WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL

Annual Report 2010

Contents

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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 Network (WHO GISN). The network was established in 1947 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 2007-2011) are:

i. to obtain and preserve representative strains from outbreaks and sporadic cases of influenza, fully characterize their antigenic properties and distribute them to research and production laboratories;
ii. to exchange information and new antigenic variants of influenza viruses with the WHO Collaborating Centres for Reference and Research on Influenza in Atlanta, London and Tokyo;
iii. to advise which strains should be included in influenza vaccines;
iv. to arrange training of research workers in specialized techniques for isolation, diagnosis and studies of influenza virus;
v. to collect epidemiological information on the prevalence of influenza, especially in countries and areas in the Region; and
vi. to assist WHO and national health authorities in developing plans on how to respond to pandemic influenza and to undertake work programmes which will improve the pandemic response.

Governance

The Centre is supported by the Australian Government Department of Health and Ageing through a funding agreement between the Commonwealth and Melbourne Health, and reports directly to the Department as well as to WHO. An Australian Government Advisory Committee (AGAC) reviews the Centre's work program and progress, provides advice to assist the Centre and the Commonwealth with its objectives under the work program, and monitors and advises on the scientific performance and direction of the Centre.

Australian Government Advisory Committee 2010

Prof Jim Bishop AO, Chair (Commonwealth Chief Medical Officer)

Dr Gary Lum, Deputy Chair (Health Emergency Management Branch)

Prof Anne Kelso AO (Director of the Centre)

Dr Mike Catton (Director, Victorian Infectious Diseases Reference Laboratory)

Prof Graham Brown AM (Director, Nossal Institute for Global Health, The University of Melbourne)

Prof Peter Doherty AC FAA FRS (Laureate Professor, Department of Microbiology and Immunology, The University of Melbourne)

Prof John Horvath AO (Principal Medical Consultant for the Department of Health and Ageing)

Prof John Mackenzie AO (Professor of Tropical Infectious Diseases, Curtin University of Technology)

Dr Greg Stewart (Director, Population Health, Planning and Performance, Sydney South West Area Health Service)

Dr Heather Wellington (Consultant, Health Law Team, DLA Phillips Fox)

Dr Martyn Jeggo, observer (Director, Australian Animal Health Laboratory, CSIRO)

Highlights of 2010

Surveillance

The Centre received and processed 4044 influenza samples from 20 countries during 2010: 66% of samples were subtyped as 2009 pandemic A(H1N1).

Research

The NHMRC Program Grant on Understanding and Controlling Influenza commenced on 1 January 2010. The 5-year Program involves investigators from six groups at three different institutions working collaboratively to understand and harness mechanisms of cellular immunity to influenza viruses.

Seroprevalence studies

Following the influenza pandemic of 2009, the Centre has been engaged in a series of serological analyses to determine infection rates and population response to the pandemic virus in Australia and elsewhere. During 2010 Centre staff members participated in several seroprevalence surveys.

Publications

Centre staff members were authors on 35 papers in 2010, the Centre's highest output to date. This included 32 research and surveillance papers. Three papers published by Centre staff members during the past five years were recognised by their respective publishers for their high number of citations and/or downloads from their websites.

Director's Report

It is a pleasure to present the Centre's 2010 Annual Report. The Report gives us an opportunity to summarise the data obtained during the year from the analysis of several thousand human influenza samples submitted to the Centre by WHO National Influenza Centres and other laboratories, and to record the range of other activities undertaken by Centre staff members in training, research and communication.

Following the emergence of the A(H1N1) 2009 pandemic virus in North America in April 2009 and its rapid spread around the globe in the following months, 2010 saw the new virus adopt a seasonal pattern of circulation in both the northern and southern hemispheres. As a consequence, the World Health Organisation (WHO) announced the end of the pandemic on 10 August 2010.

While 2010 provided a welcome return to normality, it was also our first opportunity in more than 40 years, and the first in the molecular era, to observe the evolution of a pandemic virus as it established its place in the mix of influenza viruses circulating in humans. Thus, in 2010 it became clear that the new lineage of H1N1 viruses had replaced the previous seasonal H1N1 lineage but not the other influenza A virus subtype, H3N2. Attention turned to the potential of H1N1 2009 viruses to undergo antigenic drift and acquire resistance to the antiviral drugs which had been used more widely than ever before during 2009. By the end of the year, as described in more detail later in this report, we were fortunate that the great majority of H1N1 2009 viruses remained antigenically similar to the vaccine virus A/California/7/2009 and retained sensitivity to the neuraminidase inhibitor class of antiviral drugs.

After a year in which the capacity of the WHO Global Influenza Surveillance Network (GISN) to detect and keep track of influenza viruses was profoundly tested, it was pleasing to see the continued growth of the Network in 2010. Several new WHO National Influenza Centres were designated, bringing the total number to 136 Centres in 106 countries. We also congratulate the Chinese National Influenza Centre (CNIC) on its designation as a WHO Collaborating Centre for Reference and Research on Influenza, the fifth such centre working on human influenza viruses globally (along with ours in Melbourne and those in London, Atlanta and Tokyo) and the third in the Western Pacific Region. We look forward to working closely with the Centre Director Dr Shu Yuelong and his team in this new capacity over the coming years.

Although research has long been one of Centre's core activities, both the quantity and scope of research undertaken in-house and through external collaborations have increased markedly in the last three years. This has been aided by the Centre's move to VIDRL, making it eligible to seek national competitive funding for the first time, and by key staff appointments, among other factors. The 2009 pandemic also presented new opportunities for collaborative research with colleagues within and outside Australia as all of us in the public health, biomedical and other sectors sought to understand the evolution of the new virus and its impact on population immunity. The last of these issues in particular was the stimulus for the Centre's participation in a range of seroprevalence studies, several of which were published in 2010 and have provided significant new information on likely protective immunity in various population groups in Australia and Singapore.

Our research linkages with the Department of Microbiology and Immunology (DMI) at The University of Melbourne and the Ludwig Institute for Cancer Research have been consolidated with the commencement of Australian National Health and Medical Research Council funding through a 5-year $10 million Program Grant, led by Professor Peter Doherty. In addition to enabling me to establish a small research laboratory at DMI, the Program is fostering greater interaction between other Centre staff members and researchers at the University, the Ludwig Institute, the School of Population Health at The University of Melbourne, and the Australian Animal Health Laboratory in Geelong.

It was a great pleasure to receive the news that Aeron Hurt, head of Antiviral Drug Resistance and the Centre's first PhD candidate, had been awarded his PhD and then that he had received the Mollie Holman Doctoral Medal in the Faculty of Science of Monash University for best doctoral thesis for 2010. The work Aeron performed for his thesis has been amongst the most productive and highly recognised research published from the Centre in the last few years and his achievements are a great credit to Aeron and to his supervisors, Ms Jenny Mosse (Monash University) and Dr Ian Barr.

May I take this opportunity to thank the many people who have supported our work throughout 2010, particularly Professor Jim Bishop and other members of the Australian Government Advisory Committee, colleagues in the Department of Health and Ageing, Dr Mike Catton and colleagues at VIDRL, and our many research collaborators. Special mention must be made of the WHO National Influenza Centres and other laboratories which submitted viruses to the Centre in 2010 and assisted us in many other ways, enabling us to meet our commitments to the WHO Global Influenza Surveillance Network. Finally, may I thank all the staff and students of the Centre for their outstanding work throughout 2010.

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 based on samples submitted by WHO National Influenza Centres and other laboratories. Most of the samples received at the Centre come from the Asia-Pacific region.

Twice a year (once each for the northern and southern hemisphere), 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, with various combinations of 16 antigenically different HA variants and 9 NA variants. Influenza B viruses are not classified into subtypes. Currently three families of influenza viruses circulate 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], the circulation of the previous seasonal A(H1N1) virus [A(H1N1) seasonal] has decreased to almost negligible levels.

Receipt of Influenza Viruses

The Centre received 4044 clinical specimens and virus isolates from 47 laboratories in 20 countries during 2010 (Figure 1, Table 1). Although the number of samples received at the Centre has increased over the past five years overall, numbers were highest in 2009 (6570 samples) due to the influenza pandemic (Figure 2). Of the 4044 samples received in 2010, 3595 (89%) were analysed by real-time reverse-transcription polymerase chain reaction (RT-PCR) assay and/or cultured and analysed by haemagglutination inhibition (HI) assay. Of samples received by the Centre for which the age of the patient was known, most were taken from subjects who were younger than 30 years old (Figure 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.

In 2010 the Centre received and processed 1907 original clinical specimens, from which 1652 (87%) influenza isolates were successfully obtained in MDCK cells.

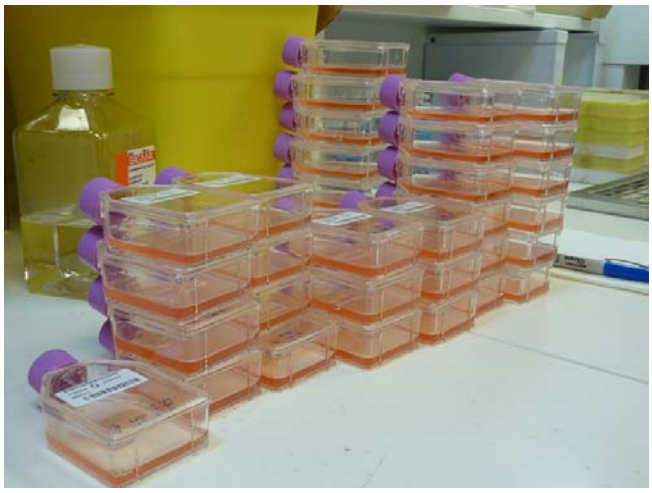


Figure 1. Geographic spread of influenza laboratories sending viruses to the Centre during 2010

