 2014 when we moved premises, along with the rest of the VIDRL, to the newly established Peter Doherty Institute for Infection and Immunity. The Doherty Institute is a joint venture between the Royal Melbourne Hospital and The University of Melbourne, and brings together over 700 scientists, researchers, academics, clinicians and graduate students working across many different facets of infectious disease and immunity, including teaching, research, epidemiology, and diagnostic and reference laboratories.

Our partner organisations at the Dohery Institute are:

- Department of Microbiology and Immunology, The University of Melbourne;
- Microbiological Diagnostic Unit Public Health Laboratory, The University of Melbourne;
- Victorian Infectious Diseases Reference Laboratory (VIDRL);
- Victorian Infectious Diseases Service (VIDS); and
- VICNISS Healthcare Associated Infection Surveillance System (VICNISS)

The Doherty Institute is a purpose-built, state-of-the-art, 5-star Green Star facility and was officially opened on 12 September 2014 by the Prime Minister The Hon Tony Abbott MP. We are excited to have moved into our new facilities, which provide access to a wider range of resources and new collaborative opportunities with other research, public health and clinical groups in the Institute.

Director's Report

It is a pleasure to present the 2014 Annual Report of the WHO Collaborating Centre for Reference and Research on Influenza at VIDRL.

2014 was an historic year for the Centre. After more than 7 years of discussion, fundraising, building and planning by the University of Melbourne and Melbourne Health, the Peter Doherty Institute for Infection and Immunity became a reality with the completion of state-of-the art laboratory and teaching facilities in the heart of the Parkville Strip in Melbourne. In April 2014, the Centre together with the rest of VIDRL relocated to our new laboratories at the Institute. While the construction and commissioning of such a complex building presented many technical challenges, regulatory approvals were in place and the Centre's laboratories were fully operational in time to respond to the heavy demands of the 2014 southern hemisphere influenza season.

The Centre's participation in the Doherty enterprise gives us new opportunities to work closely with clinical and biomedical research groups to improve understanding and responsiveness to influenza and to be part of a major national resource for responding to emerging infectious disease threats. We are grateful to the Commonwealth and Victorian State Governments for their support for the construction of the Doherty Institute and our involvement in it.

2014 was also a big year for influenza with the Centre receiving and processing the highest annual number of influenza samples since the 2009 pandemic year. While A(H1N1)pdm09 viruses were predominant, particular challenges were presented by recently circulating A(H3N2) viruses that were genetically distinct but difficult to distinguish antigenically from the 2014 vaccine virus. We continue to work closely with colleagues in the global influenza surveillance community to address these issues. The Centre's work contributed to the WHO recommendation in September 2014 to update the southern hemisphere seasonal influenza vaccine for 2015 with new A(H3N2) and B/Yamagata lineage viruses; the latter virus, B/Phuket/3073/2013, was isolated at the Centre. The Centre also supported international efforts to monitor non-human influenza viruses with pandemic potential, including the avian influenza A(H7N9) virus that emerged in March 2013, and newly emerging avian A(H5Nx) viruses.

A substantial body of research was also undertaken during 2014, much it with national and international collaborators. Among the highlights were work on molecular evolution and epidemiology of human influenza viruses, innate and adaptive immune responses to influenza virus infection in the ferret model, clinical effectiveness of neuraminidase inhibitors in animal models, and influenza vaccine effectiveness.

The Centre was pleased to host several meetings at the Doherty Institute during 2014, including the inaugural Influenza Monitoring Vaccine Effectiveness (I-MOVE) meeting, a short course on epidemiological methods and the 10th Australian Influenza Symposium. In addition to bringing together scientists and researchers working in the field, these events provided opportunities to showcase our new facilities.

This is my final Annual Report as Director of the Centre, written as I take up my new position as Chief Executive Officer of the National Health and Medical Research Council in April 2015.

It has been an extraordinary privilege to serve as the Centre's Director over the last 8 years. The Centre has undergone many changes as we made the transition from our former host CSL Limited to VIDRL in 2006/7, relocated to new laboratories at VIDRL in 2008 and then moved with VIDRL into the Doherty Institute in 2014. Over this period we have experienced the 2009 influenza pandemic, faced many challenges from ever-changing seasonal influenza viruses and maintained our readiness to respond to diverse newly emerging avian and swine influenza viruses causing human infections. We have continued to build relationships with collaborators in the WHO National Influenza Centres and have greatly increased our contribution to capacity building in influenza virus detection and characterisation by laboratories in the Asia-Pacific region. Our research productivity in-house and through national and international collaborations has grown markedly and we have extended the depth and range of our intellectual and technical skills across influenza virology, genetics, immunology and epidemiology. I thank all the scientists and support staff who have worked at the Centre over this period for the honour of working with them.

We are immensely grateful to Dr Mike Catton, Director of VIDRL, and many other members of VIDRL staff, especially Dr Bill Maskill, Renato Raimondi, Anna Ayres and Dallas Wilson, for their support of the Centre's work at every level during 2014. 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 express our Centre's thanks to all our friends and colleagues in the National Influenza Centres and other laboratories, the other WHO Collaborating Centres for Influenza and Essential Regulatory Laboratories, and WHO itself on whose collaboration we depend to make our contribution to the global response to influenza.

Professor Anne Kelso AO
Director

Surveillance

Introduction

The WHO Collaborating Centre at VIDRL in Melbourne is one of five Collaborating Centres in the world that conduct human influenza surveillance for WHO by analysing samples submitted by WHO National Influenza Centres and other laboratories. 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, 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 originally of avian origin, with various combinations of 16 antigenically different HA variants and 9 NA variants. Although influenza B viruses are not classified into subtypes, there are two co-circulating lineages, B/Victoria and B/Yamagata. Currently there are three families of influenza viruses circulating in the human population — influenza A(H1N1), influenza A(H3N2) and influenza B. Since the emergence of the pandemic A(H1N1) strain in 2009 [A(H1N1)pdm09], circulation of the former seasonal A(H1N1) virus has ceased.

Receipt of Influenza Viruses

During 2014 the Centre received 5374 clinical specimens and/or virus isolates from 35 laboratories in 14 countries (Figures 1 and 2, Table 1). A total of 5277 samples (98%) were cultured and analysed by haemagglutination inhibition (HI) assay and/or real-time reverse-transcription polymerase chain reaction (RT-PCR) reaction. Of the samples for which results could be obtained, 40.5% were identified as A(H1N1)pdm09, 24.7% were A(H3N2) viruses and 16.5% were influenza B viruses (Table 2). 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.

Amongst samples received by the Centre for which the age of the patient was known, the largest portion were from subjects aged under 5 years. (Figure 3). A total of 1055 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 direct isolation into eggs as 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, 2009-2014.

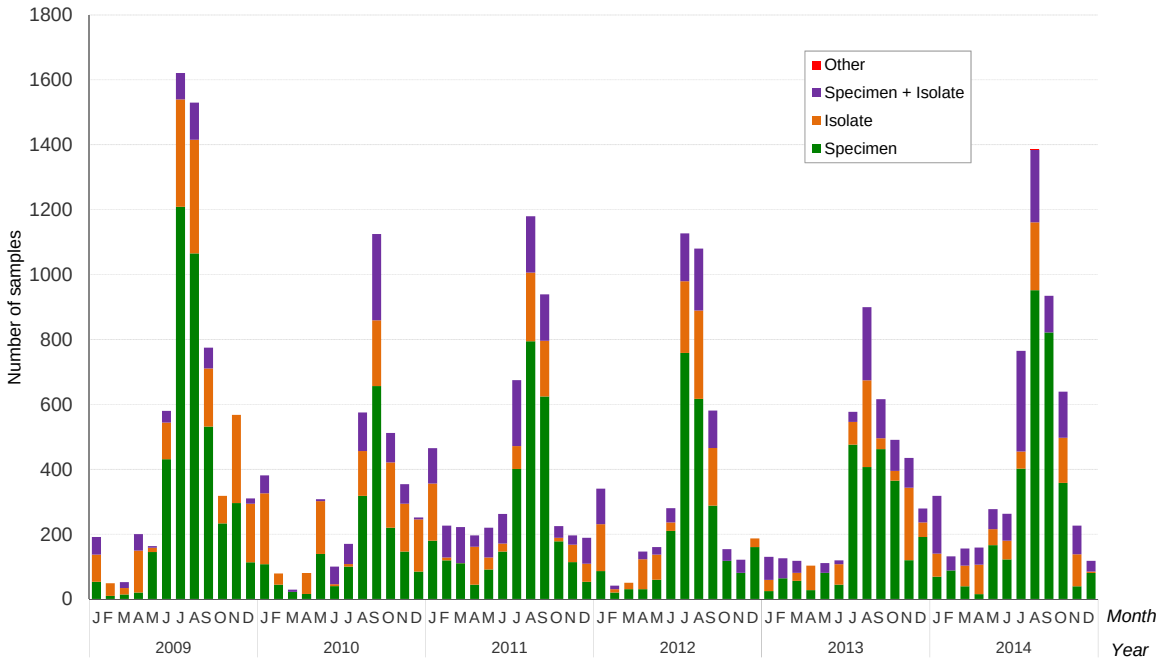


Figure 2. Geographic spread of influenza laboratories sending viruses to the Centre during 2014.

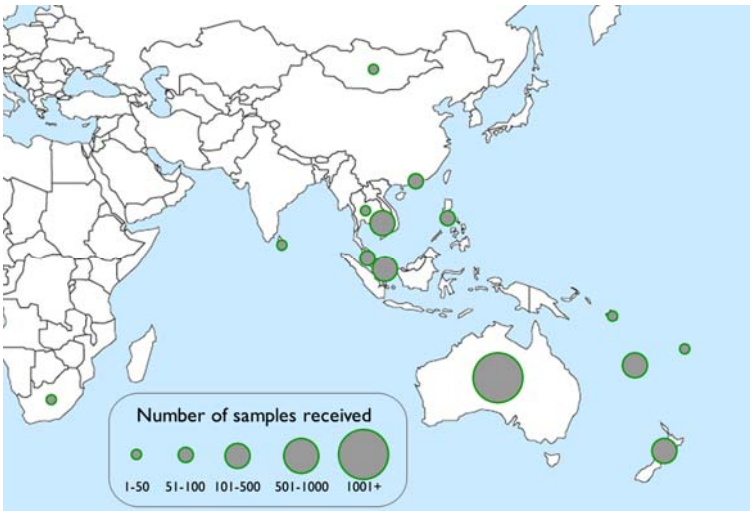


Figure 3. Age distribution of subjects from whom samples were received and the age is known at the Centre in 2014.

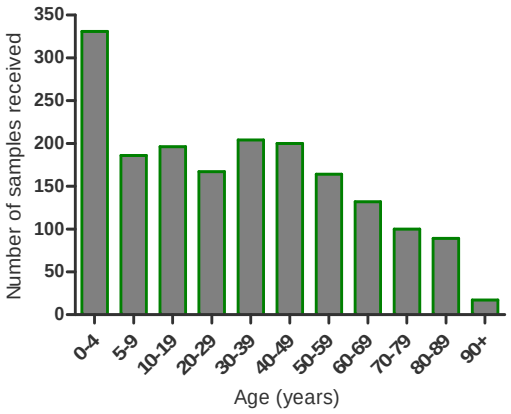


Table 1. Samples received by the Centre in 2014 by country.

Country	Samples received				Samples tested
	Specimens	Isolates	Specimen + Isolate	Other (eg. RNA)	
AUSTRALASIA	2875	551	1031	1	98%
Australia	2796	231	1031	1	98%
New Zealand	79	320	0	0	100%
SOUTH PACIFIC	159	0	0	0	100%
Fiji	29	0	0	0	100%
New Caledonia	119	0	0	0	100%
Solomon Islands	11	0	0	0	100%
SOUTH EAST ASIA	74	202	339	0	100%
Cambodia	41	105	0	0	100%
Malaysia	0	74	0	0	100%
Philippines	28	0	28	0	100%
Singapore	0	0	311	0	100%
Thailand	5	23	0	0	100%
EAST ASIA	0	77	6	0	100%
Macau SAR	0	62	3	0	100%
Mongolia	0	15	3	0	100%
SOUTH ASIA	44	0	0	0	100%
Sri Lanka	44	0	0	0	100%
AFRICA	0	0	16	0	100%
South Africa	0	0	16	0	100%
TOTAL	**3152**	**830**	**1392**	**1**	**98%**

Table 2. Samples tested by HI and/or RT-PCR assay at the Centre in 2014, by country.

Country	Samples tested by HI and/or RT-PCR assay							
	A(H1N1) pdm09	A(H3N2)	A (unsubtyped)	Mixed type	B/ Victoria	B/ Yamagata	B lineage undetermined	C
AUSTRALASIA	**1833**	**975**	**936**	**0**	**33**	**374**	**196**	**3**
Australia	1647	871	936	0	31	270	193	3
New Zealand	186	104	0	0	2	104	3	0
SOUTH PACIFIC	**72**	**42**	**2**	**0**	**2**	**9**	**3**	**0**
Fiji	1	2	0	0	0	1	1	1
New Caledonia	71	34	2	0	2	8	2	0
Solomon Islands	0	6	0	0	0	0	0	0
SOUTH EAST ASIA	**181**	**216**	**6**	**4**	**30**	**164**	**14**	**0**
Cambodia	55	50	0	0	0	39	2	0
Malaysia	30	16	0	0	2	21	1	0
Philippines	10	24	4	0	4	2	11	0
Singapore	74	121	2	3	23	92	0	0
Thailand	12	5	0	1	1	10	0	0
EAST ASIA	**27**	**23**	**0**	**0**	**16**	**17**	**0**	**0**
Macau SAR	24	21	0	0	10	10	0	0
Mongolia	3	2	0	0	6	7	0	0
SOUTH ASIA	**5**	**30**	**8**	**0**	**0**	**0**	**1**	**0**
Sri Lanka	5	30	8	0	0	0	1	0
AFRICA	**4**	**9**	**0**	**0**	**0**	**3**	**0**	**0**
South Africa	4	9	0	0	0	3	0	0
TOTAL	**2122**	**1295**	**952**	**4**	**81**	**567**	**214**	**3**

Table 3. Samples received from general practitioner based surveillance systems in Australia, 2014 .

	Australian Sentinel Practices Research Network *(ASPREN)*	GP Sentinel Surveillance network of Victoria *(VIC GPSS)*	Sentinel Practices Network of Western Australia *(SPN(WA))*
Number of samples received	414	203	438
Number of samples isolated	97	158	256
Samples analysed by HI Assay	97	157	250

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. Subtypes are based on analysis of the HA an in some cases are confirmed by genetic analysis of NA.

*Antigenic analyses 2014**

The acquisition of a Tecan EVO 200 liquid handling robot by the Centre during 2014 has enabled greater automation of HI assays, with increased efficiency and reproducibility. A total of 4877 isolates that were received at the Centre in 2014 were cultured and isolated in MDCK cells, of which 3355 (68.8%) produced a positive result. The majority of viruses were A(H1N1)pdm09 (53.2%) (Figure 4).

**Subtypes and lineages are based on analysis of the HA and in some cases confirmed by genetic analysis of NA.*

Figure 4. Influenza sub/types and lineages of samples received in 2014 and analysed by HI assay.