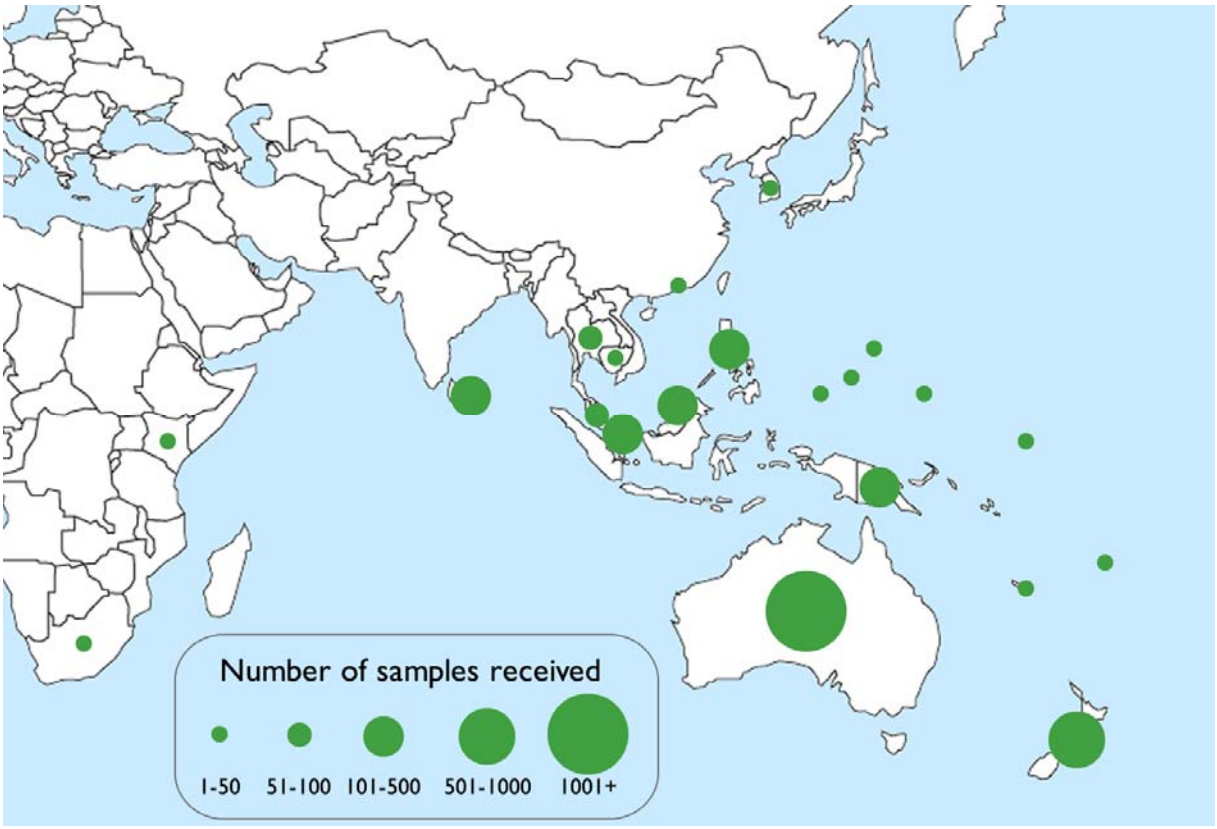
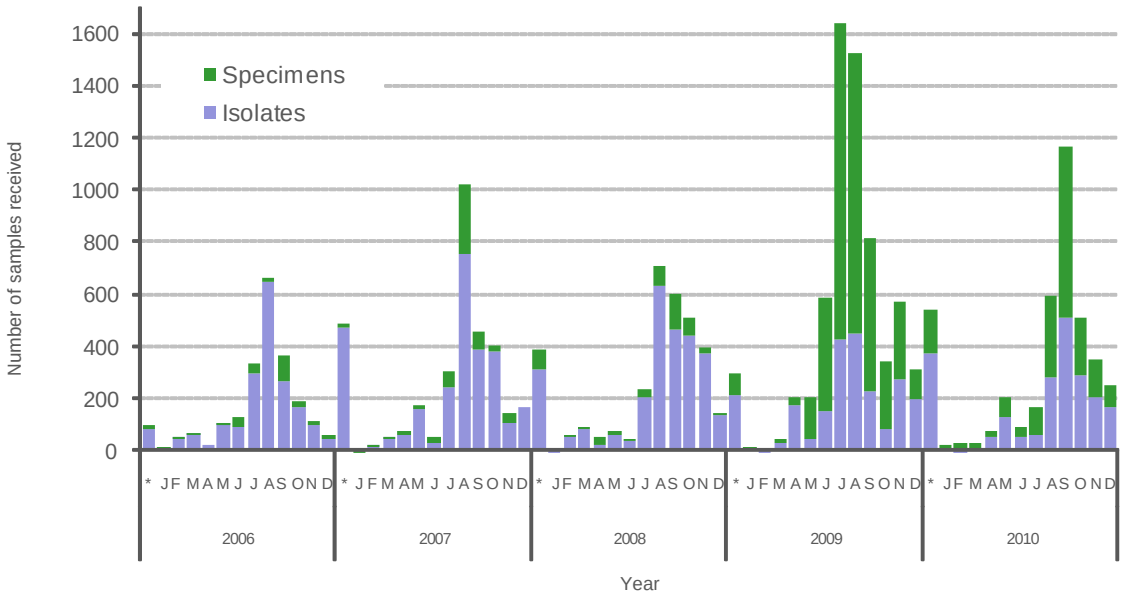


Figure 2. Samples received and analysed at the Centre, 2006-2010



** samples received early in the indicated year but with sample dates from the preceding year*

Table 1. Samples received at the Centre in 2010, by country, type and subtype

Country	Samples received		Samples tested	A (H1N1) pdm09	A (H1N1) seasonal	A(H3N2)	A (unsubtyped)	B	Mixed
	Specimens	Isolates							
AUSTRALASIA	**1237**	**1492**	**2304**	**1804**	**0**	**150**	**92**	**202**	**6**
Australia	1235	1051	1861	1369	0	146	92	198	6
New Zealand	2	441	443	435	0	4	0	4	0
SOUTH PACIFIC	**341**	**1**	**342**	**78**	**0**	**32**	**5**	**23**	**3**
Fiji	43	0	43	35	0	8	0	0	0
Federated States of Micronesia									
Pohnpei	10	0	10	0	0	0	0	0	0
Yap	13	0	13	0	0	0	0	2	0
Guam	41	0	41	7	0	0	0	0	0
Nauru	44	0	44	4	0	0	1	0	0
New Caledonia	16	0	16	0	0	0	0	16	0
Palau	40	1	41	1	0	0	2	0	0
Papua New Guinea	134	0	134	31	0	24	2	5	3
SOUTH EAST ASIA	**217**	**507**	**721**	**387**	**1**	**69**	**48**	**215**	**4**
Brunei	180	0	180	136	0	8	36	0	2
Cambodia	0	40	40	31	0	1	0	8	0
Malaysia	0	79	78	23	1	2	4	48	0
Philippines	1	155	155	75	0	2	7	70	1
Singapore	36	168	203	119	0	41	1	42	1
Thailand	0	65	65	3	0	15	0	47	0
EAST ASIA	**0**	**60**	**60**	**23**	**0**	**0**	**0**	**37**	**0**
Macau	0	50	50	21	0	0	0	29	0
Republic of Korea	0	10	10	2	0	0	0	8	0
SOUTH ASIA	**99**	**21**	**102**	**40**	**2**	**23**	**28**	**6**	**0**
Sri Lanka	99	21	102	40	2	23	28	6	0
AFRICA	**10**	**54**	**64**	**34**	**6**	**7**	**0**	**17**	**0**
Kenya	0	30	30	22	6	0	0	2	0
South Africa	10	24	34	12	0	7	0	15	0
Unknown	**3**	**2**	**2**	**1**	**0**	**0**	**0**	**1**	**0**
TOTAL	**1907**	**2137**	**3595**	**2367**	**9**	**281**	**173**	**501**	**13**

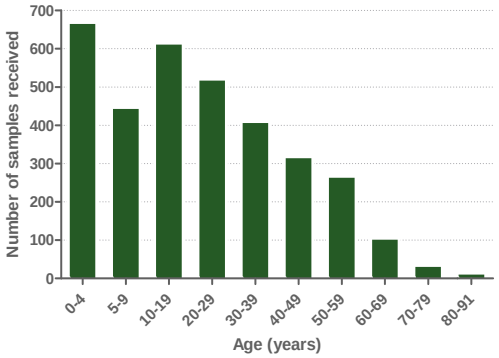


Figure 3. Age distribution of subjects from whom samples were received at the Centre in 2010

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.

Antigenic analyses 2010

A total of 3221 isolates were analysed antigenically at the Centre in 2010, of which 2518 (78%) produced a positive result. The majority of these isolates were A(H1N1)pdm09 subtype (73.9%), with 16.6% typed as influenza B and 9.0% as A(H3N2) subtype. (Figure 4). Most geographic regions submitted a majority of isolates of A(H1N1)pdm09 subtype, except East Asia, from where a larger number of B viruses were received and South Asia, where a greater proportion of samples from Sri Lanka were A(H3N2) (Figure 5).

Figure 4. Influenza sub/types of isolates received in 2010 and analysed by HI assay

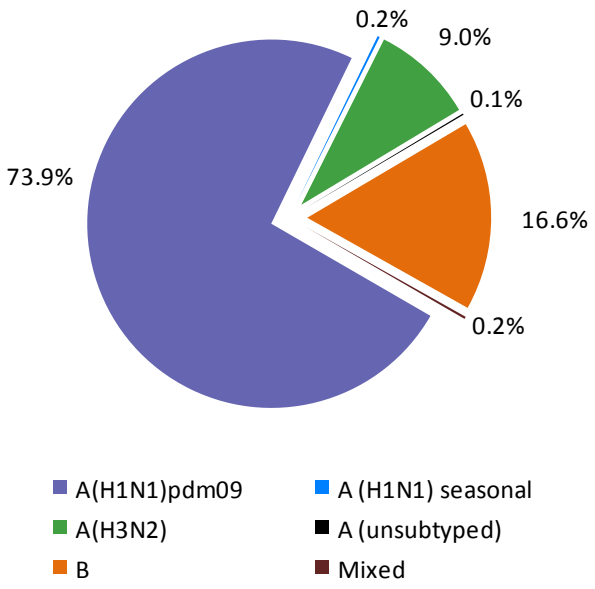
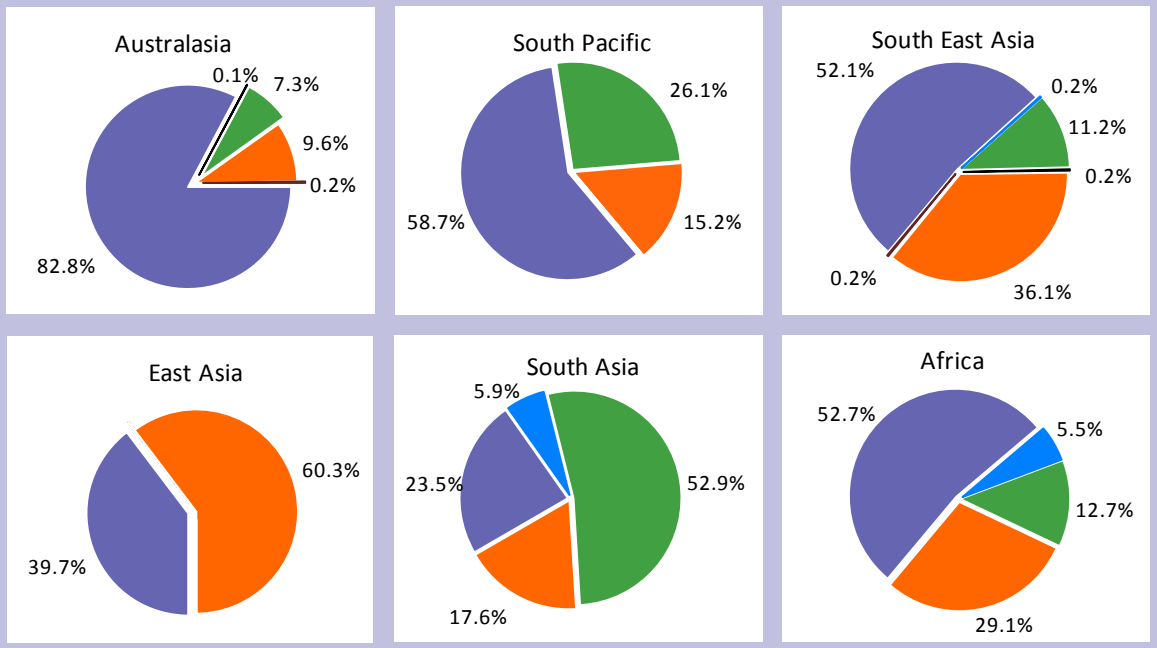


Figure 5. Influenza sub/types of isolates from different world regions as determined by antigenic analysis



Genetic Analysis of Influenza Viruses

Background

A subset of all influenza viruses analysed at the Centre undergo further 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 way to examine the extent and direction of change in circulating influenza 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 on the selection of vaccine strains.