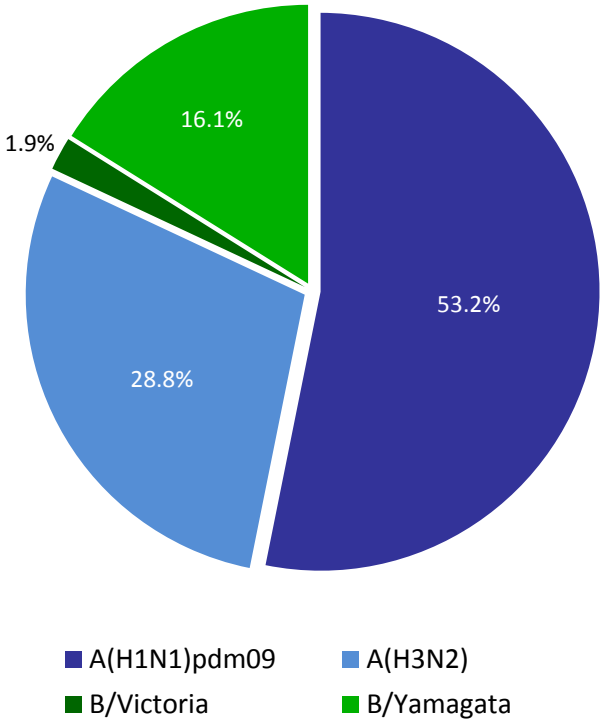
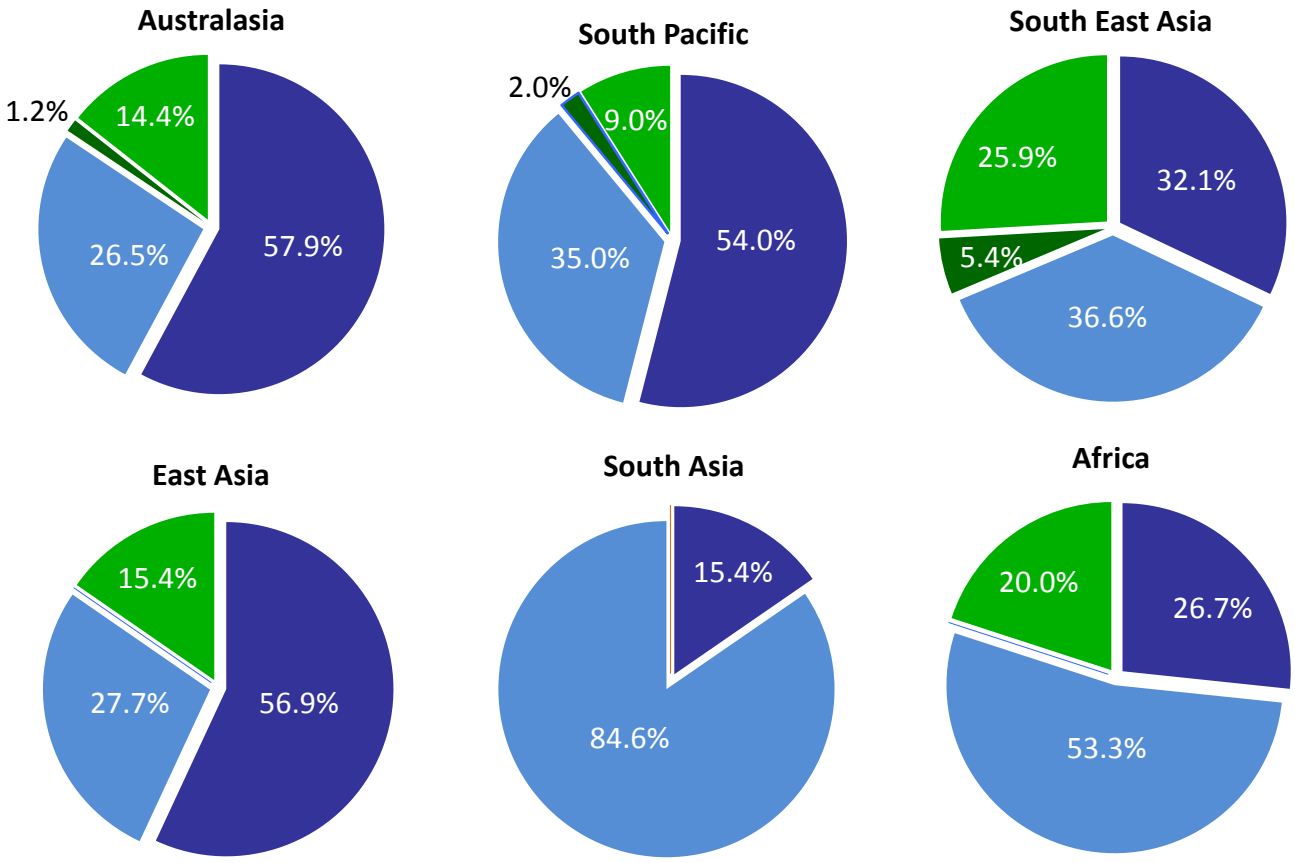


Figure 5. Influenza sub/types and lineages of isolates received from different world regions during 2014 as determined by antigenic analysis.



Genetic Analysis of Influenza Viruses

Background

A subset of all influenza viruses analysed at the Centre undergoes genetic analysis by sequencing of viral RNA 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 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 isolation. Sequence data are used to compare viruses from different parts of the world and help to inform the selection of vaccine strains.

The Centre acquired an IonTorrent PGM™ System in 2014. This has allowed Centre staff to develop and apply next generation sequencing (NGS) techniques that enable sequencing of influenza A viruses without prior knowledge of subtype, which in turn allows for more efficient and cost-effective sequencing of whole genomes of viruses. Importantly, this also enables novel or unknown influenza viruses to be fully sequenced within a few days, which would be extremely useful should a new pandemic virus emerge in our region.

Sequencing 2014

In 2014, 444 HA, 440 NA, 320 MP and 138 NS genes from 461 human viruses received at the Centre were sequenced (Figure 6). In addition, 63 viruses were analysed by full genome sequencing using traditional Sanger sequencing techniques (Figures 7). Viruses were selected for these analyses because they were representative of the viruses received and/or because they displayed unusual properties during antigenic analysis.

NGS techniques were also used to sequence the full genomes of 12 influenza A viruses (Figure 8) and the HA, NA and MP genes of 96 influenza A and influenza B (HA/NA only) viruses without prior identification of type or subtype (Figure 9).

Figure 6. Sequence analysis of samples received at the Centre in 2014.

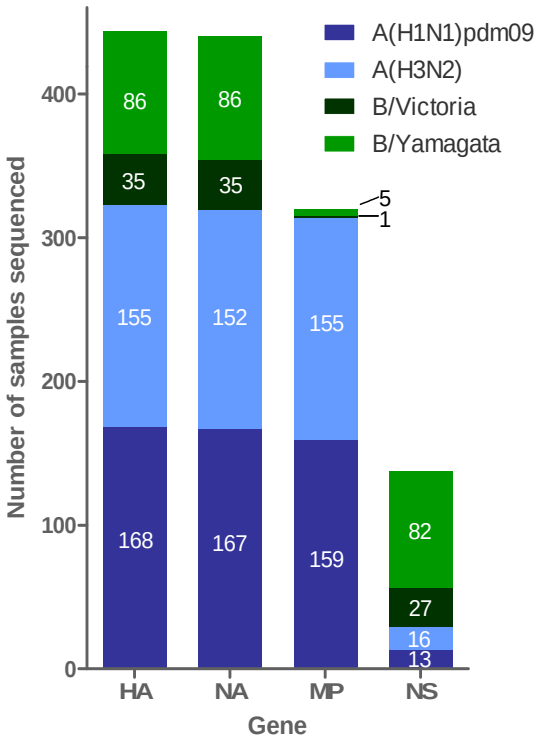


Figure 7. Geographic spread of submitting laboratories and numbers of viruses analysed by full genome sequencing using Sanger sequencing the Centre in 2014.

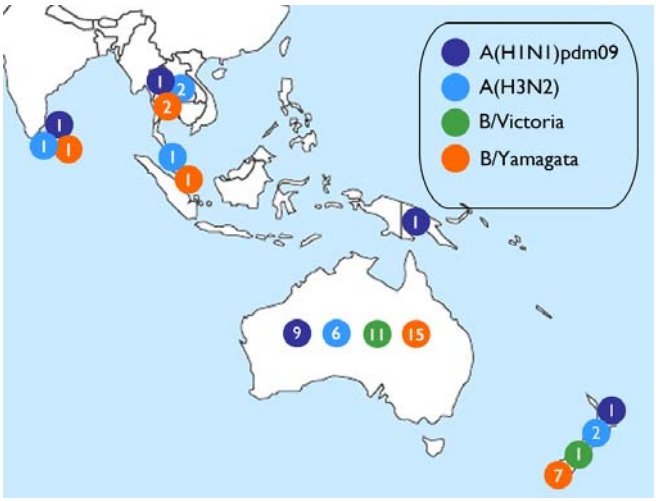


Figure 8. Geographic spread of submitting laboratories and numbers of influenza A viruses analysed by full genome sequencing using NGS techniques at the Centre in 2014.

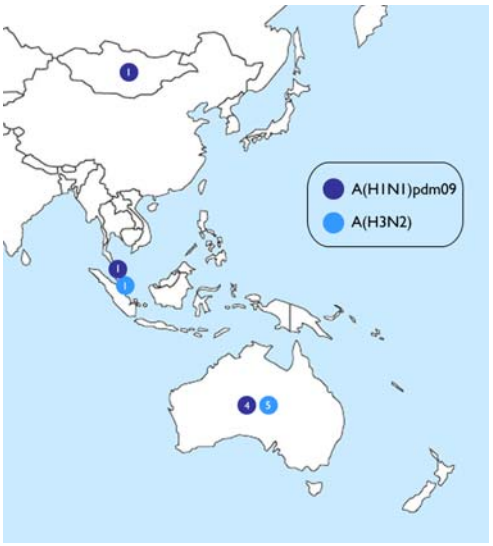
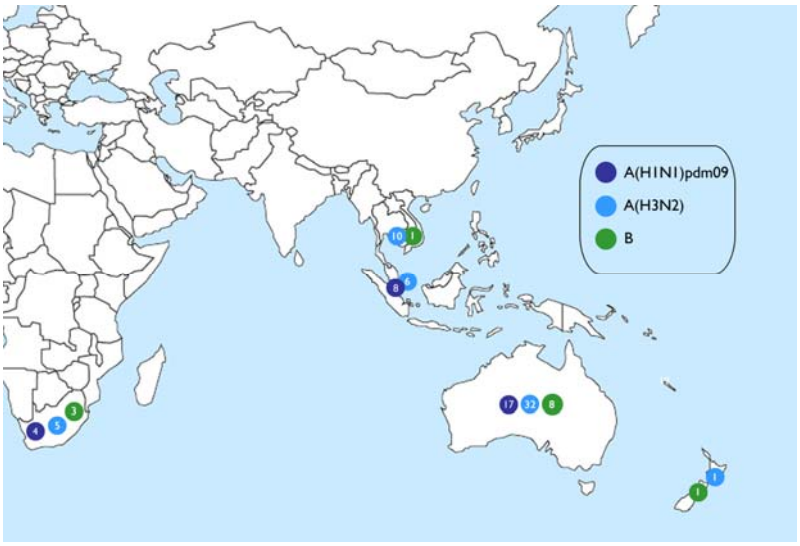


Figure 9. Geographic spread of submitting laboratories and numbers of viruses with HA, NA and MP genes sequenced using NGS techniques at the Centre in 2014.



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 publically 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 2014

A total of 1535 gene sequences from 472 viruses were deposited with GISAID in 2014 (Table 4). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 34 influenza viruses were also represented in the Centre's submissions (data not shown).

Table 4. Genetic sequences submitted to GISAID by the Centre in 2014.*

Type/ Subtype / Lineage \ Gene	HA	NA	MP	PB2	PB1	PA	NP	NS	Total
A(H1N1)pdm09	167	167	162	16	16	16	16	16	**576**
A(H3N2)	174	174	146	9	9	9	9	9	**539**
B/Victoria	23	23	0	0	0	0	0	18	**64**
B/Yamagata	107	106	10	10	10	10	9	94	**356**
Total	**471**	**470**	**318**	**35**	**35**	**35**	**34**	**137**	**1535**

** Counts include sequences submitted to the Centre during 2014, which may include viruses received in 2013.*

Surveillance Results by Influenza Subtype

Viruses were analysed by comparison with reference viruses recommended by WHO for the 2014-2015 Northern Hemisphere and 2015 Southern Hemisphere vaccines. Using the HI assay, viruses were identified as low-reactors if their titre with the reference antiserum was at least 8-fold lower than the titre of the reference virus. Results of sequencing analysis of the HA region of the haemagglutinin gene are also described in the following sections.

Influenza A(H1N1)pdm09

Antigenic analysis

A total of 1762 A(H1N1)pdm09 isolates were available for analysis by HI assay in 2014. The majority (99.5%) of these viruses displayed similar antigenic properties to the vaccine reference strain A/California/7/2009 (Table 5, Figure 10).

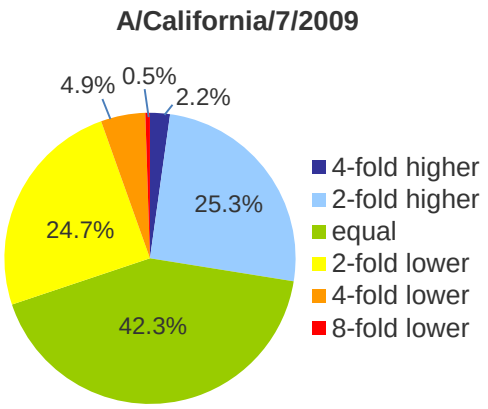
Haemagglutinin gene sequencing

Sequencing was performed on HA genes from 168 viruses. Phylogenetic analysis showed that circulating A(H1N1)pdm09 viruses sent to the Centre during 2014 contained some genetic changes compared to the vaccine reference strain A/California/7/2009. However, these changes did not affect the antigenic behaviour of the viruses (Figure 11).

Table 5. Antigenic characterisation of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/California/7/2009 reference virus.

	A(H1N1)pdm09 reference strain: A/California/7/2009	
Region	**Like**	**Low reactor (%)**
Australasia	1493	7 (0.5%)
Pacific	54	0
South East Asia	175	1 (0.6%)
East Asia	25	1 (3.8%)
South Asia	2	0
Africa	4	0
Total	**1753**	**9 (0.5%)**

Figure 10. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/California/7/2009 reference virus.



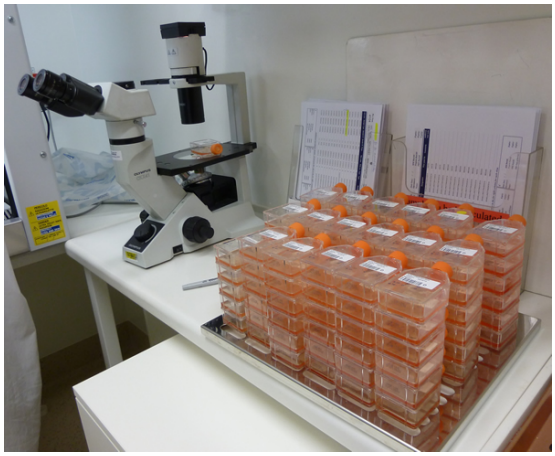
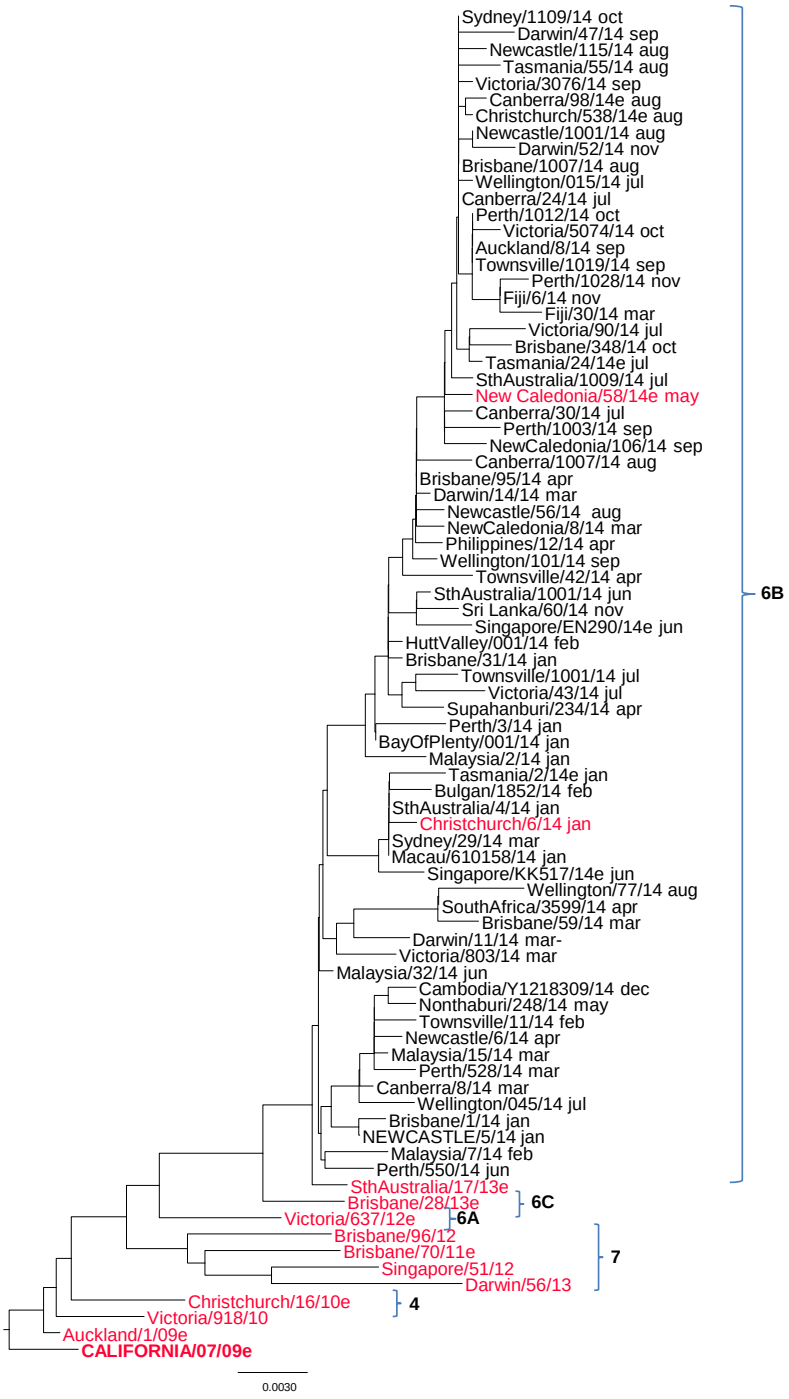


Figure 11. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2014.



Legend

2015 SOUTHERN HEMISPHERE VACCINE STRAIN

Reference virus

e: egg isolate

Scale bar represents 0.3% nucleotide sequence difference between viruses

} Brackets indicate clades

Influenza A(H3N2)

Antigenic analysis

A total of 963 A(H3N2) subtype isolates were available for analysis by HI assay. Very few low reactors to the cell -grown reference strain A/Victoria/361/2011 were detected (Table 6, Figure 12). However, evolutionary changes in A(H3N2) viruses have made it difficult to detect recent antigenic change using HI assays. Some WHO Collaborating Centres have detected antigenic changes in recent viruses using HI assays that incorporate oseltamivir carboxylate, although this was not done at the Centre. Following a change in the WHO vaccine recommendations in September 2014, A(H3N2) viruses were analysed in comparison to the new vaccine reference strain A/Switzerland/9715293/2013 (Table 6, Figure 13). Studies are under way to determine the most appropriate method for detecting antigenic change in A(H3N2) viruses.