Sequencing 2010

In 2010, 332 HA, 327 NA and 229 matrix protein (MP) genes of viruses received at the Centre were sequenced (Figure 6). In addition, 30 influenza A viruses were analysed by full genome sequencing (Figure 7) and 30 influenza A viruses were analysed by pyrosequencing for evidence of reassortment (Figure 8). Viruses were selected for these analyses because they were representative of the viruses received and/or because they displayed unusual properties during antigenic analysis.

Figure 6. Sequence analysis of samples received in 2010

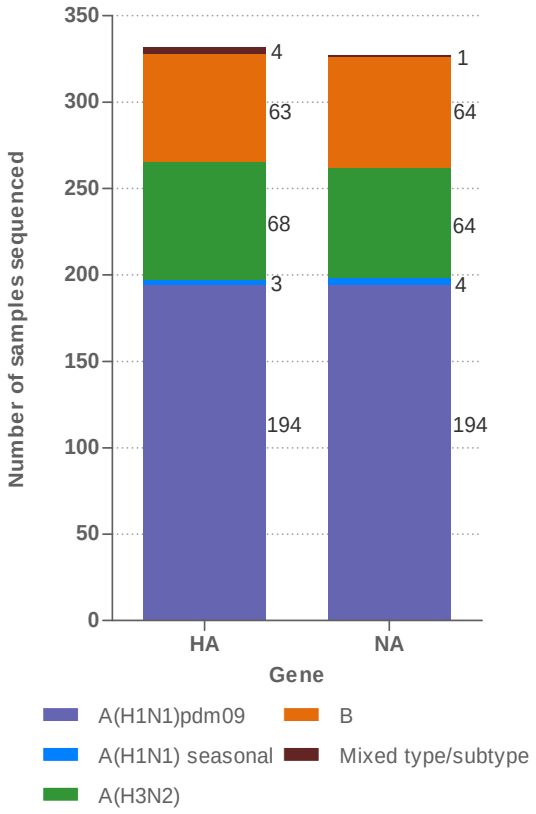


Figure 7. Geographic spread and numbers of viruses received at the Centre during 2010 and analysed by full genome sequencing

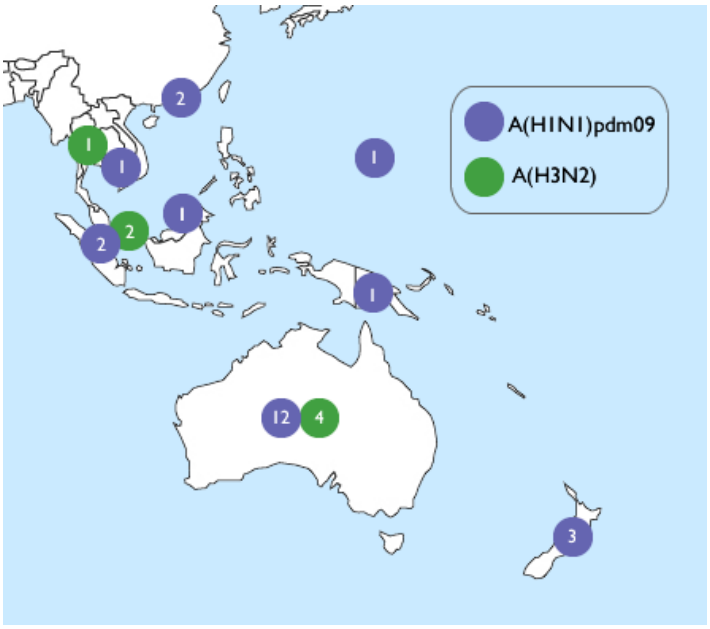
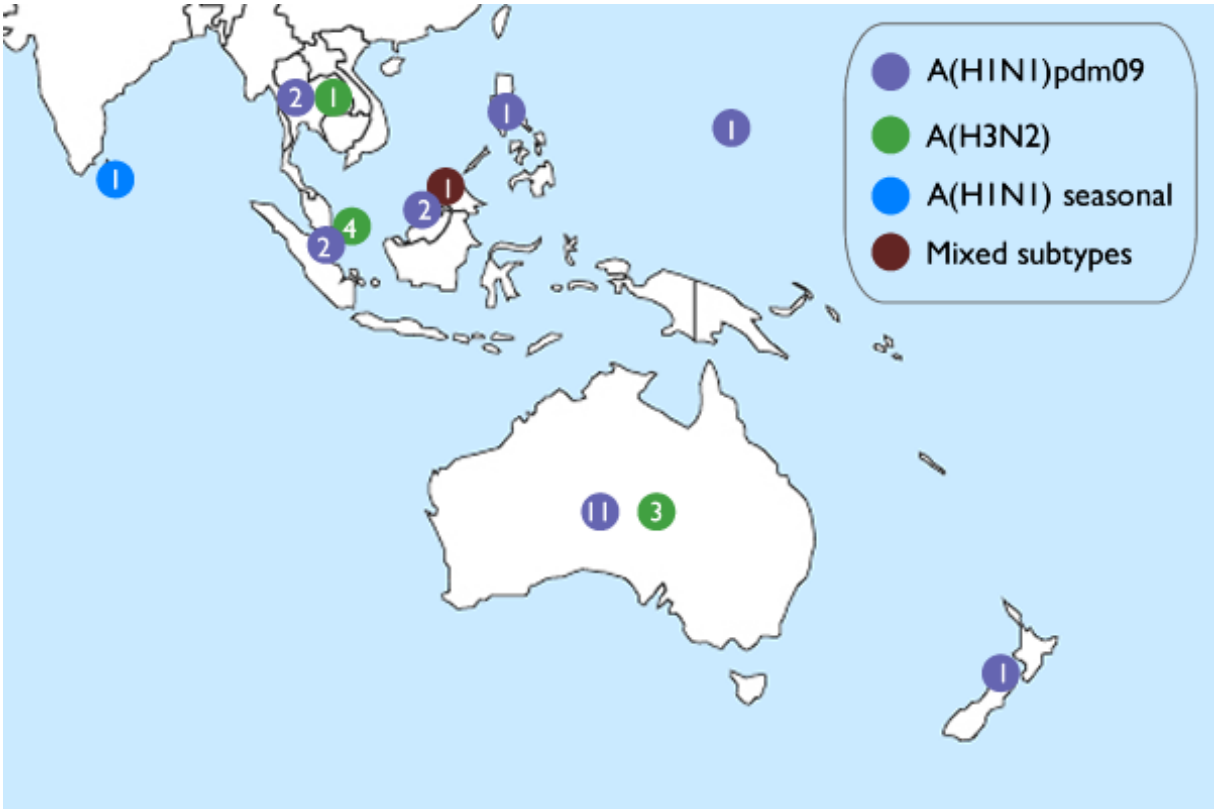


Figure 8. Geographic spread and numbers of viruses received at the Centre during 2010 and analysed by pyrosequencing for evidence of reassortment



Submission of Influenza Sequences to GISAID

Background

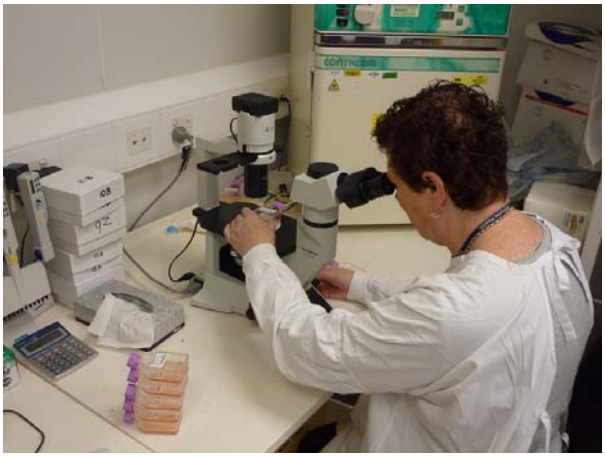
Virus sequences generated at the Centre are shared with the global influenza community through the EpiFlu™ database, a publically accessible international repository of influenza virus sequences developed by the Global Initiative on Sharing All Influenza Data (GISAID) (http://www.gisaid.org).

Sequences submitted 2010

A total of 920 gene sequences from 367 viruses submitted to the Centre in 2010 were deposited with GISAID (Table 2). The largest number of these sequences were of HA, NA and MP genes. However, full genomes of 14 influenza viruses were also represented in the Centre's submissions. Some of the sequences submitted to GISAID by the Centre were also submitted to GenBank, the genetic sequence database operated by the National Institutes of Health (NIH).

Table 2. Genetic sequences submitted to GISAID of samples received at the Centre in 2010

Subtype \ Gene	HA	NA	MP	PB2	PB1	PA	NP	NS	Total
A(H1N1)pdm09	197	167	158	15	15	15	15	14	**596**
A(H1N1) seasonal	2	2	2	0	0	0	0	0	**6**
A(H3N2)	64	53	53	2	1	2	1	1	**177**
B	65	65	0	0	0	0	2	9	**141**
Total	328	287	213	17	16	17	18	24	**920**



Surveillance Results by Influenza Subtype

Viruses were analysed by comparison with reference viruses recommended by WHO for the 2010 southern hemisphere and 2010-2011 northern hemisphere vaccines. Using the HI assay, viruses were identified as low-reactors if their titre with the reference antiserum was at least 8-fold lower than the titre of the reference virus. Results of sequencing analysis of the HA region of the haemagglutinin gene are also described in the following sections.

Influenza A(H1N1)

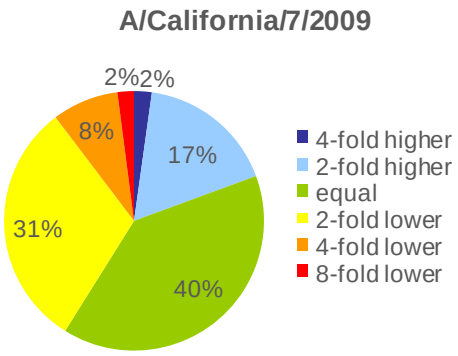
Antigenic analysis

In total, 1861 A(H1N1)pdm09 isolates were available for analysis by HI assay in 2010. There was no significant antigenic drift, with only 2% of viruses having a titre 8-fold lower than the A/California/7/2009 vaccine reference strain (Table 3, Figure 9). Only five A(H1N1) seasonal viruses were received at the Centre and all were antigenically similar to A/Brisbane/59/2007.

Table 3. Antigenic characterisation of A(H1N1)pdm09 and A(H1N1) seasonal viruses analysed at the Centre compared to A/California/7/2009 and A/Brisbane/59/2007 reference viruses, respectively

Region	A(H1N1)pdm09 reference strain: A/California/7/2009		A(H1N1) seasonal reference strain: A/Brisbane/59/2007	
	Like	Low reactor (%)	Like	Low reactor (%)
Australasia	1473	23 (1.5%)	0	0
South Pacific	53	0	0	0
South East Asia	244	13 (5.1%)	1	0
Africa	29	0	3	0
East Asia	23	0	0	0
South Asia	2	1 (33%)	1	0
Total	1824	37 (2.0%)	5	0 (0%)

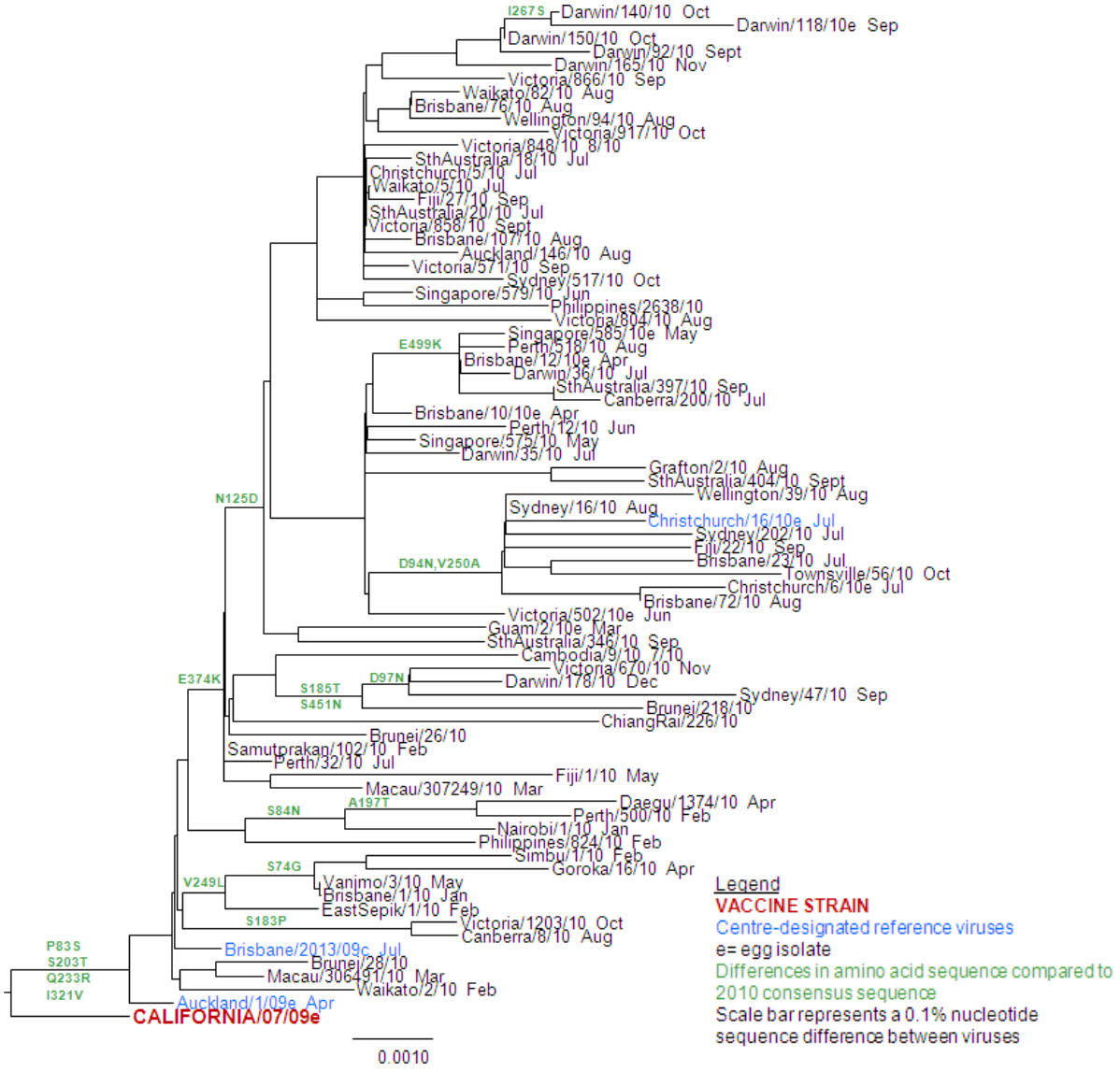
Figure 9. Summary of fold differences in HI titres of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/California/7/2009 reference virus



Haemagglutinin gene sequencing

Sequence analysis of haemagglutinin genes from 194 A(H1N1)pdm09 viruses confirmed that circulating viruses remained genetically similar to the vaccine reference strain A/California/7/2009, with only a small number of non-significant sequence changes (Figure 10).

Figure 10. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2010



Influenza A(H3N2)

Antigenic analysis

A total of 227 A(H3N2) subtype isolates were available for analysis by HI assay, with the majority (81%) displaying similar antigenic properties to the reference strain A/Perth/16/2009 (Table 4, Figure 11).

Figure 11. Summary of fold differences in HI titres of A(H1N1) seasonal viruses analysed at the Centre compared to the A/Perth//16/2009 reference virus

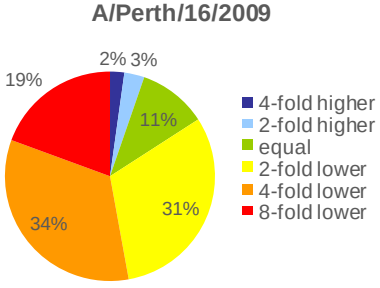


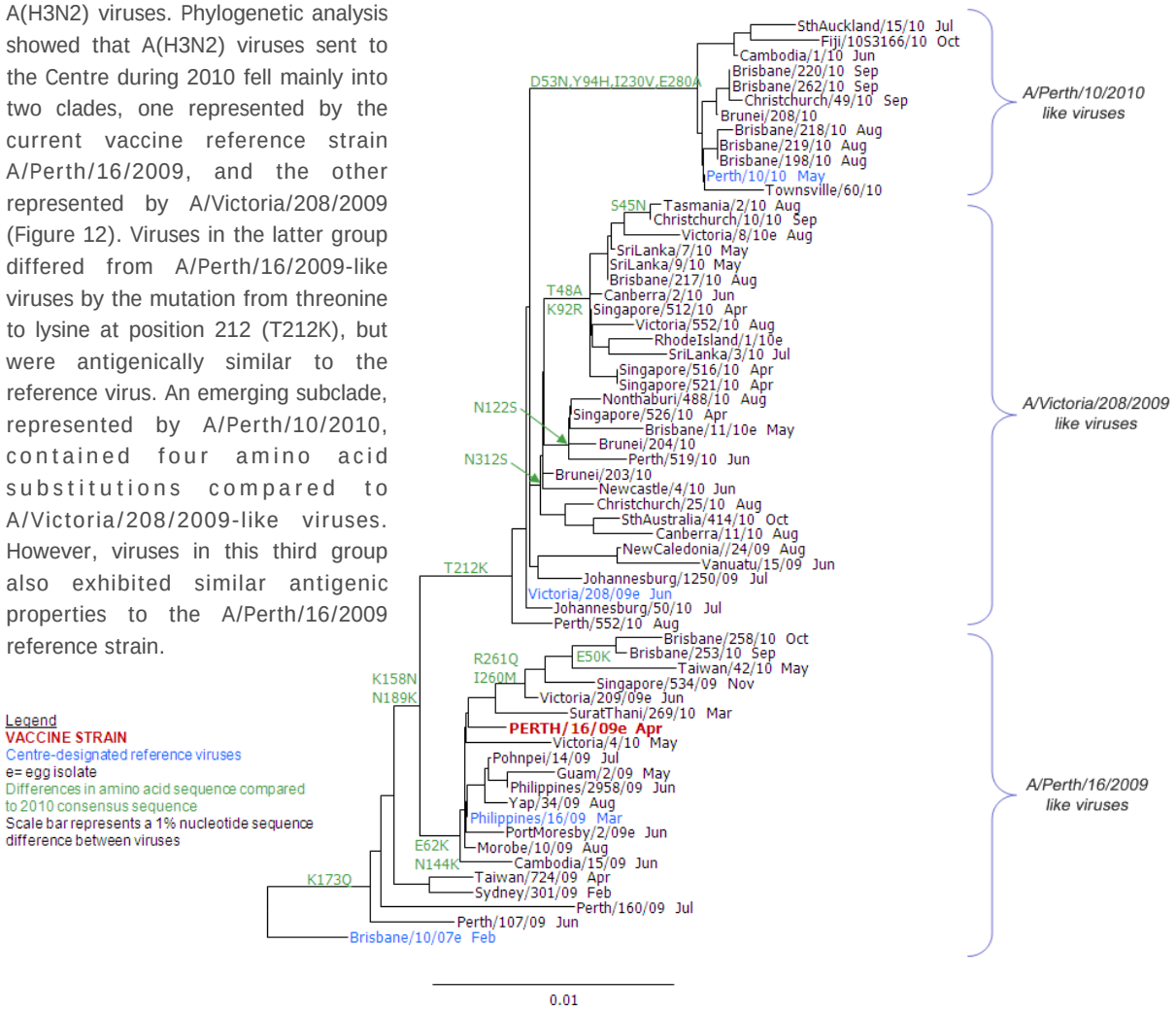
Table 4. Antigenic characterisation of A(H3N2) viruses analysed at the Centre compared to the A/Perth/16/2009 reference virus

	A(H3N2) reference strain: A/Perth/16/2009	
Region	Like	Low reactor (%)
Australasia	123	9 (6.8%)
South Pacific	5	19 (79.2%)
South East Asia	45	10 (18.2%)
Africa	3	4 (57.1%)
South Asia	7	2 (22.2%)
Total	183	44 (19.4%)

Haemagglutinin gene sequencing

Sequencing was performed on 68 A(H3N2) viruses. Phylogenetic analysis showed that A(H3N2) viruses sent to the Centre during 2010 fell mainly into two clades, one represented by the current vaccine reference strain A/Perth/16/2009, and the other represented by A/Victoria/208/2009 (Figure 12). Viruses in the latter group differed from A/Perth/16/2009-like viruses by the mutation from threonine to lysine at position 212 (T212K), but were antigenically similar to the reference virus. An emerging subclade, represented by A/Perth/10/2010, contained four amino acid substitutions compared to A/Victoria/208/2009-like viruses. However, viruses in this third group also exhibited similar antigenic properties to the A/Perth/16/2009 reference strain.