Haemagglutinin gene sequencing

Sequencing of HA genes from 155 A(H3N2) viruses indicated that recently circulating viruses have undergone genetic change compared to A/Texas/50/2012 (Figure 14). Sequencing and phylogenetic analysis of haemagglutinin (HA) genes indicate that viruses circulating during 2014 have undergone genetic change compared to A/Texas/50/2012, consistent with antigenic and genetic changes observed by other WHO Collaborating Centres and warranting a change in recommended vaccine strain. Many antigenic variants fell into clades 3C.2a and 3C.3a — viruses from these clades are genetically distinct but were not readily distinguishable antigenically in HI assays. The new recommended vaccine strain, A/Switzerland/9715293/2013, is in clade 3C.3a.

Table 6. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the A/Victoria/361/2011 and A/Switzerland/9715293/2013 reference viruses.

	A(H3N2) reference strain: A/Victoria/361/2011		A(H3N2) reference strain: A/Switzerland/9715293/2013	
Region	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**
Australasia	675	1 (0.1%)	11	0
Pacific	11	0	24	0
South East Asia	199	3 (1.5%)	0	0
East Asia	20	0	0	0
South Asia	11	0	0	0
Africa	8	0	0	0
Total	**924**	**4 (0.4%)**	**35**	**0**

Figure 12. Summary of fold differences in HI titres of A(H3N2) viruses analysed at the Centre compared to the A/Victoria/361/2011 reference virus.

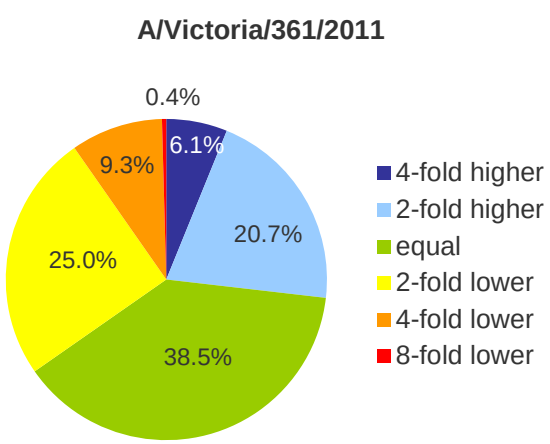


Figure 13. Summary of fold differences in HI titres of A (H3N2) viruses analysed at the Centre compared to the A/Switzerland/9715293/2013 reference virus.

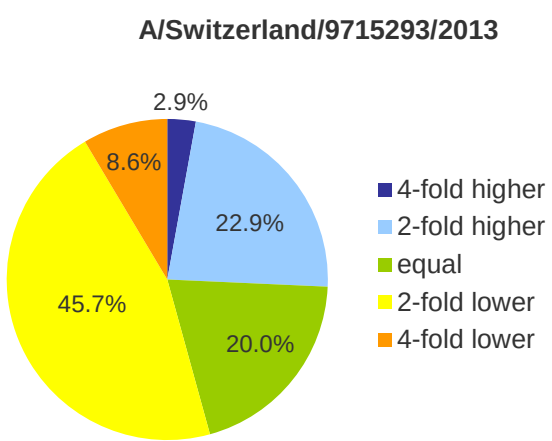
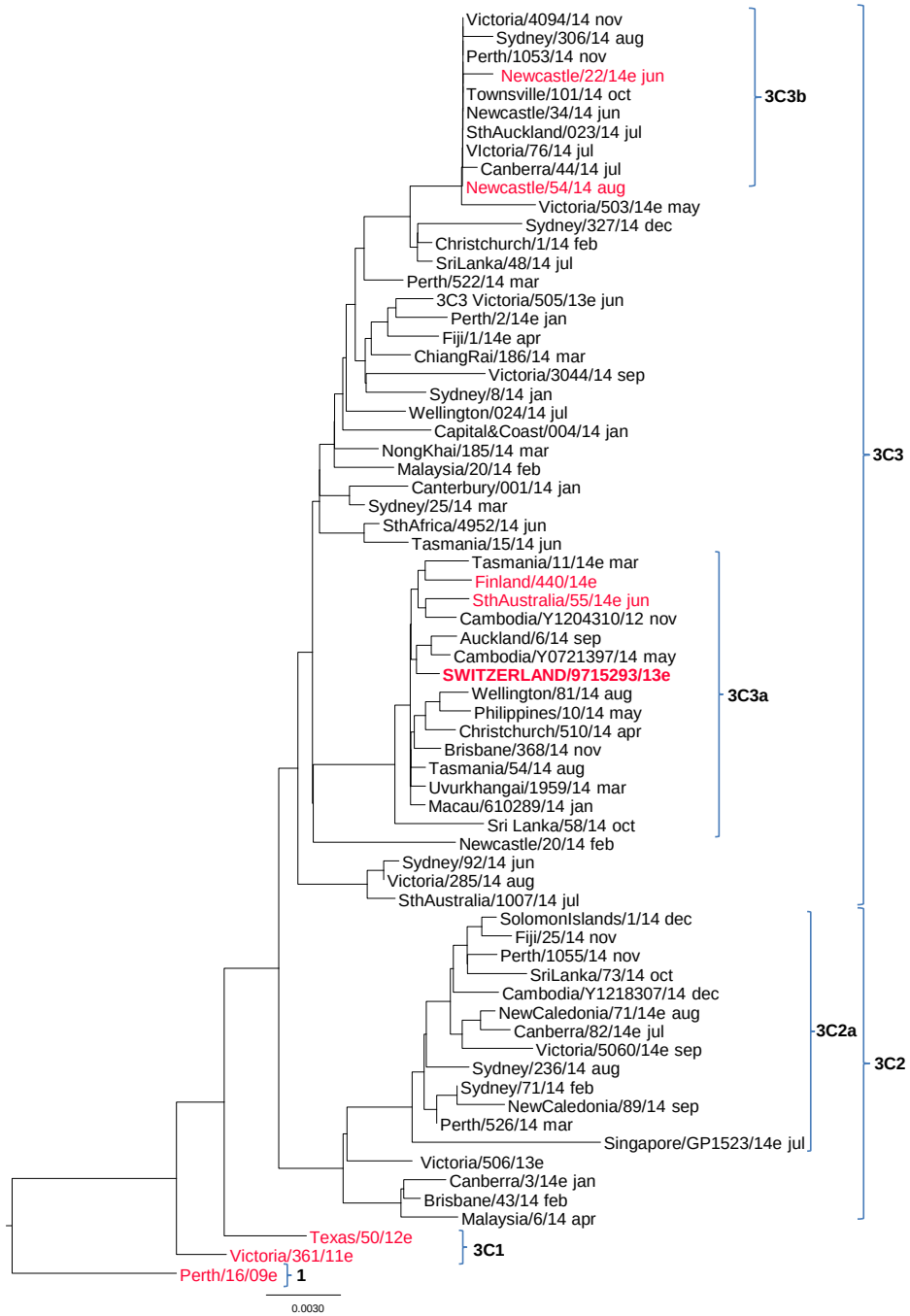


Figure 14. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2014.



Legend

2015 SOUTHERN HEMISPHERE VACCINE STRAIN

Reference virus

e: egg isolate

Scale bar represents 0.3% nucleotide sequence difference between viruses

} Brackets indicate clades

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 2011 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 2014 the B/Yamagata lineage predominated amongst circulating influenza B viruses received at the Centre. Of the 80 B/Victoria viruses received and analysed antigenically at the Centre in 2014, all but one were similar to B/Brisbane/60/2008 (Table 7, Figure 15).

Antigenic analysis indicated that the majority of circulating B/Yamagata viruses were low reactors to the northern hemisphere 2014-2015 vaccine strain B/Massachusetts/2/2012 (Table 7, Figure 16). Following the change in the WHO vaccine recommendations in September 2014, viruses were analysed in comparison to the new vaccine reference strain B/Phuket/3073/2013 (Table 7, Figure 17).

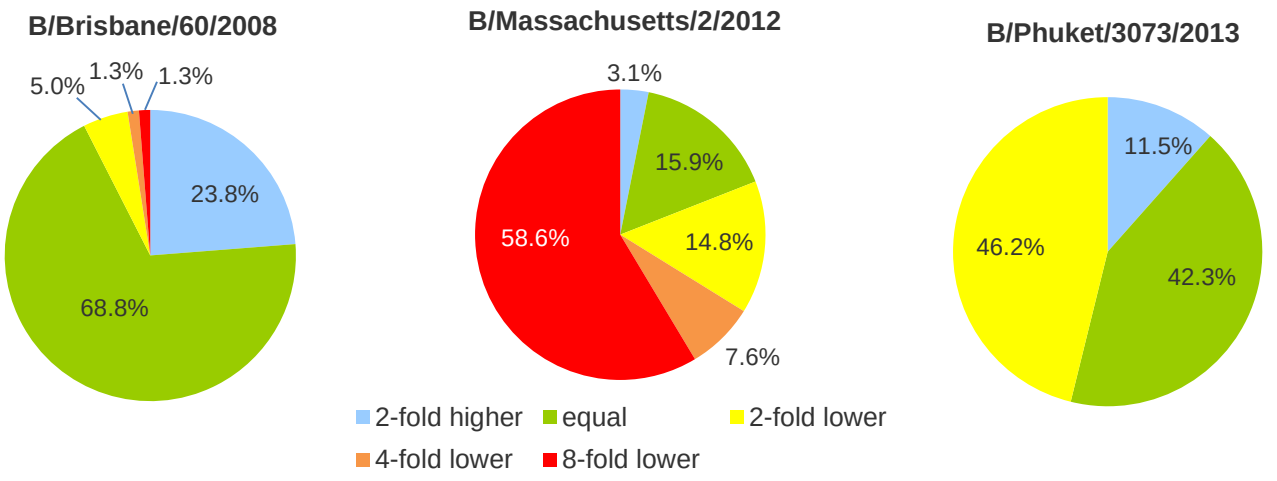
Table 7. Antigenic characterisation of B viruses received at the Centre during 2014 compared to the B/Brisbane/60/2008, B/Massachusetts/2/2012 and B/Phuket/3073/2013 reference viruses.

	B/Victoria reference strain: B/Brisbane/60/2008		B/Yamagata reference strain: B/Massachusetts/2/2012		B/Yamagata reference strain: B/Phuket/3073/2013	
Region	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**	**Like**	**Low reactor (%)**
Australasia	32	0	118	237 (66.8%)	19	0
Pacific	2	0	1	1 (50%)	7	0
South East Asia	29	1 (3.3%)	98	66 (40.2%)	0	0
East Asia	16	0	5	12 (70.6%)	0	0
South Asia	0	0	0	0	0	0
Africa	0	0	1	2 (66.7%)	0	0
Total	**79**	**1 (1.3%)**	**223**	**318 (49.1%)**	**26**	**0**

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

Figure 16. Summary of fold differences in HI titres of B/Yamagata viruses analysed at the Centre compared to the B/Massachusetts/2/2012 reference virus.

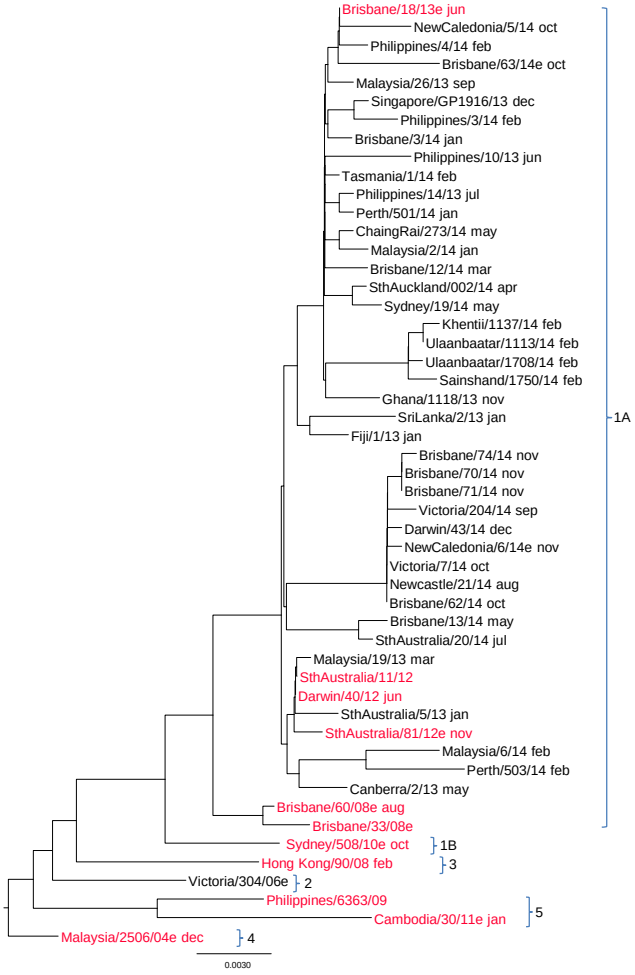
Figure 17. Summary of fold differences in HI titres of B/Yamagata viruses analysed at the Centre compared to the B/Phuket/3073/2013 reference virus.



Haemagglutinin gene sequencing

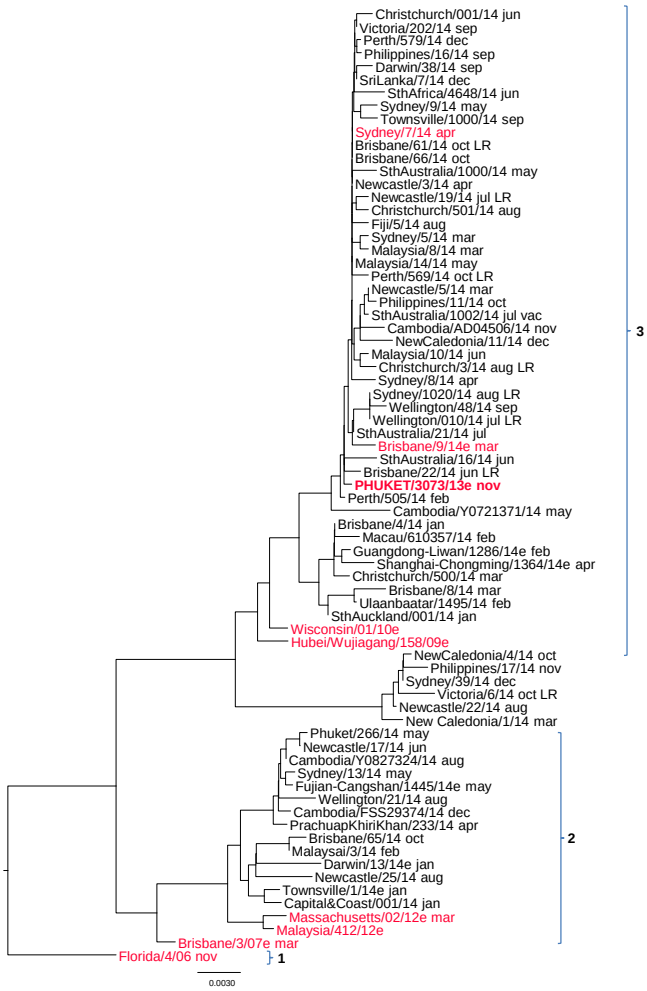
A total of 121 HA genes from B viruses were sequenced, the majority being B/Yamagata viruses. All of the viruses of B/Victoria lineage belonged to the same genetic clade as the B/Brisbane/60/2008 reference virus (Figure 18). B/Yamagata lineage viruses fell mostly into two antigenically and genetically distinct clades. The majority of viruses belonged to the clade represented by B/Phuket/3073/2013, whilst only a relatively small proportion of viruses were genetically similar to B/Massachusetts/2/2012 (Figure 19), further warranting a change in vaccine strain recommendation for the southern hemisphere 2015 vaccine.

Figure 18. Phylogenetic tree of representative HA genes of B/Victoria viruses received by the Centre during 2014.



Legend
Reference virus
e: egg isolate
Scale bar represents 0.3% nucleotide sequence difference between viruses
} Brackets indicate clades

Figure 19. Phylogenetic tree of representative HA genes of B/Yamagata viruses received by the Centre during 2014.



Legend
2015 SOUTHERN HEMISPHERE VACCINE STRAIN
Reference virus
e: egg isolate
Scale bar represents 0.3% 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 using the neuraminidase inhibition assay. The latter two inhibitors are not currently approved in Australia but are in use in Japan 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 since 2012. The application of the Tecan EVO 200 liquid handling robot to NAI assays in 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 2014

NAI assays were used to analyse 3384 viruses for reduced inhibition by the NAIs (Tables 8 and 9). In total, 11 viruses (7 A(H1N1)pdm09, 2 B/Victoria and 2 B/Yamagata) were found to have highly reduced inhibition by one or more of the NAIs . These viruses underwent further analysis to determine the presence of amino acid substitutions in the NA protein that associated with the reduction of inhibition by NAIs, for example histidine to tyrosine at position 275 (H275Y) of the neuraminidase protein of A(H1N1)pdm09 viruses, which reduces inhibition by oseltamivir, or the equivalent H273Y mutation in B viruses (Table 10).

Table 8. Viruses received by the Centre and tested by NAI assay in 2014, by country.