Figure 12. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2010



Influenza B

Antigenic analysis

There are currently two antigenically and genetically distinct lineages of influenza B virus circulating, the B/Victoria/2/87 lineage (represented by B/Brisbane/60/2008) and the B/Yamagata/16/88 lineage (represented by the former vaccine strain B/Florida/4/2006). Until 2001, B/Victoria lineage viruses had been restricted to Asia where they tended to alternate with the B/Yamagata lineage. In 2002 the B/Victoria lineage became the predominant influenza B type in most parts of the world. However this trend was reversed again 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.

The B/Victoria lineage has been predominant amongst circulating influenza B viruses since 2009, and this trend continued in 2010. Of the 429 type B viruses received and analysed antigenically at the Centre in 2010, the majority showed similar behaviour to B/Brisbane/60/2008 (Table 5, Figure 13). A significant proportion of the viruses which were B/Brisbane/60/2008 low-reactors displayed similar antigenic behaviour to a past vaccine strain, B/Malaysia/2506/2004.

Haemagglutinin gene sequencing

Sequence analysis of the HA genes of 63 B viruses received at the Centre during 2010 showed two distinct groups corresponding to the B/Brisbane/60/2008 and B/Florida/4/2006 lineages (Figure 15). The B/Brisbane/60/2008 group contained a subgroup that is represented by the reference strain B/Singapore/616/2008. Viruses in this subgroup displayed similar antigenic behaviour to the past vaccine strain B/Malaysia/2506/2004, and were low reactors with antiserum raised to the current vaccine strain B/Brisbane/60/2008. Of the small number of B/Yamagata lineage viruses received in 2010, most were like B/SthAustralia/8/2008 or B/Wisconsin/1/2010.

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

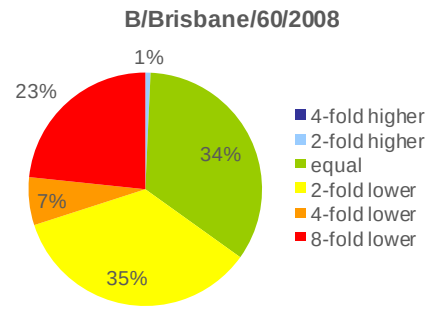


Figure 14. Summary of fold differences in HI titres of type B viruses analysed at the Centre compared to the B/Florida/4/2006 reference virus

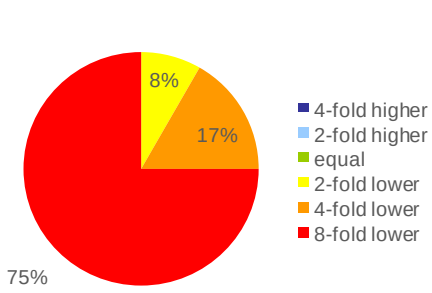
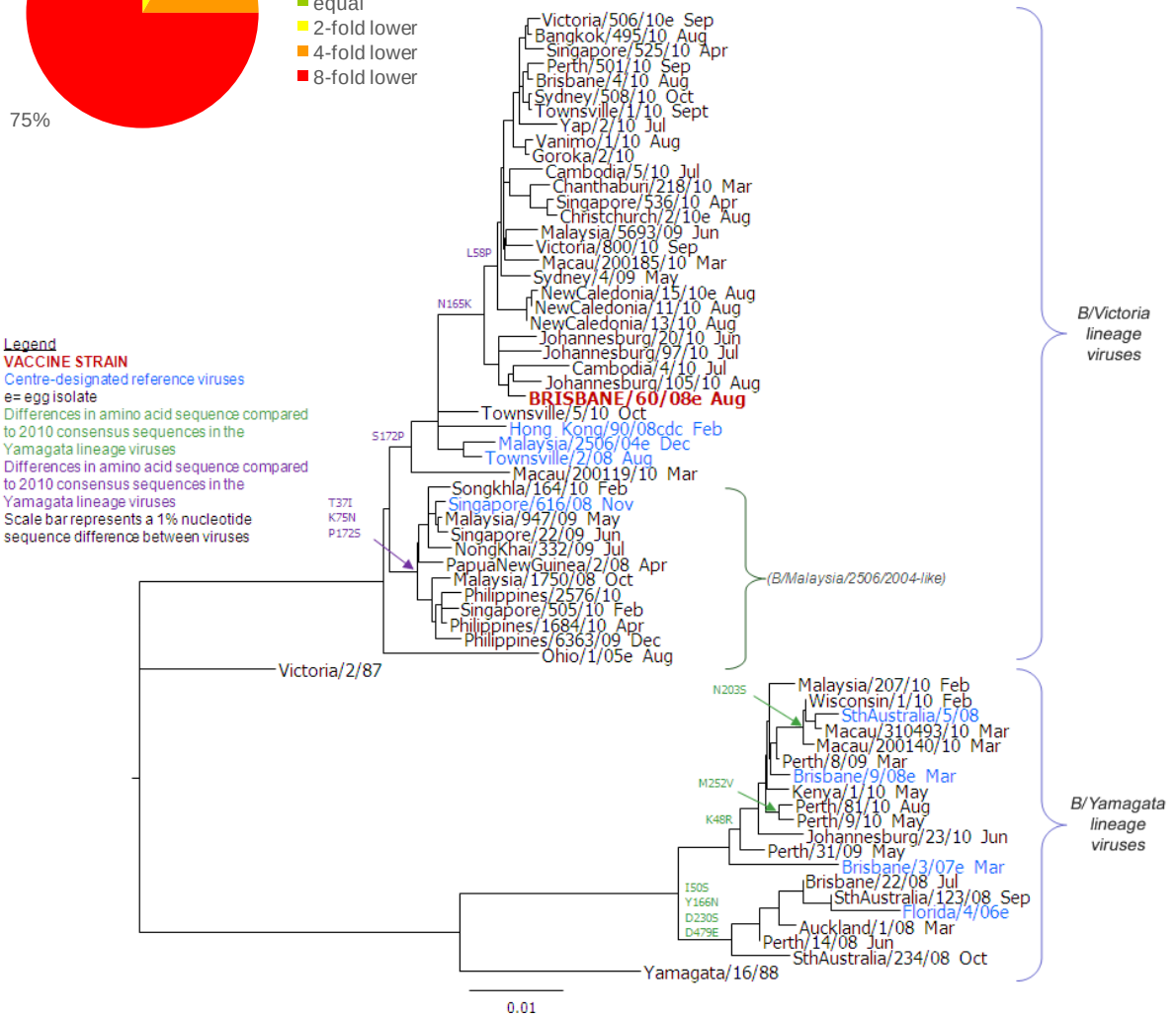


Table 5. Antigenic characterisation of B viruses analysed at the Centre compared to B/Brisbane/60/2008 and B/Florida/4/2006 reference viruses

Region	Influenza B reference strain: B/Brisbane/60/2008*		Influenza B reference strain: B/Florida/4/2006**	
	Like	Low reactor (%)	Like	Low reactor (%)
Australasia	169	2 (1.2%)	0	2 (100%)
South Pacific	13	1 (7.1%)	0	0
South East Asia	102	73 (41.7%)	2	1 (33.3%)
Africa	14	0	1	1 (50%)
East Asia	12	18 (60.0%)	0	5 (100%)
South Asia	2	1 (33.3%)	0	0
Total	312	95 (23.3%)	3	9 (75%)

*B/Victoria lineage virus **B/Yamagata lineage virus

Figure 15. Phylogenetic tree of representative HA genes of B viruses received by the Centre during 2010



Resistance to Antiviral Drugs

Resistance to Oseltamivir and Zanamivir

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) and zanamivir (Relenza) using the neuraminidase inhibition (NAI) assay. Viruses are considered to be resistant when the concentration of drug required to inhibit 50% of NA activity (IC_{50}) is greater than 200 nM.

A(H1N1)pdm09 and A(H1N1) seasonal viruses are also screened by pyrosequencing to detect the mutation from histidine to tyrosine at position 275 (H275Y) in the N1 neuraminidase that confers resistance to oseltamivir. Viruses selected for pyrosequencing include those that exhibit resistance by NAI assay, as well as original clinical specimens that did not yield a virus isolate when cultured.

Antiviral resistance analyses 2010

Analysis of 2382 viruses by NAI assay indicated that all were sensitive to zanamivir (data not shown). A total of 2462 samples were analysed for oseltamivir resistance by NAI assay and/or pyrosequencing.

A small proportion of tested A(H1N1)pdm09 (0.6%) and influenza B (0.6%) viruses showed oseltamivir resistance (Tables 6 and 7). The resistant A(H1N1)pdm09 viruses all were all confirmed to carry the H275Y mutation. However, the vast majority of currently circulating strains remained sensitive to oseltamivir.

Of the small number of A(H1N1) seasonal viruses were tested, all were resistant to oseltamivir (Table 8). This is consistent with the observation that, following the emergence and global spread of oseltamivir-resistant A(H1N1) seasonal viruses carrying the H275Y mutation in late 2007 and 2008, essentially all viruses of this subtype tested in 2009 were oseltamivir-resistant. The replacement of the A(H1N1) seasonal subtype by A(H1N1)pdm09 viruses during 2009 has resulted in a dramatic fall in the worldwide prevalence of oseltamivir resistance.

Figure 16. Geographic spread of viruses received at the Centre during 2010 and screened for resistance to oseltamivir. Where resistance was detected, the percentage (%) of viruses found to be resistant is indicated.

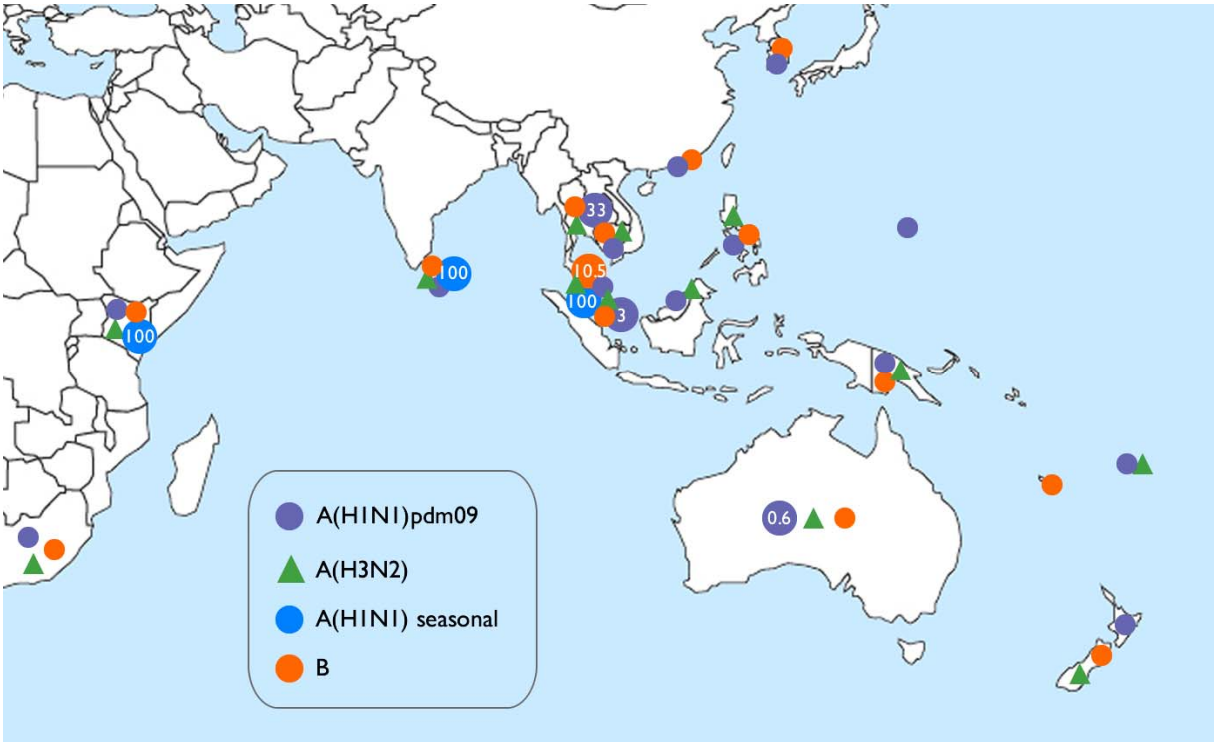


Table 6. Oseltamivir resistance in A(H1N1)pdm09 viruses received by the Centre in 2010

COUNTRY	Samples analysed by NAI assay No. tested	Samples analysed by NAI assay No. resistant	Samples analysed by pyrosequencing* No. tested	Samples analysed by pyrosequencing* No. resistant	Total % resistant
Australasia					
Australia	1060	3	59	4	0.6%
New Zealand	434	0	0	0	0
South Pacific					
Fiji	31	0	0	0	0
Guam	4	0	1	0	0
New Caledonia	0	0	0	0	0
Papua New Guinea	24	0	4	0	0
South East Asia					
Brunei	22	0	11	0	0
Cambodia	30	0	0	0	0
Malaysia	23	0	0	0	0
Philippines	70	0	0	0	0
Singapore	99	3	0	0	3.0%
Thailand	3	1	0	0	33.3%
East Asia					
Macau	21	0	0	0	0
Republic of Korea	2	0	0	0	0
South Asia					
Sri Lanka	4	0	0	0	0
Africa					
Kenya	22	0	0	0	0
South Africa	7	0	0	0	0
TOTAL	**1856**	**7**	**75**	**4**	**0.6%**

** These viruses were distinct from those tested by NAI assay*

Table 7. Oseltamivir resistance in A(H3N2) and Influenza B viruses received by the Centre in 2010

COUNTRY	A(H3N2) Samples analysed by NAI assay No. tested	A(H3N2) Samples analysed by NAI assay No. resistant (%)	Influenza B Samples analysed by NAI assay No. tested	Influenza B Samples analysed by NAI assay No. resistant (%)
Australasia				
Australia	128	0	169	0
New Zealand	4	0	3	0
South Pacific				
Fiji	3	0	0	0
Guam	0	0	0	0
New Caledonia	0	0	13	0
Papua New Guinea	21	0	1	0
South East Asia				
Brunei	2	0	0	0
Cambodia	1	0	8	0
Malaysia	1	0	19	2 (10.5%)
Philippines	1	0	43	0
Singapore	14	0	9	0
Thailand	8	0	22	0
East Asia				
Macau	0	0	13	0
Republic of Korea	0	0	8	0
South Asia				
Sri Lanka	8	0	3	0
Africa				
Kenya	0	0	2	0
South Africa	7	0	14	0
TOTAL	**198**	**0**	**327**	**2 (0.6%)**

Table 8. Oseltamivir resistance in A(H1N1) seasonal viruses received by the Centre in 2010

COUNTRY	Samples analysed by NAI assay		Samples analysed by pyrosequencing*		Total % resistant
	No. tested	No. resistant	No. tested	No. resistant	
South East Asia					
Malaysia	1	1	0	0	100%
South Asia					
Sri Lanka	1	1	1	1	100%
Africa					
Kenya	3	3	0	0	100%
TOTAL	**5**	**5**	**1**	**1**	**100%**

** These viruses were distinct from those tested by NAI assay*

Resistance to Adamantanes

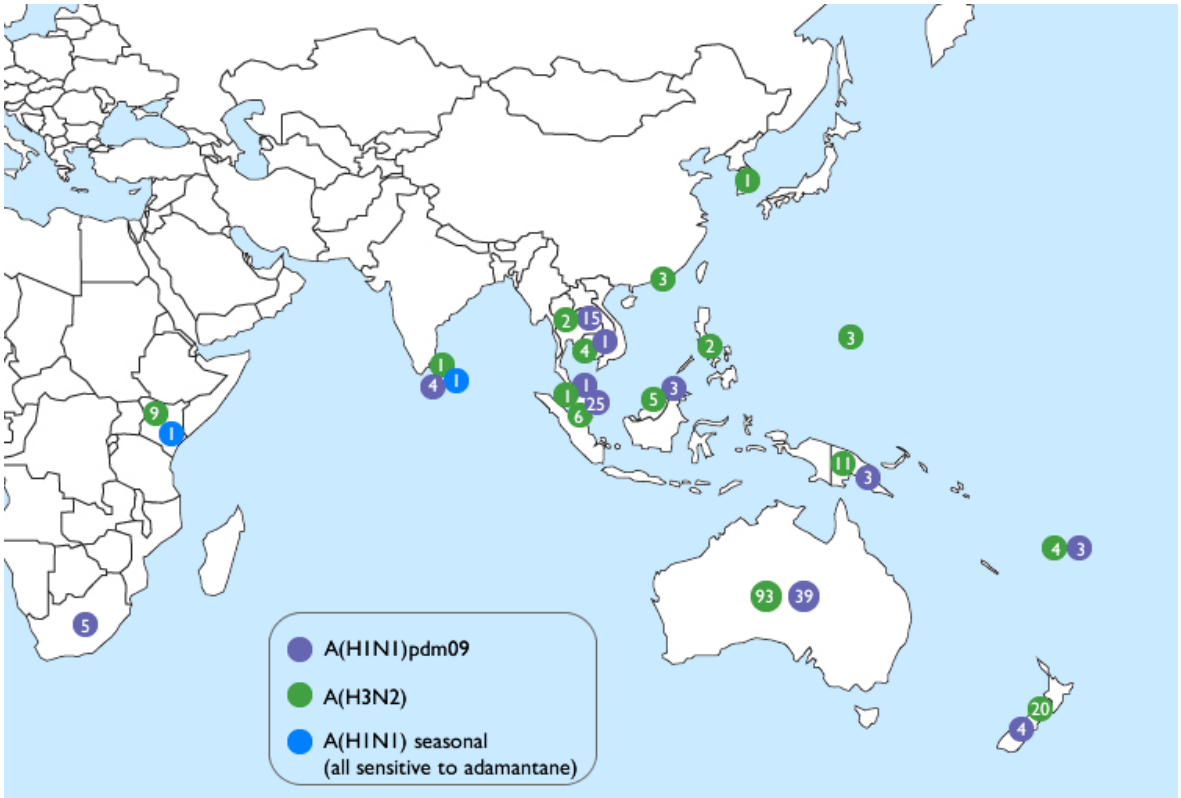
Background

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

Screening for adamantane resistance 2010

Real-time PCR or sequencing were used to analyse 270 influenza A viruses, selected as representative of those submitted to the Centre during 2010 (Figure 17). Based on S31N analysis, all of the A(H1N1)pdm09 and A(H3N2) viruses that were tested were resistant and all A(H1N1) seasonal viruses – of which there were very few – were sensitive to the adamantanes.

Figure 17. Geographic spread and number of viruses received at the Centre during 2010 and screened for adamantane resistance. All A(H1N1) seasonal viruses tested were sensitive to adamantanes.



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 influenza vaccines. Twice a year, in preparation for the biannual WHO Consultations on the Composition of Influenza Vaccines, the WHO Collaborating Centres and Essential Regulatory Laboratories in the WHO surveillance network exchange panels of sera taken from subjects pre- and post-influenza vaccination for analysis against the current vaccine and representative influenza strains using the HI assay. Serum panels from children, younger adults (20-64 years old) and older adults (>65 years old) are assessed.

Serum panel analyses 2010

In February and September 2010, the Centre in Melbourne analysed serum panels from recipients of seasonal trivalent or pandemic monovalent influenza vaccines in Australia and Japan, and Australia and Europe, respectively. The later set of data showed that, in general, vaccines containing A/California/7/2009-like, A/Perth/16/2009-like and B/Brisbane/60/2008-like antigens stimulated anti-HA antibodies of similar geometric mean titre to the relevant vaccine virus and most recent A(H1N1)pdm09, A(H3N2) and B/Victoria/2/87 lineage isolates, respectively. This indicated that influenza viruses circulating in the community during 2010 should be recognised by antibodies elicited by current vaccines. Titres were lower to some recent B/Yamagata/16/88 lineage isolates than to the B/Victoria/2/87 lineage vaccine virus.

Table 9. Representative and vaccine candidate strains for serological analyses 2010

February	September
Influenza A (H1N1)pdm09	
A/California/7/2009 A/Lviv/6/2009 A/Guam/2125/2009 A/England/195/2009 A/Iraq/8529/2009 A/Ontario/RV6559/2009 A/Oita/64/2009 (A(H1N1) seasonal)	A/California/7/2009 X179A A/California/7/2009 WT A/Brisbane/10/2010 A/South Carolina/2/2010 A/Christchurch/16/2010 A/Victoria/583/2010 A/Wellington/53/2010
Influenza A (H3N2)	
A/Victoria/208/2009 A/Uruguay/16/2007 A/Philippines/2191/2009 A/Hong Kong/26560/2009	A/Perth/16/2010 A/Rhode Island/1/2010 A/Brisbane/11/2010 A/Victoria/8/2010 A/Hiroshima-C/27/2010
Influenza B	
B/Brisbane/60/2008 B/Brisbane/3/2007 B/Bangladesh/3333/2007 B/Bangladesh/5945/2009 A/Laos/1232/2009 B/Philippines/9696/2009	B/Brisbane/60/2008 B/Hong Kong/259/2010 B/Mie/60/2010 B/Bolivia/104/2010B/ Brisbane/3/2009 B/Wisconsin/1/2010

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. It is a regulatory requirement 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, then analyses these isolates by HI assay and genetic sequencing.