Type/subtype / Country	A(H1N1)pdm09	A(H3N2)	B/Victoria	B/Yamagata	TOTAL
Australasia					
Australia	1322	598	30	269	2219
New Zealand	181	96	2	104	383
South Pacific					
Fiji	0	2	0	1	3
New Caledonia	54	30	2	8	94
Solomon Islands	0	6	0	0	6
South East Asia					
Cambodia	54	49	0	39	142
Malaysia	30	15	2	21	68
Philippines	7	13	4	2	26
Singapore	74	120	23	92	309
Thailand	11	5	1	10	27
East Asia					
Macau	23	18	10	10	61
Mongolia	3	2	6	7	18
South Asia					
Sri Lanka	2	11	0	0	13
Africa					
South Africa	4	8	0	3	15
TOTAL	**1765**	**973**	**80**	**566**	3384

Table 9. Neuraminidase inhibitor sensitivity of viruses received by the Centre in 2014.*

Type/Subtype	No. tested	Oseltamivir		Peramivir		Laninamivir		Zanamivir	
		Reduced inhibition	Highly reduced inhibition	Reduced inhibition	Highly reduced inhibition	Reduced inhibition	Highly reduced inhibition	Reduced inhibition	Highly reduced inhibition
A(H1N1)pdm09	1765	1 (0.06%)	7 (0.4%)	1 (0.06%)	6 (0.3%)	0	0	0	0
A(H3N2)	973	0	0	0	0	0	0	2 (0.21%)	0
B/Victoria	80	1 (1.3%)	1 (1.3%)	6 (7.5%)	2 (2.5%)	1 (1.25%)	1 (1.25%)	1 (1.25%)	1 (1.25%)
B/Yamagata	566	3 (0.5%)	0	4 (0.71%)	2 (0.35%)	1 (0.18%)	0	2 (0.35%)	0
TOTAL	**3384**	**5**	**8**	**11**	**10**	**2**	**1**	**5**	**1**

Based on IC_{50}, the NAI sensitivity of each strain is classified as the following:* ***Normal inhibition* *= IC_{50} values which are within or close to the median IC_{50} of type/subtype-matched viruses tested at the Centre during 2014.* ***Reduced inhibition*** *= IC_{50} values which 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*** *= IC_{50} values which 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 2014 with highly reduced inhibition by NAIs.

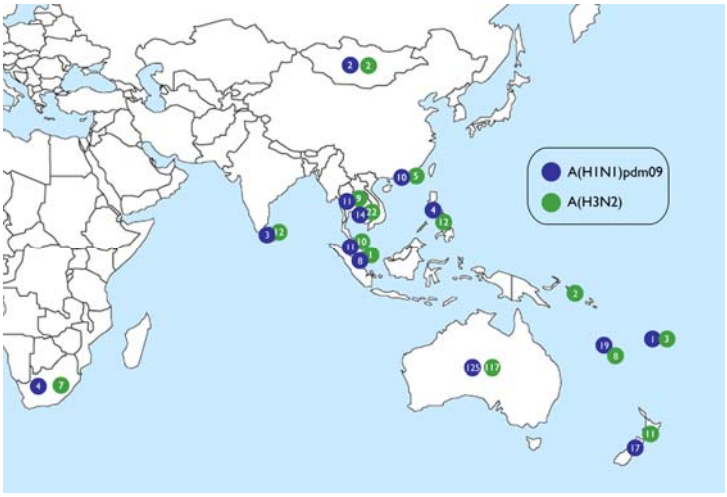
Type/Subtype/ Lineage	Country/city of submitting laboratory	NAI(s) with highly reduced inhibition (marked with •)				Mutation(s) detected
		Oseltamivir	Peramivir	Laninamivir	Zanamivir	
A(H1N1)pdm09	Macau	•	•			H275Y
	Malaysia	•	•			H275Y
	Perth	•	•			H275Y
	Perth	•	•			H275Y
	Perth	•	•			H275Y
	Thailand	•	•			H275Y
	New Caledonia	•				H275Y
B/Victoria	Mongolia		•			H101N, E105K
	Mongolia	•	•	•	•	G104R
B/Yamagata	Mongolia		•			E105K
	Macau		•			H273Y

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.

Figure 20. Geographic spread of viruses received at the Centre during 2014 and screened for adamantane resistance.



Screening for adamantane resistance in 2014

Real-time PCR or sequencing was used to analyse 450 influenza A viruses, selected as representative of those submitted to the Centre during 2014 (Figure 20). Based on S31N analysis, all tested viruses were resistant to the adamantanes except for one A(H1N1)pdm09 virus from New Zealand.

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

Serum panel analyses in 2014

In February the Centre analysed serum panels from recipients of seasonal trivalent influenza vaccines in Australia, China, Europe and USA. The combined data from all WHO Collaborating Centres and ERLs showed that in general, vaccines containing A/California/7/2009-like and B/Massachusetts/2/2012-like antigens stimulated anti-HA antibodies of similar GMT to the relevant vaccine virus and most recent representative A(H1N1)pdm09 and B/Yamagata lineage viruses respectively. Vaccines containing A/Texas/50/2012 antigens stimulated antibodies of similar GMT to the vaccine virus and the majority of representative recent A(H3N2) viruses when measured against cell-propagated A/Texas/50/2012—however, titres against cell-grown representative recent viruses were reduced when compared with titres against egg-grown A/Texas/50/2012. In addition, quadrivalent vaccines containing influenza B/Massachusetts/2/2012-like and B/Brisbane/60/2008-like antigens stimulated antibodies of similar GMT to the B/Victoria/2/87 lineage vaccine virus and representative recent B/Victoria/2/87 lineage viruses.

Table 11. Representative and vaccine candidate strains used for serological analyses during 2014.

A(H1N1)pdm09	
February	**September**
A/California/7/2009*	A/California/7/2009*
A/Brisbane/205/2013	A/Hyogo/3030/2014
A/New Hampshire/4/2013 (E)	A/South Australia/20/2014
A/New Hampshire/4/2013 (C)	
A/Sichuan-Wuhou/2259/2013	
A/Singapore/GP1796/2013	
A(H3N2)	
February	**September**
A/Texas/50/2012*(E)	A/Texas/50/2012*(E)
A/Texas/50/2012 (C)	A/Texas/50/2012 (C)
A/Victoria/506/2013	A/Tasmania/11/2014 (E)
A/Almaty/2958/2013	A/Tasmania/11/2014 (C)
A/Singapore/GP1940/2013	A/Palau/6759/2014 (E)
A/Singapore/GP1660/2013	A/Palau/6759/2014 (C)
A/Jiangxi-Yunyang/1790/2013	A/Newcastle/22/2014
	A/South Australia/55/2014
	A/Switzerland/9715293/2013
B/Victoria	
February	**September**
B/Jiangsu-Tianning/1795/2013	B/Texas/2/2013
B/Texas/2/2013	
B/Brisbane/60/2008	
B/Yamagata	
February	**September**
B/Massachusetts/2/2012*	B/Massachusetts/2/2012*
B/Phuket/3073/2013	B/Phuket/3073/2013
B/Townsville/15/2013	B/Townsville/1/2014
B/Chongqing-	B/Brisbane/9/2014

** Vaccine strain (E): Egg-grown virus (C): Cell-grown virus*

In September, the Centre analysed serum panels from Australia, Europe and USA. The combined data from all ERLs and WHO Collaborating Centres showed that, in general, vaccines containing GMTs of antibodies against representative recent A (H1N1)pdm09 viruses were not reduced significantly as compared to HI titres to A/California/7/2009. Titres against recent A (H3N2)viruses from phylogenetic clade 3C.3a were significantly reduced compared to HI titres against both cell-propagated and egg-propagated A/Texas/50/2012 viruses. Geometric mean HI titres of antibodies against representative recent B/ Yamagata/16/88 lineage viruses in phylogenetic Group 2 were similar HI titres to the B/Massachusetts/2/2012 vaccine virus—however, in a majority of panels, GMT of antibodies against representative recent group 3 viruses were significantly reduced compared to HI titres against the vaccine virus. Titres to B/Victoria/2/87 lineage viruses also were reduced.

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.

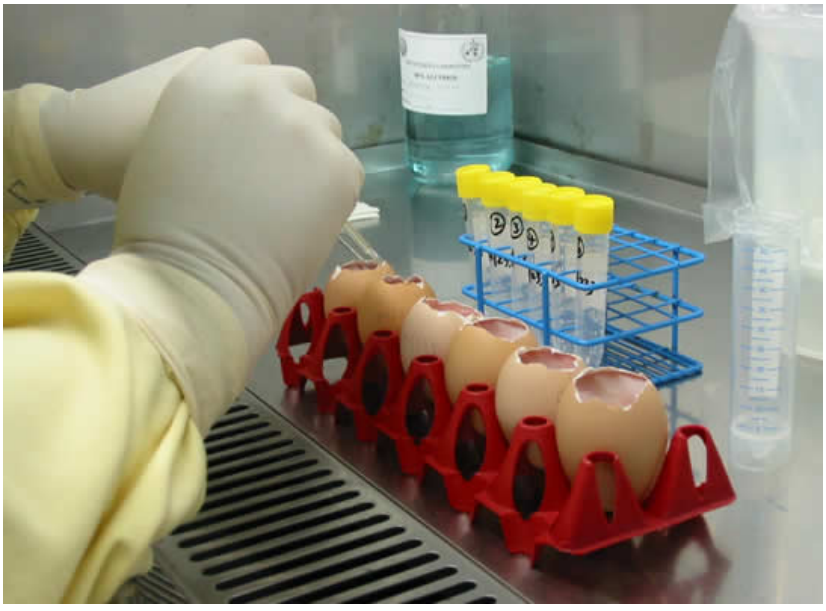
Since 2009, the number of viruses isolated in eggs at the Centre has increased as a result of additional support received under a Letter of Agreement with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). In 2014, an overall isolation rate of 32% was achieved (Table 12).

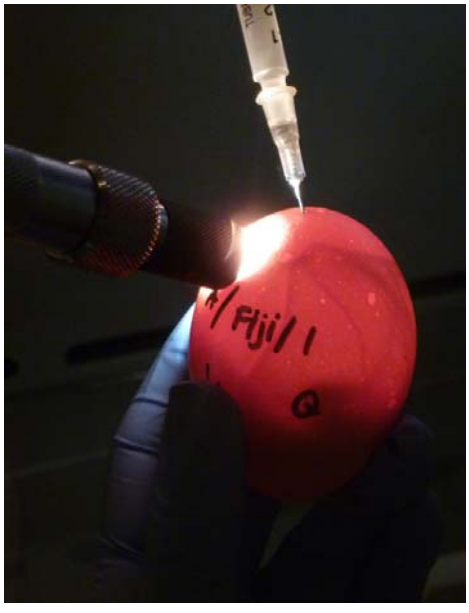
Table 12. Virus isolation in eggs at the Centre in 2014.

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	19	10	53%
A(H3N2)	78	23	29%
B/Victoria	7	0	0%
B/Yamagata	16	5	31%
Total	**120**	**38**	**32%**

Table 13. Potential candidate vaccine strains isolated in eggs at the Centre in 2014.

A(H1N1)pdm09	A(H3N2)
A/Tasmania/2/2014	A/Sri Lanka/56/2013
A/Christchurch/6/2014	A/Brisbane/204/2013
A/South Australia/20/2014	A/Brisbane/198/2013
A/Christchurch/538/2014	A/Singapore/GP1599/2013
A/Canberra/98/2014	A/Perth/2/2014
A/Tasmania/24/2014	A/Perth/1/2014
A/New Caledonia/72/2014	A/Singapore/GP1940/2013
A/New Caledonia/58/2014	A/Canberra/2/2014
A/Singapore/EN290/2014	A/Canberra/3/2014
A/Singapore/KK517/2014	A/Sydney/37/2014
	A/Sydney/30/2014
B/Yamagata	A/Tasmania/11/2014
B/Phuket/3073/2013	A/Victoria/503/2014
B/Darwin/13/2014	A/South Australia/40/2014
B/Darwin/20/2014	A/Newcastle/22/2014
B/Townsville/1/2014	A/South Australia/55/2014
B/Brisbane/9/2014	A/Newcastle/25/2014
	A/South Australia/24/2014
	A/Singapore/GP1523/2014
	A/New Caledonia/71/2014
	A/Canberra/82/2014
	A/Fiji/1/2014
	A/Victoria/5060/2014





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 2014, 28 candidate vaccine viruses were received from other WHO Collaborating Centres and laboratories and then passaged in eggs at the Centre (Table 14).

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

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

Table 14. Potential candidate vaccine viruses received from other WHO Collaborating Centres during 2014.

A(H1N1)pdm09	A(H3N2)
A/New Hampshire/04/2013	A/Hong Kong/146/2013
A/Sichuan-Wuhou/SWL2259/2013	A/Serbia/NS-210/2013
A/Mississippi/10/2013	A/Almaty/2958/2013
A/Sichuan-Yucheng/SWL1693/2013	A/Utah/07/2013
A/Chongqing-Yuzhong/SWL11434/2013	A/Massachusetts/11/2013
B/Victoria	A/Costa Rica/4700/2013
B/Jiangsu-Tianning/1795/2013	A/South Africa/4655/2013
NYMC BX-53C (B/Texas/02/2013)	A/Stockholm/1/2013
B/Yamagata	A/Palau/6759/2014
B/Chongqing-Yuzhong/11616/2013	A/Switzerland/9715293/2013
B/Guangdong-Liwan/1133/2014	A/Norway/466/2014
B/Shanghai-Hongkou/1286/2014	A/Stockholm/6/2014
B/Shanghai/Chongming/1364/2014	A/Finland/440/2014
B/Fujian-Cangshan/1445/2014	A/Hong Kong/5738/2014
	NYMC x-247 (A/Switzerland/9715293/2013)
	NIB-88 (A/Switzerland/9715293/2013)

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). 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 from time to time. In 2014, WHO made the recommendations reported here.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2014–2015, Geneva, Switzerland, 18–21 February 2014

It is recommended that vaccines for use in the 2014–2015 influenza season (northern hemisphere winter) contain the following:

- an A/California/7/2009 (H1N1)pdm09-like virus;
- an A/Texas/50/2012 (H3N2)-like virus;
- a B/Massachusetts/2/2012-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.

WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2015, Geneva, Switzerland, 22–24 September 2014

It is recommended that vaccines for use in the 2015 influenza season (southern hemisphere winter) contain the following:

- an A/California/7/2009 (H1N1)-like virus;
- an A/Switzerland/9715293/2013 (H3N2)-like virus[a];
- 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.

[a] A/South Australia/55/2014, A/Norway/466/2014 and A/Stockholm/6/2014 are A/Switzerland/9715293/2013-like viruses.*

** These viruses were originally isolated at the WHO Collaborating Centre in Melbourne.*

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 relevant authority is the Therapeutic Goods Administration which 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 9 October AIVC accepted the September WHO recommendation and decided that the Australian influenza vaccine for 2015 should contain the following:

- A(H1N1): an A/California/7/2009 (H1N1)-like virus, 15 µg HA per dose
- A(H3N2): an A/Switzerland/9715293/2013 (H3N2)-like virus, 15 µg HA per dose
- B: a B/Phuket/3073/2013-like virus, 15 µg HA per dose

Quadrivalent vaccines should contain viruses listed above, plus the additional B virus: B/Brisbane/60/2008-like virus, 15 µg HA per dose.

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 2014, 38 kits were sent to 18 laboratories in 10 countries. Each kit contained 10 mL each of the reference antigens A/Texas/50/2012, A/California/7/2009, B/Massachusetts/2/2012 and B/Brisbane/60/2008, and homologous antisera.

Recipients of the 2014 Kit

AUSTRALIA: SA Pathology Adelaide, South Australia; Queensland Health Scientific Services, Brisbane, Queensland; Westmead Hospital, Sydney, New South Wales; Australian Institute for Bioengineering & Nanotechnology (AIBN), Brisbane, Queensland

CAMBODIA: Institut Pasteur du Cambodge, Phnom Penh

INDIA: Manipal University, Karnataka; Vallabhbhai Patel Chest Institute, New Delhi

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

MALAYSIA: Institute for Medical Research, Kuala Lumpur

NEW ZEALAND: Institute of Environmental Science and Research, Wellington; Auckland City Hospital, Auckland; Canterbury Health Services, Christchurch

PHILIPPINES: Research Institute for Tropical Medicine, Mutinlupa City

SINGAPORE: Singapore General Hospital ; Duke-NUS Graduate Medical School (2 laboratories)

TAIWAN: National Cheng Kung University, Tainan

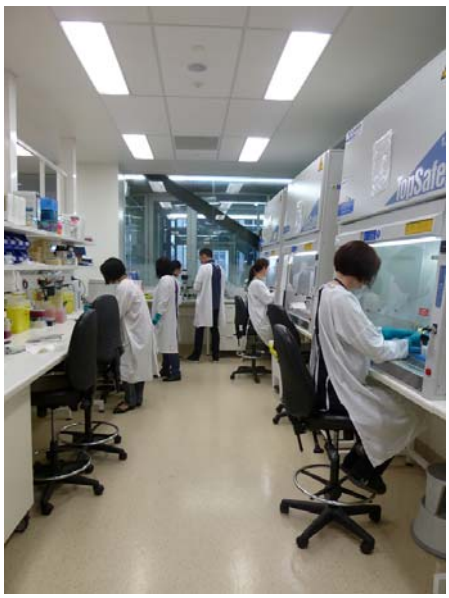
THAILAND: National Institute of Health, Bangkok

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 2014 panel kits were sent to the Naval Health Research Centre, San Diego CA, USA, and Nagasaki University Hospital, Nagasaki, Japan. Kits were composed of 2 vials (250 µL) of each of the reference viruses listed in the table below.