Isolation of viruses in eggs 2010

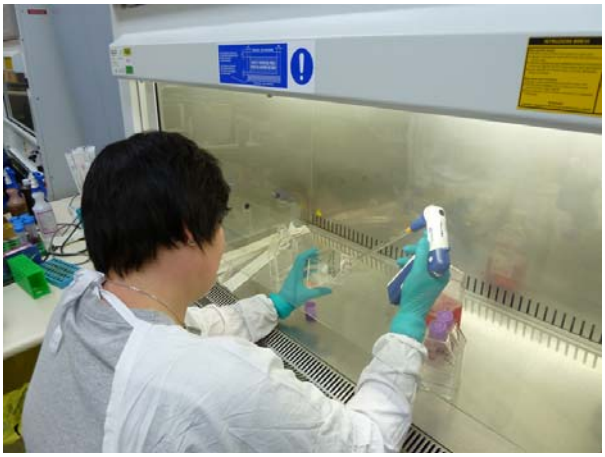
In 2010 52 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 50% of isolations (Tables 10 and 11). Since 2009, the number of viruses isolated in eggs at the Centre has increased as a result of additional support received under a Letter of Agreement with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

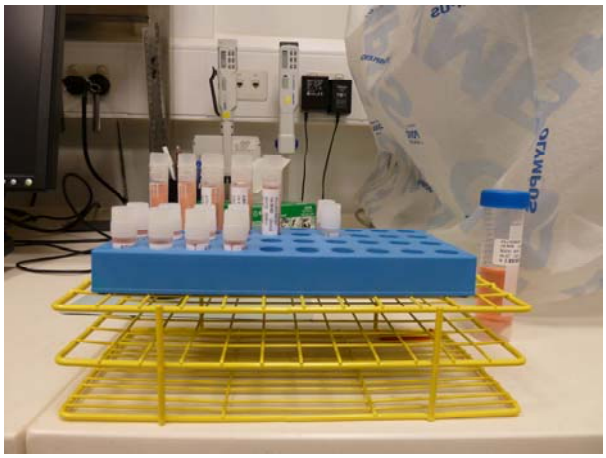
Table 10. Virus isolation in eggs at the Centre in 2010

Type / subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	44	30	68%
A(H1N1) seasonal	5	3	60%
A(H3N2)	23	9	39%
B	32	10	31%
Total	**104**	**52**	**50%**

Table 11. Potential candidate vaccine strains successfully isolated in eggs at the Centre in 2010

Type / Subtype	Strain	Type / Subtype	Strain
A(H1N1)pdm09 (30 isolates)	A/Guam/2122/2009	A (H1N1) seasonal (3 isolates)	CDC (200911001)
	A/Wellington/1/2010		CDC (200911010)
	A/Wellington/2/2010		CDC (200911017)
	A/Wellington/4/2010		
	A/Goroka/16/2010	A (H3N2) (9 isolates)	CDC (200911036)
	A/Guam/2/2010		A/Finland/584/2009
	A/Brisbane/10/2010		A/Perth/501/2010
	A/Brisbane/12/2010		A/Victoria/8/2010
	A/Singapore/567/2010		A/Brisbane/11/2010
	A/Singapore/575/2010		A/Perth/10/2010
	A/Singapore/576/2010		A/Victoria/563/2010
	A/Singapore/585/2010		A/Brisbane/210/2010
	A/Victoria/501/2010		A/Brisbane/220/2010
	A/Victoria/502/2010		
	A/Christchurch/2/2010	B (10 isolates)	CDC (200911002)
	A/Christchurch/8/2010		CDC (200911003)
	A/Christchurch/13/2010		CDC (200911005)
	A/Christchurch/16/2010		B/Finland/214/2009
	A/Christchurch/5/2010		B/Singapore/616/2008
	A/Christchurch/6/2010		B/Singapore/617/2008
	A/Christchurch/7/2010		B/New Caledonia/15/2010
	A/Darwin/55/2010		B/Johannesburg/57/2010
	A/Darwin/118/2010		B/Victoria/506/2010
	A/South Australia/404/2010		B/Christchurch/2/2010
	A/South Australia/397/2010		
	A/Perth/198/2010		
	A/Perth/219/2010		
	A/Townsville/56/2010		
	A/Townsville/64/2010		
	A/Brisbane/209/2010		





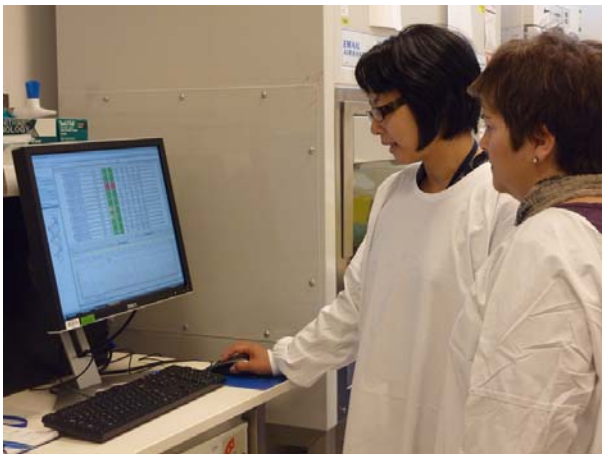
Candidate vaccine viruses isolated in eggs and post-infection ferret antisera raised against these and other reference viruses are exchanged with the other WHO Collaborating Centres to enable direct comparison of strains isolated in the five centres. During 2010, 29 candidate vaccine viruses were received from other WHO Collaborating Centres and laboratories and then passaged in eggs at the Centre (Table 12).

Selected egg-isolated candidate vaccine strains are made available to the three laboratories that undertake virus reassortment for WHO — CSL Limited (Melbourne, 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 undergo analysis 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 Center for Biologics Evaluation and Research, Food and Drug Administration (USA).

Table 12. Potential candidate vaccine viruses received from other WHO Collaborating Centres during 2010

Type / subtype	Strain	Type / subtype	Strain
A(H1N1)pdm09	NIB-74 (A/Christchurch/16/2010)	A(H1N1) seasonal	A/Fujian-Gulou/1896/2009
	A/South Carolina/2/2010	B	NYMC BX-35 (HY B/Brisbane/60/2008)
	A/New Hampshire/2/2010		NYMC BX-33B (HY B/Brisbane/60/2008)
	A/Thessaloniki/788/2010		B/Bangladesh/5945/2009
	A/St. Petersburg/204/2010		B/Hubei-Wujiagang/158/2009
	A/Puerto Montt/11868/2010		NYMC BX-31B (B/Brisbane/60/2008)
A(H3N2)	NYMC X-185XP (HY A/Guangdong-Luohu/1256/2009)		NYMC BX-37 (B/Bangladesh/5945/2009)
	A/Philippines/2191/2009		B/Hong Kong/259/2010
	A/Hong Kong26560/2009		B/Wisconsin/1/2010
	NYMC X-191 (HY A/Philippines/2191/2009)		B/Taiwan/11/2010
	NYMC X-189 (HY A/Hong Kong/26560/2009)		B/Mie/6/2010
	A/Rhode Island/1/2010		B/Bolivia/104/2010
	NYMC X-193 (HY A/Finland/97/2009)		B/Panama/307237/2010
	NYMC X-193B (HY A/Finland/97/2009)		
	NYMC X-195A (HY A/Finland/97/2009)		
	NYMC X-197 (HY A/Brisbane/11/2010)		



Preparation and Distribution of Diagnostic Reagents

Each year the Centre prepares and distributes kits of diagnostic reagents to regional and reference laboratories. These kits enable the preliminary analysis and characterisation of influenza specimens prior to submission of samples to the Centre. The kits contain polyclonal sera, monoclonal antibodies and viral antigens for reference influenza strains.

During 2010, 47 kits were sent to 23 laboratories in 16 countries. Each kit contained 10 mL each of the following reference antigens:

A/Perth/16/2009
A/Brisbane/59/2007
A/California/7/2009
B/Florida/4/2006
B/Brisbane/60/2008

Recipients of the 2010 Kit

Australia	Institute of Medical and Veterinary Science, Adelaide, South Australia Queensland Health Scientific Services, Coopers Plains, Queensland PathWest, QEII Medical Centre, Nedlands, Western Australia Centre for Infectious Disease and Microbiology Laboratory Services, Westmead, New South Wales
Cambodia	Institut Pasteur du Cambodge, Phnom Penh
Fiji	National Centre for Scientific Services for Virology and Vector Borne Diseases, Suva
Hong Kong	Hong Kong SAR Government Virus Unit
India	University of Delhi, Delhi Manipal University, Karnataka
Kenya	Center for Virus Research Laboratories, Kenya Medical Research Institute, Nairobi
Macau, China	Public Health Laboratory
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, Muntinlupa City
Singapore	Singapore General Hospital National Public Health Laboratory
South Africa	National Institute for Communicable Diseases, Johannesburg
Sri Lanka	Medical Research Institute, Colombo
Taiwan	National Cheng Kung University, Tainan
Thailand	National Institute of Health, Nonthaburi
USA	Dynavax Technologies, Berkeley, California

Recommendations on Influenza Vaccines

WHO Consultations on the Composition of Seasonal Influenza

Twice each year, the antigenic, genetic, antiviral resistance and candidate vaccine 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; 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 OFFLU, the University of Cambridge, several WHO National Influenza Centres and other relevant organisations from time to time.

In 2010, WHO made the recommendations reported here. These recommendations were the same as those made in September 2009, reflecting the findings that antigenic, genetic and human serological analyses detected little antigenic drift in any of the three vaccine virus types/subtypes during 2010.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2010–2011, Geneva, Switzerland, 14–17 February 2010

It is recommended that vaccines for use in the 2010–2011 influenza season (northern hemisphere winter) contain the following:

- an A/California/7/2009 (H1N1)-like virus;
- an A/Perth/16/2009 (H3N2)-like virus*†;
- a B/Brisbane/60/2008-like virus†.

* A/Wisconsin/15/2009 is an A/Perth/16/2009 (H3N2)-like virus and is a 2010 southern hemisphere vaccine virus.
† These viruses were initially isolated at the WHO Collaborating Centre in Melbourne.

WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2011, Geneva, Switzerland, 26–29 September 2010

It is recommended that vaccines for use in the 2011 influenza season (southern hemisphere winter) contain the following:

- an A/California/7/2009 (H1N1)-like virus;
- an A/Perth/16/2009 (H3N2)-like virus*†;
- a B/Brisbane/60/2008-like virus†.

* A/Wisconsin/15/2009 and A/Victoria/210/2009 are A/Perth/16/2009-like viruses.
† These viruses were initially 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, the decision on the composition of vaccines used in each country 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 6 October, AIVC accepted the September WHO recommendation and decided that the Australian influenza vaccine for 2011 should contain the following components:

A (H1N1): an A/California/7/2009 (H1N1)-like strain, 15 µg HA per dose
A (H3N2): an A/Perth/16/2009 (H3N2)-like strain, 15 µg HA per dose
B: a B/Brisbane/60/2008-like strain, 15 µg HA per dose

Training

Training and Support of National Influenza Centres

The Centre plays an active role in strengthening infrastructure and capabilities for laboratory-based influenza surveillance by GISN, in particular in the Asia-Pacific region. Building relationships, maintaining communication and sharing knowledge with WHO National Influenza Centres (NICs) and other diagnostic laboratories in the region are crucial to expanding their capacity to detect and characterise influenza viruses infecting humans, thereby strengthening global surveillance of seasonal and potential pandemic viruses.

Throughout the year, the Centre's Educator, **Dr Patrick Reading,** provided expertise as a facilitator and influenza specialist in several workshops and projects:

Sub-regional laboratory training workshops for improved influenza surveillance.

These workshops included presentations on laboratory techniques of rapid test kits, immunofluorescence and molecular diagnostics. Practical exercises also enabled participants to learn immunofluorescence techniques that could be implemented in their own laboratories.