Viruses in the 2014 NAI assay panel

Reference virus	Inhibition by antiviral drugs			
	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)**	Highly reduced	Normal	Highly reduced	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)**	Highly reduced	Normal	Normal	Normal
(B/Sichuan/379/1999-like)				
B/Perth/211/2009 wild-type	Normal	Normal	Normal	Normal
B/Perth/211/2009 variant **(D197E)**	Highly reduced	Normal	Highly reduced	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)**	Highly reduced	Normal	Highly reduced	Normal

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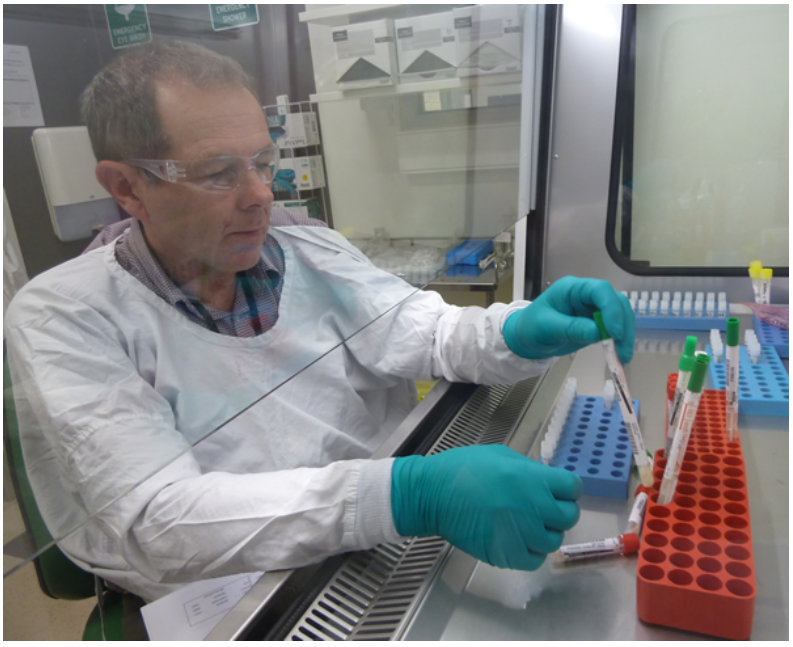
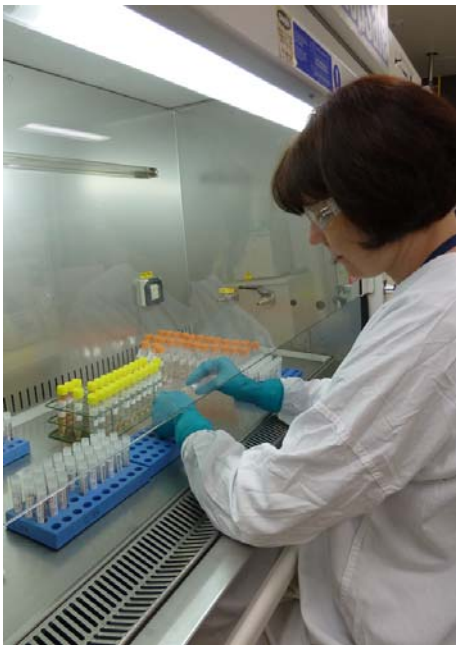




Training

Training and Support of National Influenza Centres

The Centre regularly provides 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.

In-house Training

Ms Hsu Jung Pu, Mr Loh Wai Yong and Ms Tan Chyi Lin, from the National University of Singapore, Singapore, visited the Centre on 13–17 January to undertake training in HI assays.

Ms Nurwendy Ashikin Abdullah Lim (left) and Ms Mazmah Ahmad Morshidi (right) from the Biomedical Science Research Unit, Bandar Seri Begawan, Brunei, visited the Centre 6–17 October. They undertook training in serology, molecular biology, rapid tests and influenza surveillance techniques.

Ms Pham Thi Thu Hang (left), from the National Institute of Hygiene and Epidemiology, Hanoi, Vietnam, and Ms Nguyen Thu Ngoc (right), from the Pasteur Institute, Ho Chi Minh City, Vietnam, visited the Centre 2–12 December for training in high-throughput HI assays and microneutralisation assays.

Short course: Bayesian and Penalised Regression Methods for Epidemiological Analysis

This course was held at the Doherty Institute on 24–25 July and was coordinated by **Dr Sheena Sullivan** and A/Prof Julie Simpson (School of Population and Global Health, University of Melbourne). A total of 65 delegates attended the course. The course was presented by Professor Sander Greenland (UCLA, Los Angeles USA), one of the most prolific and influential researchers and authors on epidemiological methods of the past 20 to 30 years.

Other Training

Visit to the National Institute of Health Research and Development (NIHRD), Jakarta, Indonesia, 16–20 June
Prof Anne Kelso and Dr Patrick Reading visited NIHRD to discuss strategies for strengthening laboratory-based detection and characterisation of influenza viruses in Indonesia. Dr Reading also worked with staff in the virology laboratory at NIHRD to establish serology assays to characterise immune responses to influenza viruses. Prof Kelso and Dr Reading also presented talks.

Laboratory Based Surveillance of Influenza and Other Outbreak Prone Diseases Workshop, Noumea, New Caledonia, 29 September – 3 October.
Dr Patrick Reading worked with the Secretariat of the Pacific Community to coordinate this workshop, which was attended by representatives from 7 countries from the Pacific region. The workshop focused on efficient collection, storage and transport of influenza samples, as well as interpretation of reports from WHO Collaborating Centres. Dr Reading was a workshop facilitator and presented 3 talks.

Visit to the Fiji Centre for Communicable Disease Control, Suva, Fiji, 6–9 October
Dr Patrick Reading assisted in establishing the use of new primers and probes for the detection of influenza viruses.

Instructors at "Managing influenza through networking and information sharing - 2nd GISAID Symposium and Training Workshop".

Managing influenza through networking and information sharing - 2nd GISAID Symposium and Training Workshop, Singapore, 23–24 October.
Ms Naomi Komadina was an instructor and presented a lecture at this workshop which was attended by delegates from the South East Asia region and provided training on the use of the GISAID EpiFlu™ database.

International Course on Surveillance of Influenza-Like Illness, Ho Chi Minh City, Vietnam, 17–21 November
Dr Sheena Sullivan participated and gave two lectures at this course, which was attended by 25 delegates from Fiji, China, Singapore, Cambodia, Italy, Laos, Vietnam, Indonesia, Cambodia, Thailand, Palau, Mongolia and the United Kingdom. The course focused on the rationale, application and use of surveillance techniques for influenza-like illness.

Staff Development

Sheena Sullivan attended the course "Causal inference with time varying exposure: current state of the art and introduction to systematic review and meta-analysis", run by the Society for Epidemiologic Research, in Seattle WA, USA, on 24 June.

Sheena Sullivan attended the Summer Institute for Statistics and Modelling in Infectious Diseases, in Seattle WA, USA, on 7–18 July.

Yi-Mo Deng attended 2014 BioInfoSummer, in Melbourne on 1–5 December.

Research

The Centre's research interests continue to expand and develop with a broad range of projects, both within the Centre and with external collaborators.

Evolution and Modelling of Influenza Viruses

Centre staff

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

Research overview

The Centre is pursuing two major projects in collaboration with other groups that investigate influenza evolution and immune responses to influenza viruses. We have a longstanding collaboration that aims to understand how the immune response in humans evolves in an attempt to control or prevent infection with influenza viruses. Using serum panels from adults taken before and after influenza vaccination, and sera from naturally infected children and adults, we have developed a method known as antibody landscapes to show how an individual or a group of people respond to previous, current and "future" influenza viruses.

The second project investigates the phylodynamics of the two currently circulating influenza B virus lineages (B/Victoria and B/Yamagata) collected from humans in Eastern Australia and New Zealand during the period 2002-2012. We have sequenced the full genomes of over 900 influenza B viruses and analysed the genetic diversity of Yamagata and Victoria lineage viruses during this period. We are also examining the occurrence of inter-seasonal influenza viruses and investigating their origin - for example, whether they emerged in the Northern Hemisphere or arose locally.

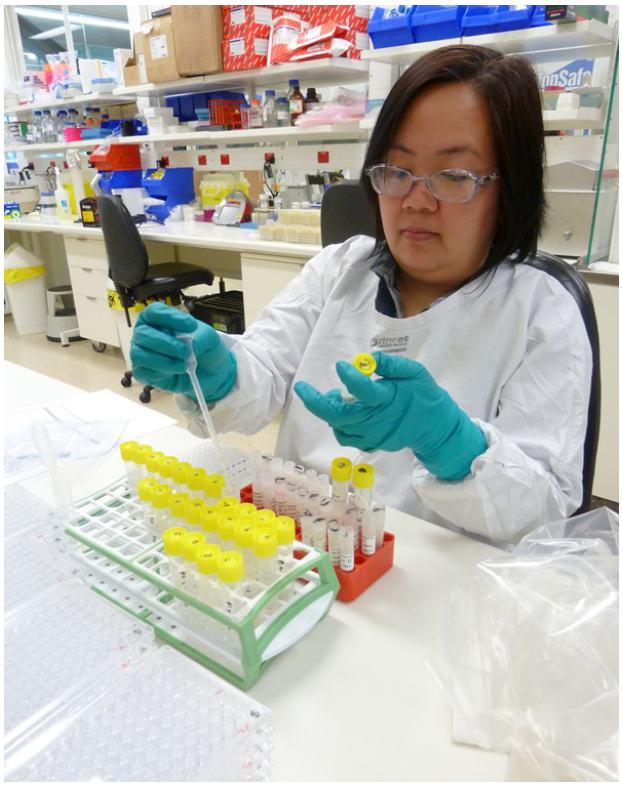
Collaborators

Derek Smith (Cambridge University, UK); Yoshihiro Kawaoka (The University of Wisconsin, Madison WI, USA and The University of Tokyo, Japan); Vijaykrishna Dhanasekaran and Gavin Smith (Duke-NUS Graduate Medical School, Singapore); Rebecca Halpin and Das Suman (J. Craig Venter Institute, Rockville MD, USA); Edward Holmes (University of Sydney, NSW)

Highlights and developments 2014

Data describing the development of antibody landscapes and subsequent analysis were published in the journal Science in November 2014. Further studies are continuing to determine if antibody landscapes differ when adults are given adjuvanted influenza vaccines and other studies will look at the antibody landscapes in a community cohort from geographically distinct locations and compare their responses following influenza virus infections.

Our study of the phylodynamics of influenza B viruses found significant differences in the rate of evolutionary change and genetic variation of the B/Victoria and B/Yamagata lineage. These results were submitted for publication. Further studies investigating the continuing evolution of B/Yamagata lineage viruses are underway.



Understanding the Interplay between the Immune Response and Influenza Viruses

Centre staff

Karen Laurie, Louise Carolan, Malet Aban , Teagan Guarnaccia (PhD student)

Research overview

Our research encompasses two areas—characterising immune responses to influenza infection and human seroepidemiological studies. Increasing our understanding of the immune response can lead to improved strategies for prevention or treatment of infection. To this end, we use a ferret model to investigate the immune response following influenza virus infection. We have developed real time PCR assays to measure mRNA encoding ferret cytokines and chemokines to enable characterisation of the early and late immune response and are developing additional complementary assays. By combining these methods with various infection and challenge experiments, we can determine the contribution of different aspects of the immune response in controlling virus infections in the ferret model.

Following infection or vaccination with influenza viruses, most people develop antibodies that can be measured by serological assays. Assessing antibody titres using serodemiological surveys can provide insight into the likely impact of a novel influenza virus on a population, and can inform public health decisions. We are involved in various local and international serological studies, including investigating seroconversion following infection and vaccination with influenza virus in infants under the age of 1 year and the protective effect and persistence of maternal antibodies to influenza virus, and in a separate study, assessing the response to influenza vaccines in children undergoing cancer therapy. Centre staff are also part of CONSISE, the Consortium for the Standardization of Influenza Seroepidemiology, which aims to improve standardisation and assay development for seroepidemiological studies.

Highlights and developments 2014

We published a paper reporting the real time PCR assays developed in our laboratory and observations of *in vitro* response of ferret leukocytes to virus and mitogens. We extended this study to characterise the localised immune response in the ferret respiratory tract following infection with different influenza viruses. A manuscript is under preparation. We have also collaborated with scientists at CSIRO to test commercial and 'in-house' reagents to measure specific aspects of the immune response in the ferret model. A manuscript describing the generation, crystallisation and functional activity of recombinant ferret interleukin-2 is in preparation. We also investigated the potential for viral interference, whereby following infection with an influenza virus the host experiences lower susceptibility to infection by any strain of influenza or other respiratory virus for a short period of time. We showed that viral interference can occur between antigenically related and unrelated viruses and that there is a hierarchy between the ability of different viruses to induce interference. Two manuscripts have been submitted describing this study.

We measured antibody levels to A(H1N1)pdm09 virus for a prospective birth cohort study that followed mothers and infants from birth for the first year of life in Vietnam, to characterise the immune response following primary infection and influenza vaccination. A manuscript is in preparation. We also assessed a cohort of paediatric oncology patients who have been followed since 2009 for seroconversion to the 2014 seasonal influenza vaccine. As part of CONSISE, we tested an enzyme-linked lectin assay to measure antibodies to neuraminidase. A total of 35 laboratories participated in this study, in which each laboratory assessed a common shared serum panel. A manuscript is in preparation.

Collaborators

Steve Rockman (bioCSL, Victoria); Jennifer Mosse (Federation University, Victoria); James McCaw, Stephen Petrie, Ada Yan, Pengxing Cao, Jodie McVernon (Melbourne School of Population and Global Health, The University of Melbourne); Cameron Simmons (Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam and the Department of Microbiology and Immunology, The University of Melbourne); Katie Anders (Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam); Ushma Wadia (Princess Margaret Hospital, Western Australia), Lorena Brown, Brad Gilbertson (Department of Microbiology and Immunology, The University of Melbourne), CONSISE, Timothy Adams, William McKinstry, Bin Ren, Tam Phan and Janet Newman (CSIRO, Victoria)

Antivirals and Viral Fitness

Centre staff

Aeron Hurt, Ding Yuan Thomas Oh, Sook Kwan Leah Leang, Danielle Tilmanis

Research overview

Our research focuses on improving our understanding of the effectiveness of influenza antivirals and the risk that drug resistant viruses may spread widely amongst the community. In a project funded by the National Health and Medical Research Council (NHMRC) and the Agency for Science, Technology and Research (A*STAR, Singapore), we use a ferret model to investigate the effect of oseltamivir treatment on influenza A and B infection, with the final goal being to understand whether certain mutations result in clinical resistance to the drug.

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.

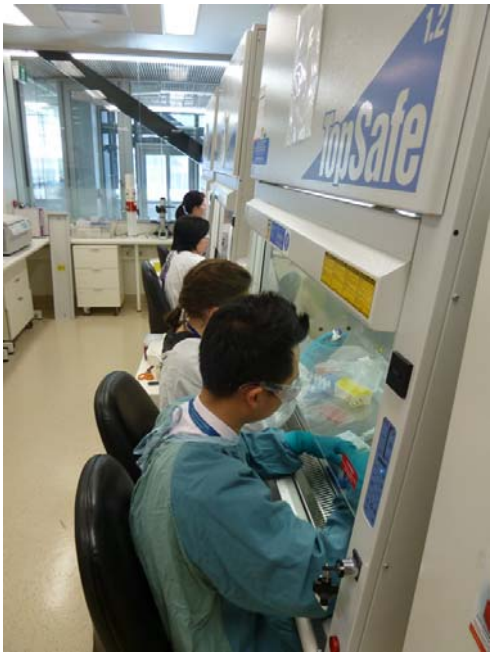
Highlights and developments 2014

The NHMRC/A*STAR-funded project has made substantial progress in establishing and optimising the ferret antiviral treatment model. This has included the measurement of addition variables such as infiltrating cell numbers and protein levels to assess inflammatory responses. We also developed a novel video tracking method to assess ferret activity (wellness) and submitted a manuscript describing this technique. In addition, we have completed a pharmacokinetic/dynamic analysis of oseltamivir in the ferret. The model will be fully optimised in 2015 which will allow the assessment of different variant viruses.

We have assessed a number of viruses with different neuraminidase mutations to determine if the mutations resulted in compromised viral function. This was completed for a number of influenza A and B viruses detected via our surveillance testing at the Centre.

Collaborators

Sebastian Maurer-Stroh (A*STAR, Singapore); Gary Lau (Duke-NUS Graduate Medical School, Singapore); Carl Kirkpatrick (Monash University, Victoria)



Animal Influenza Viruses

Centre staff

Aeron Hurt, Chantal Baas, Yi-Mo Deng, Heidi Peck, Natalie Spirason

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. Avian species are routinely sampled by our collaborators in Australia to determine the types of avian influenza viruses circulating in either resident ducks or migratory waders in Australia. The Centre is involved with the characterisation of viruses sampled from birds in Australia, including culture, sequencing and phylogenetic analysis. As part of ongoing analyses of avian influenza in Antarctica, further samples from penguins in Antarctica were collected by our Chilean collaborators and sent to the Centre for analysis during 2014.

Swine influenza viruses collected from pig farms in Western Australia and Queensland are also being assessed by the Centre to determine the risk that these viruses pose to humans. Using the ferret model we are assessing the infectivity of the viruses and whether the viruses transmit between ferrets by either contact and/or aerosol transmission.

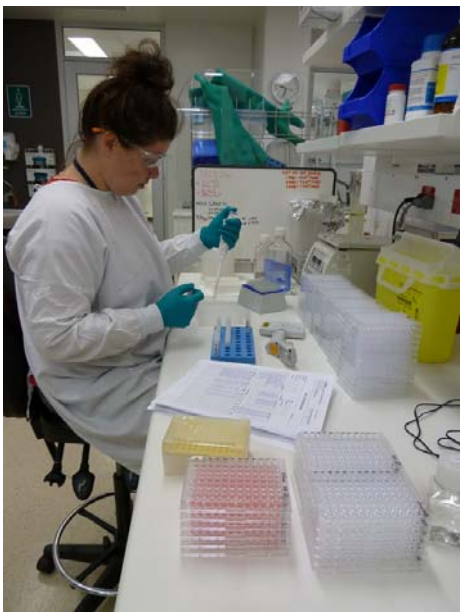
Highlights and developments 2014

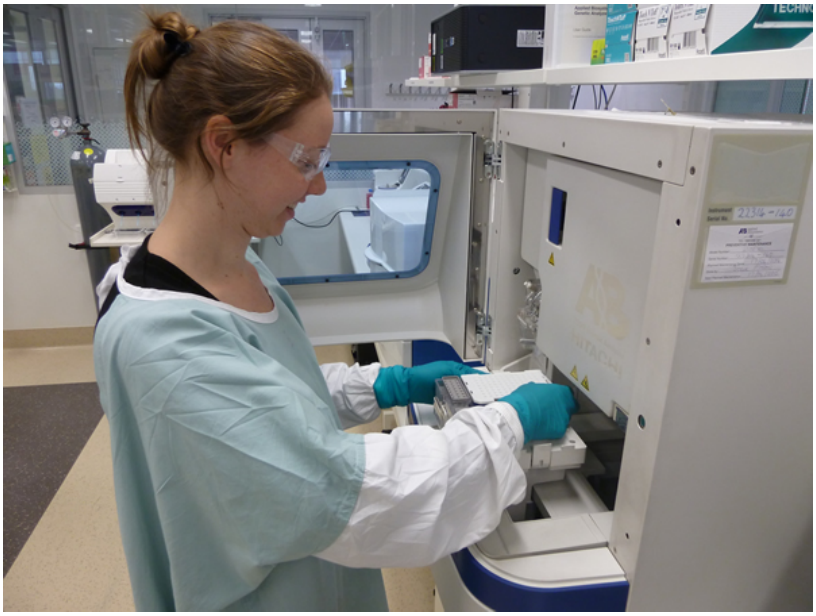
A large number of avian influenza viruses from Australia were characterised and isolated in embryonated hens' eggs. These viruses included many different subtypes and assist in the understanding of the ecology of avian influenza viruses in Australia. None of the viruses detected contained markers that would indicate they were highly pathogenic. One avian influenza virus was detected in the samples collected from Antarctica, although it could not be successfully cultured. Interestingly the virus was genetically very similar to the A(H11N2) viruses detected in penguins and other birds from the same location in Antarctica 12 months earlier.

The swine influenza viruses collected from pigs farms were shown to readily infect ferrets at a range of virus dilutions and could easily transmit between ferrets housed within the same cage. Studies in 2015 will determine if the viruses are able to transmit via aerosol transmission i.e. between ferrets housed in different cages but separated by a mesh screen. Should the viruses transmit via aerosol transmission then they will be considered a potential risk to public health.

Collaborators

Marcel Klaassen (Deakin University, Victoria); Simone Warner (Department of Primary Industries, Victoria); Daniel González-Acuña (University of Concepción, Chile)





Epidemiology

Centre staff

Sheena Sullivan, Vivian Leung

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 sentinel practices network of WA (SPNWA), the Victorian General Practice Sentinel Surveillance (GPSS) network, and the Influenza Complications Alert Network (FluCAN) to estimate influenza vaccine effectiveness in the community. We are also interested in the problems of estimating vaccine effectiveness from observational data, including how modifications to study design can affect the validity of estimates across seasons and sub-populations as well as the statistical problems encountered. Much of this work has focused on understanding the validity of the test-negative design.

Influenza vaccines can only be expected to be highly effective when the vaccine is closely matched to the circulating strains. Thus, it is important to understand how vaccine strains are selected and whether the viruses used to inform strain selection are representative of the viruses circulating during a season. While it is infeasible to ensure equal representation of each virus strain, it is possible to examine whether there is any bias in how samples are submitted, whether there are differences in successful isolation of particular strains, and whether there is any bias in the selection of samples for antigenic and genetic analysis. To this end, we have been attempting to compare the viruses submitted to the Centre with viruses obtained as part of sentinel surveillance systems around the country. This information has also been used to aid the interpretation of vaccine effectiveness estimates.

Highlights and developments 2014

Vivian Leung (picture at right) joined the Centre in 2014. She comes with 7 years' experience working in infectious diseases control at the Peter MacCallum Cancer Centre. Vivian's appointment has permitted expansion of epidemiological activities and created new opportunities for collaborative research on influenza with the Cancer Centre.

To enhance monitoring of influenza vaccine effectiveness, we worked with nationwide influenza surveillance systems to obtain virus samples for antigenic and genetic analysis. In addition, we worked with these surveillance networks to estimate the effectiveness of the 2013 influenza vaccine and worked on several methods papers with colleagues at the University of Hong Kong. Findings have been the subject of published and drafted publications and were presented at national and international conferences.

Collaborators

Heath Kelly, James Fielding, Kylie Carville, and Kristina Grant (Epidemiology Unit, VIDRL, Victoria); Avram Levy, David Smith (PathWest Laboratory Medicine, Western Australia); Paul Effler, Annette Regan (Department of Health, Western Australia); Nigel Stocks, Monique Chilver (Australian Sentinel Practices Research Network, Australia); Geoff Higgins (SA Pathology, South Australia); Allen Cheng (Influenza Complications Alert Network, Australia); Ben Cowling, Shuo Feng (University of Hong Kong); Monica Slavin, Leon Worth, Susan Harper (Department of Infectious Diseases/Infection Prevention, Peter MacCallum Cancer Centre, Victoria)

Early Recognition and Response to Influenza Infection

Centre staff

Patrick Reading (Centre Educator and Associate Professor, Department of Microbiology and Immunology, The University of Melbourne)

Research overview

Our research, which is undertaken at the University of Melbourne, investigates how the body first recognises and responds to infections with respiratory viruses. We employ *in vitro* studies using human proteins and cells, as well as *in 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) the soluble proteins present in airway fluids that limit early replication and spread of influenza viruses, (iii) the characteristics of the early inflammatory response associated with virus clearance and recovery compared to those associated with severe disease, and (iv) novel strategies aimed at manipulating innate immune responses to reduce the severity of respiratory disease.

Highlights and developments 2014

During 2014, we developed novel approaches to allow for over-expression of putative virus receptors in cell lines that are resistant to influenza infection. We have used these approaches to identify and characterise receptors expressed on mouse cells that act as virus attachment and entry receptors. We also defined the antiviral activities of a family of soluble proteins of the innate immune system, known as pentraxins, that are present in airway fluids from humans and mice. We also commenced studies using novel liposomes to deliver siRNA to the lung in an effort to develop a novel therapeutic that delivers antiviral siRNA in combination with stimulation of the innate immune response.

Our research contributed to 7 peer-reviewed publications during 2014, including senior author publications in 'The Journal of Virology', 'The Journal of Immunology' and the 'Viruses' journal. Dr Reading also presented several research talks at conferences and institutes during the year and is Chief Investigator on a new NHMRC Project Grant, with funding to commence in 2015. New staff members to join the group in 2014 were Joel Ma (post-doctoral scientist), Angela Pizzolla (post-doctoral scientist), Leah Gillespie (research assistant) and Eva Fuglsang (visiting PhD student from Denmark).

Collaborators

Alberto Mantovani (Instituto Clinico Humanitas, IRCCS & State University of Milan, Italy); Erika Crouch (Washington University School of Medicine, St. Louis, MO, USA); Stuart Turville (Westmead Millennium Institute, New South Wales); Nigel McMillan (Griffith University, Queensland); Andrew Brooks, Stephen Kent, David Jackson, Lorena Brown (Department of Microbiology and Immunology, The University of Melbourne); Carol Hartley and Joanne Devlin (Department of Veterinary and Agricultural Sciences, The University of Melbourne)

NHMRC Program Grant: Understanding and Controlling Influenza (2010 - 2014)

Centre staff:

Anne Kelso, Patrick Reading, Karen Laurie

Research overview

The Centre is a participant in a National Health and Medical Research Council Program Grant which commenced on 1 January 2010. The Program has two broad goals:

- to understand fundamental mechanisms that establish maximum effective cellular immunity to influenza A viruses
- to build the foundations for clinical application of strategies to induce cellular immunity to these viruses.

These goals are being addressed through a range of collaborative projects between the chief investigators and team members at the Department of Microbiology and Immunology at the University of Melbourne (UM), the WHO Collaborating Centre for Reference and Research on Influenza, La Trobe University, the School of Population and Global Health (UM) and the CSIRO Australian Animal Health Laboratory.

Highlights and developments 2014

Dr Annette Fox, Kim Harland and Ida Candiloro, working in the Department of Microbiology and Immunology under Anne Kelso's supervision, have continued their work on functional specialisation in $CD8^+$ T cells in the response to influenza virus infection, with results being published in Nature Communications. Recent studies have focussed on the regulation and plasticity of gene expression in naïve and memory $CD8^+$ T cells in the mouse and extension of the work to human T cells.

A Program retreat held on 20–21 October was attended by 81 people representing all of the research groups in the Program. Louise Carolan, Aeron Hurt, Anne Kelso and Karen Laurie attended.

With the renewal of the NHMRC Program Grant on influenza administered through the University of Melbourne (2015 – 2019; CIA Anne Kelso; new title "Limiting the impact of influenza"), the Centre will continue its collaboration with colleagues in the University of Melbourne and La Trobe University on a range of biomedical and clinical studies of influenza virus infection.

Chief Investigators

Peter Doherty (The University of Melbourne); David Jackson (The University of Melbourne); Anne Kelso (WHO Collaborating Centre for Reference and Research on Influenza); Weisan Chen (La Trobe University); Stephen Turner (The University of Melbourne); Lorena Brown (The University of Melbourne)

Research Funding and Awards

Dr Patrick Reading is chief investigator in a project grant awarded by the NHMRC in 2014:

> *Identification of host factors that restrict influenza virus replication in macrophages*
> $548,008 awarded for the period 1 January 2015– 31 December 2017. Chief Investigators **Patrick Reading** and Sarah Londrigan. The grant will be administered by The University of Melbourne and the work will be undertaken at the University.

Professor Anne Kelso is lead chief investigator in the program grant "Limiting the impact of influenza", renewed by the NHMRC in 2014:

> *Limiting the impact of influenza*
> $13,617,890 awarded for the period 1 January 2015– 31 December 2019. Chief Investigators **Anne Kelso,** Stephen Turner, David Jackson, Lorena Brown, Katherine Kedzierska and Peter Doherty (The University of Melbourne) and Weisan Chen (La Trobe University). **Patrick Reading** and **Karen Laurie** are Associate Investigators. The grant will be administered by The University of Melbourne.

Collaborative Agreements

The Centre is party to two ongoing 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) (2013-2014)

Centre staff: Chantal Baas, Hilda Lau, Robert Shaw, Anne Kelso, Ian Barr

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 2014

A total of 38 egg isolates were obtained from 120 inoculations with original clinical specimens from various geographical locations. With the exception of B/Victoria lineage viruses, isolation rates varied from 29% to 53% according to virus type/subtype and lineage. Suitable isolates were made available to other laboratories and industry for reassortment and assessment as vaccine candidates.

Cooperative Research and Development Agreement with Novartis Vaccines & Diagnostics (Marburg, Germany): Development and provision of influenza virus strains isolated on MDCK 33016PF cells for vaccine production (2014–2015)

Centre staff: Heidi Peck, Joelle Dharmakumara, Robert Shaw, Anne Kelso, Ian Barr

Project overview

The suitability of a proprietary Novartis cell line for isolating and growing influenza viruses as a basis for cell-based vaccine manufacture is being evaluated. A number of original clinical specimens are used to isolate viruses directly into the MDCK33016PF cell line in parallel with egg isolation. The resultant isolates undergo analysis of their growth, antigenic and other properties.

Highlights and developments 2014

During 2014, 114 clinical specimens were cultured in MDCK 33016PF cells, of which 82 (71.9%) produced isolates. As in previous years, this was much higher than the rate of isolation in eggs. The isolates, which comprised A(H1N1) pdm09, A(H3N2) and B viruses, were sent to Novartis in Marburg, Germany, and Holly Springs NC, USA, for further evaluation as potential vaccine candidates produced by cell culture. Heidi Peck presented a poster based on this work at the 5th Australasian Vaccines and Immunotherapeutics Development Meeting, Melbourne, 7–9 May.

Research Students

PhD Candidate

Ms Teagan Guarnaccia submitted her thesis entitled "Analysis of the contribution of immune pressure on antigenic drift of influenza A viruses", under the supervision of Dr Karen Laurie and Ms Jenny Mosse (Monash University, Gippsland).

MSc Candidate

Ms Chantal Baas, who commenced her MSc candidature part-time at the Centre in 2012, has continued her project entitled" "Investigating the risk of non-human influenza viruses for public health by using a ferret model", under the supervision of Dr Aeron Hurt, Dr Ian Barr and Ms Jenny Mosse (Monash University, Gippsland).

Honours Students

Two BSc(VetBioSci) students from Monash University, Gippsland, completed research projects at the Centre in 2014. Both students achieved a grade of First Class Honours.

Ms Kathryn Borg was supervised by Dr Karen Laurie. Her project was titled "The development of strategies to identify ferret leukocytes in *in vitro* and *in vivo* systems". This project developed assays to identify and characterise various leukocytes of the ferret by their surface markers and the immune mediators they produce. The assays were verified *in vitro* by assessing the responses of leukocytes to different stimuli, and *in vivo* by analysing the immune response following influenza virus infection in the ferret model.

Ms Jacqui Panozzo was supervised by Dr Aeron Hurt and Dr Ding Yuan Thomas Oh. Her project, titled "Evaluation of dry powder insufflator as a delivery system for laninamivir in a ferret model of influenza infection", investigated the feasibility of administering powder drugs into ferrets by dry powder insufflator (DPI). Preliminary findings indicate that laninamivir octanoate (LO) administered by this method marginally improve influenza infections. However improvements such as further optimisation of drug delivery, pharmacokinetics and pharmacodynamics analysis of laninamivir in ferrets should be investigated before DPI can be routinely used for assessing LO drug efficacy in ferrets.

Masters Student

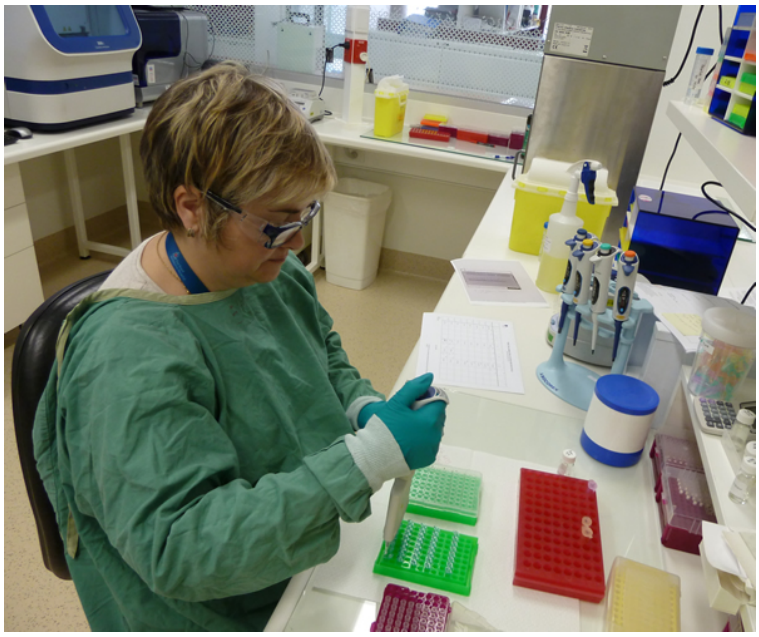
Ms Chiedza Machingaidze, a Masters of Public Health student from The University of Melbourne, undertook a research project titled "Is there evidence of waning influenza vaccine effectiveness against seasonal laboratory confirmed influenza in the Victorian population between 2007 and 2013?" , under the supervision of Dr Sheena Sullivan from August to November.

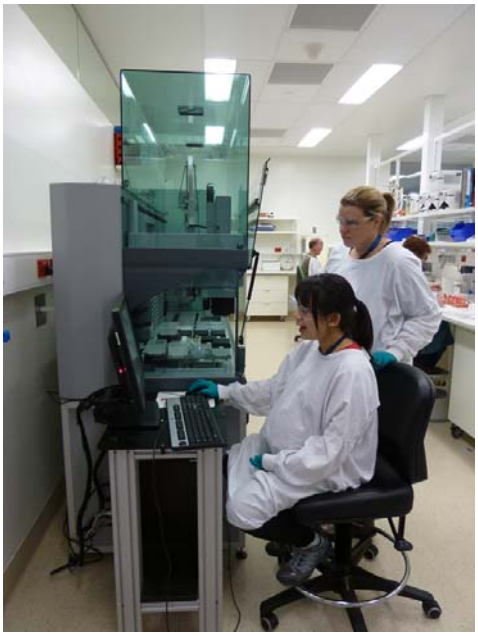
Undergraduate Student

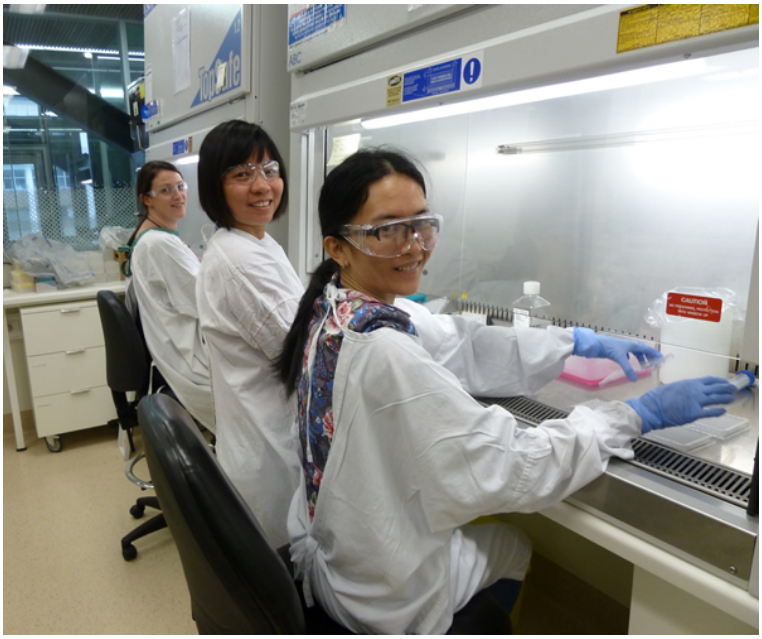
Miss Hannah Lin, Bachelor of Medicine/Bachelor of Surgery student from James Cook University, Townsville, Queensland, completed a work placement at the Centre 14–24 January.

School Students

Miss Wade Osmani, from Gladstone Park Secondary College, and Mr Andrew Yong, from Christian Brothers College St Kilda, completed work experience placements at the Centre on 19 June and 26 June respectively.







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 also co-organise the Australian Influenza Symposium, publish peer-reviewed journal papers and present numerous talks and posters.

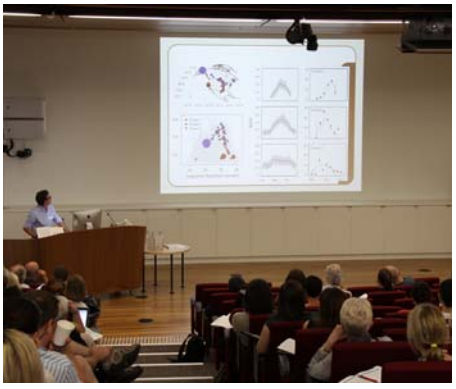
Australian Influenza Symposium

The 10th Australian Influenza Symposium was held at the Doherty Institute on 12–13 November, co-hosted by the Centre and the Therapeutic Goods Administration (TGA). Over 200 participants from Australia, the USA, Hong Kong, Singapore and Cambodia attended the conference, including six invited international speakers:

Ben Cowling, The University of Hong Kong, Hong Kong SAR, China
Paul Horwood, Institut Pasteur du Cambodge, Phnom Penh, Cambodia
Martha Nelson, Fogarty International Center, NIH, Bethesda MD, USA
Stacey Schultz-Cherry, St Jude Children's Research Hospital, Memphis TN, USA
Paul Thomas, St Jude Children's Research Hospital, Memphis TN, USA
Cécile Viboud, Fogarty International Center, NIH, Bethesda MD, USA

Attendees enjoyed a wide variety of talks encompassing influenza epidemiology, immunology, viral evolution, vaccine development, zoonotic influenza viruses and public health issues. The program also included a lively panel discussion on the issues involved in mandatory influenza vaccination for Australian health care workers. First-time visitors to the Doherty Institute also had an opportunity to see the Institute's facilities and tour Centre laboratories.

The organising committee for the symposium was **Ian Barr**, Gary Grohmann (TGA), **Anne Kelso**, **Katie Milne** and **Jayde Simpson**. Almost all staff members from the Centre attended the symposium. Anne Kelso chaired a plenary session and presented a talk.



I-MOVE meeting

The Centre and VIDRL co-hosted the inaugural Influenza Monitoring Vaccine Effectiveness (I-MOVE) Meeting at the Doherty Institute on 23–24 April 2014. This was the first meeting for vaccine effectiveness networks ever held in the southern hemisphere, and the first gathering of all of the influenza vaccine effectiveness study sites in Australia and New Zealand. The meeting was attended by 48 delegates. The organising committee was Heath Kelly, **Ian Barr** and **Jayde Simpson.** Sheena Sullivan presented two talks. Ian Barr presented a talk and chaired a session. Anne Kelso chaired a session. Several staff from the Centre also attended.

Visitors to the Centre

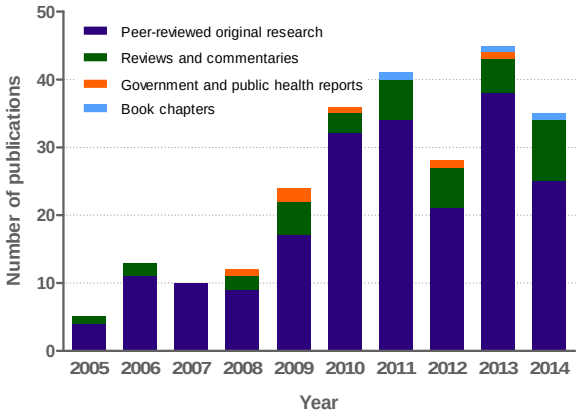
The Centre was pleased to host the following visitors during 2014:

Date	Visitor and affiliation
16 January	Delegation from DSO National Laboratory, Singapore: Ms Aw Lay Tin (Facility Manager/ Biosafety Officer), Mr Koh Wee Hong Victor, Mr Chye De Hoe, Mr Leong Kok Mun Daniel *Discuss the Centre's and VIDRL's high containment laboratories and tour*
18–21 February	Prof Edward Holmes, Australia Fellow, Sydney Institute of Emerging Infectious Diseases and Biosecurity, Sydney Medical School, The University of Sydney, Sydney
22 April	Miss Monique Chilver, Australian Sentinel Practices Research Network (ASPREN), The University of Adelaide
22 April	Miss Feng Shuo, School of Public Health, The University of Hong Kong, Hong Kong SAR
14 July	Master of Veterinary Public Health (Emergency Animal Diseases) students: Ms Laura Brisbane-Cohen, Ms Emily Glass, Mr Mesula Korsa, Mr Faheem Noor; accompanied by Dr Simon Firestone, Prof Mark Stevenson and Mr Colin Wilks, The University of Melbourne, Melbourne *Tour of Centre facilities*
23 July	Dr Guillaume Conort, Hôpital Saint-Louis, Service des Maladies Infectieuses et Tropicales, Paris, France
23–25 July	Prof Sander Greenland, University of California, Los Angeles, USA
1 August	Mr Rob Cameron, Assistant Secretary, Health Management Branch, Australian Government Department of Health
8 September	Delegation from the Bangladesh Ministry of Health and Family Welfare, Dhaka, Bangladesh: Dr Shua Chai (Resident Advisor, Center for Global Health, CDC), Md Habibur Rahman Khan (Joint Secretary), Prof Mahmudur Rahman (Director, Institute of Epidemiology, Disease Control & Research and NIC), Prof Md Sayedur Rahman (Department of Pharmacology, Bangabandhu Sheikh Mujib Medical University), Mr Subhash Chandra Sarker (Joint Secretary, Public Health and WHO), Mr Md Ayubur Rahman Khan (Additional Secretary, Development & Medical Education)
12 September	Ms Kylie Jonasson (First Assistant Secretary) and Dr Jenny Firman (Principal Medical Adviser), Office of Health Protection, Australian Government Department of Health, Canberra
27 October	A/Prof Raymond Lin, Head and Senior Consultant, National Public Health Laboratory, Singapore
28–29 October	Delegation from the Defense Threat Reduction Agency, Fort Belvoir VA, USA
10 November	Dr Stacey Schultz-Cherry, St Jude Children's Research Hospital, Memphis TN, USA
10 November	Dr Cécile Viboud and Dr Martha Nelson, Fogarty International Center, NIH, Bethesda MD, USA

Publications and Reports

The Centre continued to build its research and surveillance profile with the publication of 35 original research papers, reviews, reports and book chapters in 2014 (Figure 21).

Figure 21. Centre publications 2005–2014.



Of especial note during 2014 was a paper published in *Science*, co-authored with collaborators in the United Kingdom, the Netherlands and Vietnam. The paper describes the use of antibody landscapes to develop immune system profiles of individuals previously exposed to influenza and how this analysis could be applied to improve influenza vaccine selection processes.

> *Fonville JM, Wilks SH, James SL, Fox A, Ventresca M,* ***Aban M, Xue L****, Jones TC, Le NMH, Pham QT, Tran ND, Wong Y, Mosterin A, Katzelnick LC, Labonte D, Le TT, van der Net G, Skepner E, Russell CA, Kaplan TD, Rimmelzwaan GF, Masurel N, de Jong JC, Palache A, Beyer WEP, Le QM, Nguyen TH, Wertheim HFL,* ***Hurt AC****, Osterhaus ADME,* ***Barr IG****, Fouchier RAM, Horby PW and Smith DJ. Antibody landscapes after influenza virus infection or vaccination. Science. 2014 Nov 21;346(6212):996-1000.*

Centre Publications 2014

1. **Barr IG**, Russell C, Besselaar TG, Cox NJ, Daniels RS, Donis R, Engelhardt OG, Grohmann G, Itamura S, **Kelso A**, McCauley J, Odagiri T, Schultz-Cherry S, Shu Y, Smith D, Tashiro M, Wang D, Webby R, Xu X, Ye Z, Zhang W and Writing Committee of the World Health Organization Consultation on Northern Hemisphere Influenza Vaccine Composition for 2013-2014. WHO recommendations for the viruses used in the 2013-2014 Northern Hemisphere influenza vaccine: Epidemiology, antigenic and genetic characteristics of influenza A(H1N1)pdm09, A(H3N2) and B influenza viruses collected from October 2012 to January 2013. *Vaccine*, 2014. 32(37): 4713-25.
2. **Butler J**, Hooper KA, Petrie S, Lee R, Maurer-Stroh S, **Reh L**, **Guarnaccia T**, **Baas C**, **Xue L**, **Vitesnik S**, **Leang SK**, McVernon J, **Kelso A**, **Barr IG**, McCaw JM, Bloom JD and **Hurt AC**. Estimating the fitness advantage conferred by permissive neuraminidase mutations in recent oseltamivir-resistant A(H1N1)pdm09 influenza viruses. *PLoS Pathog*, 2014. 10(4): e1004065.
3. **Carolan LA**, **Butler J**, Rockman S, **Guarnaccia T**, **Hurt AC**, **Reading P**, **Kelso A**, **Barr I** and **Laurie KL**. TaqMan real time RT -PCR assays for detecting ferret innate and adaptive immune responses. *J Virol Methods*, 2014. 205C: 38-52.
4. Dewar B, **Barr I** and Robinson P. Hospital capacity and management preparedness for pandemic influenza in Victoria. *Aust N Z J Public Health*, 2014. 38(2): 184-90.
5. Donis RO, **Influenza Cell Culture Working Group**. Performance characteristics of qualified cell lines for isolation and propagation of influenza viruses for vaccine manufacturing. *Vaccine*, 2014. 32(48): 6583-90. doi:10.1016/j.vaccine.2014.06.045
6. Fonville JM, Wilks SH, James SL, Fox A, Ventresca M, **Aban M**, **Xue L**, Jones TC, Le NM, Pham QT, Tran ND, Wong Y, Mosterin A, Katzelnick LC, Labonte D, Le TT, van der Net G, Skepner E, Russell CA, Kaplan TD, Rimmelzwaan GF, Masurel N, de Jong JC, Palache A, Beyer WE, Le QM, Nguyen TH, Wertheim HF, **Hurt AC**, Osterhaus AD, **Barr IG**, Fouchier RA, Horby PW and Smith DJ. Antibody landscapes after influenza virus infection or vaccination. *Science*, 2014. 346(6212): 996-1000.
7. Harland KL, Day EB, Apte SH, Russ BE, Doherty PC, Turner SJ and **Kelso A**. Epigenetic plasticity of Cd8a locus during $CD8^+$ T-cell development and effector differentiation and reprogramming. *Nat Commun*, 2014. 5: 3547.
8. Horm SV, Mardy S, Rith S, Ly S, Heng S, Vong S, Kitsutani P, Ieng V, Tarantola A, Sar B, Chea N, Sokhal B, **Barr I**, **Kelso A**, Horwood PF, Timmermans A, **Hurt A**, Lon C, Saunders D, Ung SA, Asgari N, Roces MC, Touch S, **Komadina N** and Buchy P. Epidemiological and virological characteristics of influenza viruses circulating in Cambodia from 2009 to 2011. *PLoS One*, 2014. 9 (10): e110713.
9. Hsu JP, Zhao X, Chen MI, Cook AR, Lee V, Lim WY, Tan L, **Barr IG**, Jiang L, Tan CL, Phoon MC, Cui L, Lin R, Leo YS and Chow VT. Rate of decline of antibody titers to pandemic influenza A (H1N1-2009) by hemagglutination inhibition and virus microneutralization assays in a cohort of seroconverting adults in Singapore. *BMC Infect Dis*, 2014. 14: 414.
10. **Hurt AC**. The epidemiology and spread of drug resistant human influenza viruses. *Curr Opin Virol*, 2014. 8: 22-9.
11. Hurt AC, Vijaykrishna D, Butler J, Baas C, Maurer-Stroh S, Silva-de-la-Fuente MC, Medina-Vogel G, Olsen B, Kelso A, Barr IG and Gonzalez-Acuna D. Detection of evolutionarily distinct avian influenza A viruses in Antarctica. MBio, 2014. 5(3).
12. Jegaskanda S, Reading PC and Kent SJ. Influenza-specific antibody-dependent cellular cytotoxicity: toward a universal influenza vaccine. J Immunol, 2014. 193(2): 469-75.

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15. **Komadina N**, McVernon J, Hall R and Leder K. A historical perspective of influenza A(H1N2) virus. *Emerg Infect Dis*, 2014. 20(1): 6-12.
16. **Laurie KL**, Engelhardt OG, Wood J and Van Kerkhove MD, *Global seroepidemiology: value and limitations*, in *Clinical Insights: Influenza Surveillance*, J. Oxford, Editor. 2014, Future Medicine Ltd: eBook. p. 51-66.
17. **Leang SK**, **Kwok S**, **Sullivan SG**, Maurer-Stroh S, **Kelso A**, **Barr IG** and **Hurt AC**. Peramivir and laninamivir susceptibility of circulating influenza A and B viruses. *Influenza Other Respir Viruses*, 2014. 8(2): 135-9.
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23. **Oh DY** and **Hurt AC**. A review of the antiviral susceptibility of human and avian influenza viruses over the last decade. *Scientifica (Cairo)*, 2014. 2014: 430629.
24. **Oh DY**, Lowther S, McCaw JM, **Sullivan SG**, **Leang SK**, Haining J, Arkinstall R, **Kelso A**, McVernon J, **Barr IG**, Middleton D and **Hurt AC**. Evaluation of oseltamivir prophylaxis regimens for reducing influenza virus infection, transmission and disease severity in a ferret model of household contact. *J Antimicrob Chemother*, 2014. 69(9): 2458-69.
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33. Sullivan SG, Komadina N, Grant K, Jelley L, Papadakis G and Kelly H. Influenza vaccine effectiveness during the 2012 influenza season in Victoria, Australia: influences of waning immunity and vaccine match. J Med Virol, 2014. 86(6): 1017-25.
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35. Zhou B, Lin X, Wang W, Halpin RA, Bera J, Stockwell TB, Barr IG and Wentworth DE. Universal influenza B virus genomic amplification facilitates sequencing, diagnostics, and reverse genetics. J Clin Microbiol, 2014. 52(5): 1330-7. doi:10.1128/JCM.03265-13

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30. **Sullivan SG** and **Barr IG**. Communicating the imperfect protection from today's influenza vaccines. *Australas Epidemiol*, 2014. 21(1): 40-43.

31. **Sullivan SG**, Chilver MB, Higgins G, Cheng AC and Stocks NP. Influenza vaccine effectiveness in Australia: results from the Australian Sentinel Practices Research Network. *Med J Aust*, 2014. 201(2): 109-11. doi:10.5694/mja14.00106

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Presentations

Centre staff members presented talks and posters at numerous events during 2014, including national and international conferences, WHO meetings, government advisory meetings, educational lectures and research seminars.

ORAL PRESENTATIONS

Event; Location, date	Speaker, *Title(s)*
Influenza Specialist Group Annual Scientific Meeting; Melbourne, 2–3 February	Ian Barr: *Flu epidemiology update.* Aeron Hurt: *Update on antivirals & other therapeutic approaches; An Expedition to the Antarctic (did you know that penguins flu?)*
Departmental Seminar, Department of Microbiology and Immunology, The University of Melbourne; Melbourne, 18 March	Patrick Reading: *Cells, sialic acid and C-type lectins in innate immunity to influenza virus infection.*
3rd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection; Geneva, Switzerland, 1–3 April	Ian Barr: *Challenges and recent progress for influenza virus characterisation by WHO Collaborating Centres..* Karen Laurie: *CONSISE efforts to improve antibody assay standardisation and relevance for vaccine virus selection.*
Lecture to 3rd year Medical Microbiology students, School of Applied Science, RMIT University; Melbourne, 3 April	Patrick Reading: *Laboratory-based surveillance of influenza virus in the Western Pacific region.*
Airway, Inflammation and Remodelling (AIR) 2nd Annual Scientific Meeting; Melbourne, 10–11 April	Patrick Reading: *WHO and influenza surveillance in the Asia/Pacific region.*
Influenza Monitoring Vaccine Effectiveness (I-MOVE) meeting; Melbourne, 23–24 April	Ian Barr: *Can annual vaccine effectiveness estimates influence vaccine strain selection*? Sheena Sullivan: *Data pooling: the Australian experience; Commentary: What to adjust for in the case test-negative design.*
Australia Indonesia Innovative Research Seminar Series – Biomedical Research Seminar; Yogyakarta, Indonesia, 5 May; Jakarta, Indonesia, 6 May	Anne Kelso: *Surveillance, evolution and prospects for control of influenza viruses in our region.*

ORAL PRESENTATIONS (continued)

Event; Location, date	Speaker, *Title(s)*
5th Australasian Vaccines & Immunotherapeutics Development Meeting; Melbourne, 7–9 May	Anne Kelso: *Influenza and another year of living dangerously.*
4th Meeting of the WHO Expert Working Group for GISRS on Surveillance of Antiviral Susceptibility of Influenza Viruses; Geneva, Switzerland, 8–9 May	Aeron Hurt: *Status of neuraminidase inhibition susceptibility of circulating viruses including A(H7N9) - Oceania and Pacific; Alternative sources of reagents.*
Lecture to 3rd year students, University Breadth Subject "Global health, security and sustainability", The University of Melbourne; Melbourne, 14 May	Anne Kelso: *Influenza.*
International society for Influenza and Other Respiratory Virus Infections: Advances in Clinical Management; Tokyo, Japan, 4–6 June	Ding Yuan Thomas Oh: *Evaluation of oseltamivir prophylaxis regimens for reducing influenza virus infection, transmission and disease severity in a ferret model of household contact.*
Microbiology and Infectious Diseases Asia Congress; Singapore, 10–11 June	Aeron Hurt: *Influenza antivirals - the past, present and the future.*
Public Health England; London, UK, 11 June	*Yi-Mo Deng: Influenza surveillance at the WHO CC Melbourne.*
University of Cambridge; Cambridge, UK, 13 June	Yi-Mo Deng: *Chasing the ever changing influenza viruses.*
PHAA National Immunisation Conference; Melbourne, 16–19 June	Sheena Sullivan: *Pooled influenza vaccine effectiveness estimates for Australia, 2012-2013; Understanding the representativeness of influenza viruses used to inform seasonal influenza vaccine strain selection.*
National Institute of Health Research and Development; Jakarta, Indonesia, 16–20 June	Anne Kelso: *WHO Collaborating Centre for Reference and Research on Influenza at VIDRL.* Patrick Reading: *Detection and characterisation of influenza viruses at NIHRD, Jakarta - technical issues.*
WHO PCR Working Group Meeting; Geneva, Switzerland, 19–20 June	Yi-Mo Deng: *Molecular surveillance updates (2013-2014) at the WHO CC Melbourne, Australia.*
Geelong Centre for Emerging Infectious Diseases workshop; Geelong, 4 July	Ian Barr: *WHO Collaborating Centres*.
The Australian Society for Microbiology Annual Scientific Meeting; Melbourne, 6–9 July	Ian Barr: *Animal–human interactions with influenza viruses and their potential impact on human health.*
Zoonoses 2014; Brisbane, 24–26 July	Anne Kelso: *Sharing influenza viruses - H7N9 and other pandemic threats.*
QIMR Berghofer Medical Research Institute - Kidson Lecture; Brisbane, 29 July	Anne Kelso: *Influenza in the 21st century – for better or worse?*
8th Meeting of the National Influenza Centres and Influenza Surveillance in the Western Pacific and South-East Asia Regions; Jakarta, Indonesia, 11–15 August	Aeron Hurt: *Results of the WHO survey on NICs.* Ian Barr: *Influenza activity in the Southern Hemisphere.*
Immunology Group of Victoria; Creswick, Victoria, 1–2 September	Anne Kelso: *The special relationship between humans and influenza viruses.*

ORAL PRESENTATIONS (continued)	
Event; Location, date	Speaker, *Title(s)*
The Hermitage Old Girls Association Annual General Meeting and Luncheon; Geelong, Victoria, 6 September	Anne Kelso (guest speaker)
Respiratory Viruses 2014; Oxford, UK, 8 September	Karen Laurie: *Improving standardisation and timeliness of seroepidemiological studies through the global partnership CONSISE (the Consortium for the Standardization of Influenza Seroepidemiology).*
Influenza 2014; Oxford, UK, 9–11 September	Karen Laurie: *Improving standardisation and timeliness of seroepidemiological studies through the global partnership CONSISE (the Consortium for the Standardization of Influenza Seroepidemiology).*
Laboratory based surveillance of influenza and other outbreak prone diseases workshop; Noumea, New Caledonia, 29 September – 3 October	Patrick Reading: *Laboratory testing for influenza viruses; Reference laboratories and how they can be useful to you; Understanding and interpreting reports from reference laboratories.*
Victorian Infection & Immunity Network Young Investigator Symposium; Melbourne, 3 October	Anne Kelso: *From lab bench to global health. (Invited Keynote speaker)*
Seminar at Griffith Health Institute, Griffith University; Brisbane, Queensland, 3 October	Patrick Reading: *Barriers to infection: understanding innate immunity to influenza virus.*
Doherty Epidemiology Group; Melbourne, 15 October	Sheena Sullivan: *Data pooling: influenza vaccine effectiveness data.*
Managing influenza through networking and information sharing - 2nd GISAID Symposium and Training Workshop; Singapore, 23–24 October	Naomi Komadina: *GISAID for sharing and analysis of sequence data.*
Defense Threat Reduction Agency visit to the Centre; Melbourne, 28-29 October	Aeron Hurt: *Influenza virus research: antiviral drug susceptibility and non-human influenza viruses.*
Departmental seminar, Department of Biochemistry, The University of Melbourne; Melbourne, 5 November	Patrick Reading: *Understanding innate immunity to influenza virus.*
International Congress on Medical Virology; Bangkok, Thailand, 5–6 November	Anne Kelso: *Challenges in influenza vaccine virus selection.*
APACI Workshop on Epidemiology and Control of Influenza; Delhi, India, 7–8 November	Anne Kelso: *How effective are influenza vaccines?*
National Institute of Virology; Pune, India, 10 November	Anne Kelso: *Influenza in the 21st century – for better or worse?*
10th Australian Influenza Symposium; Melbourne, 12–13 November	Anne Kelso: *NHMRC Program on Limiting the Impact of Influenza.*
Surveillance of influenza-like illness; Ho Chi Minh City, Vietnam, 17–21 November	Sheena Sullivan: *Analysis of seasonality of ILI and different viruses; Estimation of influenza vaccine effectiveness.*

POSTER PRESENTATIONS	
Event; Location, date	Title and authors *(presentations are posters unless otherwise indicated, Centre authors are marked in bold, presenting author is underlined)*
5th Australasian Vaccines & Immunotherapeutics Development Meeting; Melbourne, 7–9 May	Evaluation of influenza A and B viruses isolated and passaged in the qualified MDCK suspension cell line (MDCK33016PF) and embryonated chicken eggs. **Peck H**, Foust A, **Dharmakumara J**, Atteberry G, **Baas C**, Johnson A, Chen L-M, **Galletti J**, Xu X, Trusheim H, Donis RO and **Barr IG**.
	Assessing cytokine and chemokine profiles in ferret lymph node cells following stimulation with mitogens or influenza virus. **Carolan LA**, **Butler J**, **Guarnaccia T**, Rockman S, **Hurt AC**, **Reading P**C, **Kelso A**, **Barr IG** and **Laurie KL**.
Society for Epidemiological Research Annual Meeting; Seattle WA, USA, 24–27 June	Understanding the test-negative study design using causal diagrams. **Sullivan SG**, Freeman G and Cowling B.
5th ESWI Influenza Conference; Riga, Latvia, 14–17 September	Airway fluids from mice and ferret contain different innate immune proteins that mediate antiviral activity against influenza A viruses. Job E, Short K, **Deng YM**, **Laurie K**, Brooks A, Saelens X, **Reading P**
	Investigating the potential for temporary immunity between influenza viruses in the ferret model. **Laurie K**, **Guarnaccia T**, **Carolan L**, **Aban M**, **Reading P**, **Kelso A**, Morse J, McCaw J, **Barr I**
	Improving standardisation and timeliness of seroepidemiological studies through the global partnership CONSISE (the Consortium for the Standardization of Influenza Seroepidemiology) Van Kerkhove MD, **Laurie KL**, Engelhardt OG and Wood J, on behalf of the CONSISE steering committee

Engagement in WHO Activities

Event; Location, Date	Centre staff involved
WHO Consultation on Composition of Influenza Vaccines for the Northern Hemisphere 2014-2015; Geneva, Switzerland, 18–21 February, and preparatory teleconferences	Ian Barr and Anne Kelso participated.
3rd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection; Geneva, Switzerland, 1–3 April	Ian Barr and Karen Laurie presented talks.
4th Meeting of the WHO Expert Working Group for GISRS on Surveillance of Antiviral Susceptibility of Influenza Viruses; Geneva, Switzerland, 8–9 May	Aeron Hurt presented two talks.
Meeting of the WHO PCR Working Group; Geneva, Switzerland, 19–20 June	Yi-Mo Deng presented a talk and was a session facillitator. A report from the meeting was released in November 2014.
Visit to WHO Regional Office for the Western Pacific Region; Manila, The Philippines, 28 July – 8 August	Patrick Reading
8th Meeting of the National Influenza Centres and Influenza Surveillance in the Western Pacific and South-East Asia Regions; Jakarta, Indonesia, 11–15 August	Ian Barr and Aeron Hurt presented talks. Anne Kelso was a rapporteur and presented a summary overview of sessions from two days. Naomi Komadina, Patrick Reading, Sheena Sullivan and Yi-Mo Deng also attended.
WHO Consultation on Composition of Influenza Vaccines for the Southern Hemisphere 2015; Geneva, Switzerland, 22–24 September, and preparatory teleconferences	Ian Barr and Anne Kelso participated.

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
International society for Influenza and Other Respiratory Virus Infections: Advances in Clinical Management; Tokyo, Japan, 4–6 June	Aeron Hurt was a session rapporteur.
PHAA National Immunisation Conference; Melbourne, 16–19 June	Vivian Leung attended.
The Australian Society for Microbiology Annual Scientific Meeting; Melbourne, 6–9 July	Pina Iannello and Lauren Jelley attended.
AAHL & NHMRC Forum - optimising capabilities in animal and human health infectious disease research; Geelong, 6–7 August	Anne Kelso attended.
Scientific Forum to mark the retirement of Professor Graham Brown; Melbourne, 7 August	Anne Kelso attended.
Flip Class for 3rd Year Bachelor of Biomedicine students at the University of Melbourne, Melbourne, 10 October	Anne Kelso and Aeron Hurt participated.
44th Australasian Society for Immunology Annual Scientific Meeting; Wollongong, 1–5 December	Anne Kelso participated in the Lafferty Debate.

Community Engagement

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

Anne Kelso
Interview with ABC Radio PM, 3 February
Interview with The New York Times Magazine, 7 March
"Our researchers lead the way to fight influenza", The Herald Sun, 23 April
Interview with ABC Radio National, 30 July
SBS Insight Program, “Pandemic”, broadcast 23 September 2014
Panel member in the Science & Technology Australia Topical Science Forum at the Wheeler Centre, "Immunisation: when science isn’t enough", Melbourne, 6 October
Panel member in a facilitated discussion following the public lecture: “Gavi, the Vaccine Alliance: health and sustainable development 2015 and beyond”, given by Dr Seth Berkley (CEO of Gavi), Melbourne, 27 October.

Ian Barr
"Google Flu Trends predictions not reliable: researchers", The Age, 28 March
"Scientists hold new hope for measles drug", The Conversation, 17 April
"The Making of a Flu Vaccine", Wall Street Journal, 22 December

Aeron Hurt
Interviews with several print and online media outlets about avian influenza found in Antarctic penguins, 6-7 May
- “Researchers find unique avian influenza virus in Antarctica penguins”, Nature World News
- “Researchers identify avian influenza viruses in Antarctic penguins”, RedOrbit
- “Avian flu discovered in penguins in Antarctica - scientist “, Reuters
- “Avian flu discovered in penguins in Antarctica”, The Sydney Morning Herald

Website

The Centre website was maintained and updated throughout the year. During 2014, the website was viewed by 10,918 unique visitors from 148 different countries. The majority of visits to the website came from Australia, followed by the United States. Most of the traffic to the website came from search engines.

Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2014.

Chantal Baas
Doherty Institute, *Shared PC3 Laboratory Advisory Committee*

Ian Barr
2014 ESWI (European Scientific Working Group on Influenza) Young Scientist Award, *International Selection Committee*
Australian Influenza Vaccine Committee (Therapeutic Goods Administration)
Australian Vaccine and Immunotherapeutics Development (AVID) Group, *Organising Committee*
Doherty Institute, *Shared PC3 Laboratory Advisory Committee*
Influenza Research and Treatment, *Editorial Board*
Influenza and Other Respiratory Viruses, *Editorial Board*

Public Health Laboratory Network (Department of Health)
16th International Congress of Immunology, Melbourne 2016, *Organising Committee*

Michelle Chow
Doherty Institute, *Communications Working Group*

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

Aeron Hurt
Antiviral Research, *Editorial Board*
Avian Influenza in Wild Birds, Australian Wildlife Health Network, *Steering Committee*
Infection, Ecology and Epidemiology – The One Health Journal, *Editorial Advisory Board*
Influenza Specialist Group, *Scientific Committee*
Neuraminidase Inhibitor Susceptibility Network Meeting/Committee of Antiviral Special Interest Group of the International Society for Influenza and other Respiratory Virus Diseases, *Committee member*
Virology Journal, *Associate Editor*
WHO Expert Group for GISRS Surveillance on Antiviral Susceptibility, *Chair*

Anne Kelso
Australian Influenza Vaccine Committee (Therapeutic Goods Administration)
Australian Technical Advisory Group on Immunisation (Department of Health), *Influenza Working Party*
BioMed Central Immunology, *Editorial Advisor*
Burnet Institute, *Research Advisory Committee*
Doherty Institute, *Operational Management Committee (Chair until Aug 2014), Leadership Group*
Florey Institute of Neuroscience and Mental Health, *Board*, *Council of Governors* and *Nomination Committee*
Influenza Pandemic Planning Steering Committee (Victorian Department of Health)
Influenza Surveillance Strategy Working Group/ National Influenza Surveillance Committee (Department of Health)
International Immunology, *Associate Editor*
International Society for Influenza and other Respiratory Virus Diseases, *Board of Trustees*
National Health and Medical Research Council, *Council* and *Assigners Academy*
Nossal Institute for Global Health (The University of Melbourne), *Advisory Council*
Telethon Kids Institute, *Board*
WHO/OIE/FAO H5N1 Evolution Working Group

Katie Milne
Victorian Infectious Disease Reference Laboratory, *NATA Action Group*

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

Karen Laurie
Consortium for the Standardization of Influenza Seroepidemiology (CONSISE), *Steering Committee*
Doherty Institute, *Bioresources Facility Executive Committee; Operational Health and Safety and Environment Advisory Committee*
Global Influenza Seroepidemiology Standardisation Working Group
Victorian Infectious Diseases Reference Laboratory, *Safety Committee*

Patrick Reading
Influenza and Other Respiratory Viruses, *Editorial Board*

Sheena Sullivan
Influenza Surveillance Strategy Working Group/ National Influenza Surveillance Committee (Department of Health), *Observer*

Management and Staff

SURVEILLANCE

ANTIGENIC ANALYSIS

Head: Robert Shaw
Medical Scientist: Helen Sjogren
Medical Scientist: Tasoula Mastorakos
Medical Scientist: Lauren Jelley
Medical Scientist: Hilda Lau
Medical Scientist: Greg Waller
Laboratory Technician: Iwona Buettner

GENETIC ANALYSIS

Head: Dr Yi-Mo Deng
Medical Scientist: Pina Iannello
Medical Scientist: Natalie Spirason
Medical Scientist: Lauren Jelley
Medical Scientist: Hilda Lau

ANTIVIRAL DRUG SENSITIVITY

Head: Dr Aeron Hurt
Medical Scientist: Sook-Kwan Leah Leang
Medical Scientist: Dr Danielle Tilmanis

CONTRACTS

INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTUERS AND ASSOCIATIONS

Medical Scientist: Chantal Baas
Medical Scientist: Hilda Lau

NOVARTIS VACCINES AND DIAGNOSTICS

Medical Scientist: Heidi Peck
Medical Scientist: Joelle Dharmakumara

RESEARCH

RESEARCH I

Senior Virologist: Dr Karen Laurie
Research Assistant: Louise Carolan
Research Assistant: Malet Aban

RESEARCH II

Research Scientist: Dr Aeron Hurt
Medical Scientist: Dr Ding Yuan Thomas Oh
Medical Scientist: Malet Aban

PhD Candidate: Teagan Guarnaccia
MSc Candidate: Chantal Baas (P/T)

Staff Changes 2014

Ms Vivian Leung was appointed as epidemiologist in May.

Dr Danielle Tilmanis joined the Centre in September in the Antiviral Drug Sensitivity group.

Mr Greg Waller was appointed in November in the Antigenic Analysis group.