- Polynesian Islands workshop: Wellington, New Zealand, 16–19 March, attended by laboratory scientists and managers from Western Samoa, American Samoa, Tonga, Cook Islands, Tokelau and Niue.
- Melanesian Islands workshop: Suva, Fiji, 25–28 May, attended by laboratory scientists and managers from Fiji, Vanuatu, Solomon Islands, Kiribati, Tuvalu, Nauru and Papua New Guinea.

Pacific Avian and Pandemic Influenza Taskforce Meeting (PAPITaF).

PAPITaF was a regional forum held in Nadi, Fiji, 23–24 May, and attended by health delegates from 18 Pacific Island Countries and Territories (PICTs) to discuss the management and response of PICTs to possible outbreaks of avian influenza, pandemic influenza and other emerging diseases.

Enhancement training for the use of immunofluorescence for influenza diagnosis in the Pacific Islands.

Mr Eric Fole (NIC, Solomon Islands), Mr Sitanieli Hoko (NIC, Tonga) and Mrs Taina Naivalu (NIC, Fiji) visited the Centre 27–28 September for training in immunofluorescence to diagnose influenza. Additional training in rapid test kits and real-time PCR was also provided. Ms Sala Elbourne from the Secretariat of the Pacific Community also attended as an observer.

Procurement of equipment and consumables to improve analysis and surveillance of influenza in regional laboratories.

Dr Reading collaborated with representatives from WHO regional offices over several months to improve infrastructure for influenza surveillance in regional laboratories.

- Cell culture and virus isolation capabilities are to be established at Mataika House in Suva, Fiji. Dr Reading has been working in collaboration with Dr Jacob Kool from the WHO Office for the South Pacific and staff at Mataika House to procure appropriate equipment and reagents for this purpose. Training is to be conducted in 2011.
- Dr Reading has been providing assistance and advice to Dr Boris Pavlin from the WHO Office for the North Pacific in regard to establishing real-time PCR capabilities in the Federated States of Micronesia (Pohnpei) and the Republic of the Marshall Islands (Majuro).

Regional Workshop "LabNet 2010"

LabNet is a human health network that was formed in 2000 to provide support in diagnostic techniques to laboratory professionals in 22 PICTs. This workshop in Suva, Fiji, 1–4 November, focussed on assessing and establishing appropriate systems for specimen shipping procedures in LabNet countries, as well as identifying specific training needs in different countries.

Related Links
Secretariat of the Pacific Community Inform'ACTION newsletter article
http://www.spc.int/phs/ENGLISH/Publications/InformACTION/IA32/PPHSN_lab-based_Influenza_Surveillance_Project.pdf

Regional Workshop "LabNet 2010"
http://www.spc.int/php/index.php?option=com_content&task=view&id=74&Itemid=57

In-house training for New Zealand influenza laboratory scientist.
Ms Michelle Luck, Medical Laboratory Scientist at Canterbury Health Laboratories, Christchurch, New Zealand, visited the Centre 17–21 May for laboratory training in HI assays.

WHO Training Workshop on Influenza Sequencing and Sequence Analysis.
This workshop was held in Singapore 13–17 December and attended by 18 scientists from WHO GISN laboratories in Africa, the Middle East and Asia. **Dr Yi-Mo Deng**, Senior Medical Scientist at the Centre, ran training seminars and practical exercises in sequencing techniques and data submission.

Centre Educator, Dr Patrick Reading (far right), with participants at the Polynesian Islands workshop in Wellington, New Zealand, held in March

Staff Development

Laboratory accreditation
The Centre maintains its PC3 facilities, regulatory approvals and technical expertise in preparedness to receive and characterise influenza viruses with pandemic potential. To this end, Centre staff members undertake regular procedural training to maintain regulatory accreditation.

Centre staff members have also undertaken training courses as listed below in preparation for seeking accreditation with the National Association of Testing Authorities (NATA).

- NATA - Understanding ISO 15189 Accreditation Requirements for Medical Laboratories, 5 August 2010 (attended by Katie O'Bryan and Tasoula Mastorakos)
- NATA - Quality Management in the Laboratory, 7–9 December 2010 (attended by Katie O'Bryan and Tasoula Mastorakos)
- Medical Laboratory Quality Network - Laboratory Internal Auditing training, 1–2 July 2010 (attended by Katie O'Bryan)

Other
Karen Laurie attended the Monash University Doctoral Supervisors Accreditation Program on 4 November and 8 November.

Research

The Centre's research activities have grown over the past few years and staff members are now engaged in a range of in-house and collaborative influenza-related research projects. Efforts in 2010 have focused on the areas described in the following pages.

Research Projects

Effectiveness of anti-viral treatments in a ferret model

Centre staff Aeron Hurt, Karen Laurie, Ian Barr, Anne Kelso
Collaborators Deborah Middleton and Sue Lowther, Australian Animal Health Laboratory
James McCaw and Jodie McVernon, The University of Melbourne

Project overview
This project investigates the effectiveness of oseltamivir as a treatment or prophylactic agent in reducing infectivity, transmissibility and growth of different viruses. To investigate the impact of different treatment strategies, ferrets are dosed with different concentrations of the drug at various time intervals either pre- or post-exposure to the virus. Virological, symptomatic and immunological variables are then measured over the course of infection and treatment.

2010 Highlights and developments
Experiments were conducted to compare single- and double-dose oseltamivir prophylaxis with no treatment, and to measure the impact of pre- and post-exposure treatments on viral load and duration of shedding. The data were presented at an international conference and will be prepared for publication in 2011.

Related publications 2010 (see Papers Published in 2010, page 34)
Reference: 14

Immune responses in ferret models

Centre staff and student Collaborators
Karen Laurie, Louise Carolan, Teagan Guarnaccia
Jenny Mosse, Monash University Gippsland
Heath Kelly, Victorian Infectious Diseases Reference Laboratory
Steve Rockman, CSL Limited
Katherine Kedzierska, The University of Melbourne
Jodie McVernon, The University of Melbourne
James McCaw, The University of Melbourne

Project overview
This project assesses the impact of past exposure(s) to influenza virus infection on protection against subsequent infections with the same or different subtypes. To determine how the immune response protects ferrets from subsequent virus challenges and how this response can be enhanced to protect against newly emerging strains, Centre staff members are developing techniques to measure immune responses in ferrets after vaccination or infection with human influenza viruses. Current work is focused on *in vitro* assays to measure cross-reactive T cell responses and cytokine production.

2010 Highlights and developments
Progress has been made in developing several methods to monitor cytokines of interest. Protocols for analysing cytokine expression by real-time PCR have been optimised and several cytokine and control housekeeping genes have been cloned into expression vectors. Methods are also being developed for the identification and purification of T cells and B cells from ferret tissues and blood.

Related publications 2010
References: 19,22

Serological analyses of antibody responses to A(H1N1)pdm09

Centre staff Karen Laurie, Louise Carolan, Robert Shaw, Chris Durrant, Ian Barr, Anne Kelso

Collaborators
Wolfram Haller, The Royal Children's Hospital
Gary Dowse, Western Australian Government Department of Health
James Trauer, Northern Territory Government Department of Health
Peter Markey, Northern Territory Government Centre of Disease Control
Katherine Kedzierska, The University of Melbourne
Jodie McVernon, The University of Melbourne
Terry Nolan, The University of Melbourne
Rhonda Owen, Australian Government Department of Health and Ageing
David Irving, Hugh Capper, Catherine Hyland and Helen Faddy, Australian Red Cross Blood Service
Mark Chen, Tan Tock Seng Hospital, Singapore
Vernon Lee, Ministry of Defence, Singapore

Project overview

The Centre is participating in serological surveys to determine rates of exposure to A(H1N1)pdm09 virus in 2009 and 2010, predominantly in Australia. Several patient and community collections of blood samples are being assessed for antibodies to the A(H1N1)pdm09 virus by HI assay and in some cases by micro-neutralisation assay, to determine the proportion of people exposed to the new virus by infection or vaccination. Research is also being undertaken to assess the ability of patients with various disease states to respond to A(H1N1)pdm09 vaccines

2010 Highlights and developments

Centre staff members collaborated on numerous serosurveys, including a national survey of Australian Red Cross blood donors and several studies in Singapore. These studies resulted in seven publications, a report to the Australian Government Department of Health and Ageing and nine presentations by collaborators at conferences in 2010.

Related publications 2010

References: 7,8,9,12,23,24,25,26

Viral fitness in ferret models

Centre staff Aeron Hurt, Ian Barr

Collaborators James McCaw and Jodie McVernon, The University of Melbourne

Project overview:

This project uses a competitive mixtures model in ferrets to investigate the relative fitness and transmissibility of different influenza viruses. A series of ferrets are infected with a mixture of two influenza strains and the relative proportions of those viruses are monitored over time and over multiple generations of transmission. The data are analysed by mathematical modelling to determine the relative fitness cost of one virus compared with another. The model has been applied to determining the fitness of neuraminidase inhibitor-resistant viruses and new antigenic variants.

2010 Highlights and developments:

Data were published on the relative fitness of two different oseltamivir-resistant viruses carrying the H275Y or R292K mutation (Ref. 15) and a theoretical manuscript was submitted on the mathematical analysis of data from competitive mixtures transmission experiments. The data were also presented at an international conference. The project was awarded grant funding for one year from the University of Melbourne Faculty Research Grants Support Scheme, to enable its further development.

Related publications 2010

Reference: 15

Early recognition and response to influenza infection

Centre staff Patrick Reading

Collaborators Alberto Mantovani, Instituto Clinico Humanitas, IRCCS & State University of Milan, Italy
Erika Crouch, Washington University School of Medicine, St. Louis, Missouri, USA
Melinda Dean, Australian Red Cross Blood Service, Queensland
Stuart Turville, Westmead Millennium Institute, New South Wales
Andrew Brooks, The University of Melbourne
Lorena Brown, The University of Melbourne

Project overview

This project is characterising how influenza virus is first recognised and destroyed by immune cells and soluble factors of the innate immune system. The innate immune system comprises pre-existing or rapidly induced defences that limit the spread of pathogens in the body during the first few days of infection before the development of more targeted adaptive immune responses. Many innate defences have been highly conserved throughout evolution and, as such, animal models of infection are widely used to investigate the role of innate defences and to gain insight as to how they might limit human disease.

Current studies in Dr Reading's laboratory at the University of Melbourne are focused on understanding the role of (i) soluble C-type lectins of the collectin and pentraxin superfamilies in early host defence against influenza virus, and (ii) membrane-associated C-type lectins expressed by macrophages and dendritic cells as receptors for influenza virus entry and destruction. The research involves both *in vitro* studies using human proteins and cells and *in vivo* studies using mouse and ferret models of infection.

2010 Highlights and developments

This research resulted in the publication of four papers in peer-reviewed journals during 2010. Dr Reading also presented several research talks at conferences and other institutes during the year, as well as continuing to supervise several PhD students, one of whom (Michelle Tate) completed her thesis which was passed during 2010.

Related publications 2010

References: 16,28,32,35

Molecular analysis and structural modelling of influenza proteins

Centre staff

Ian Barr, Yi-Mo Deng, Aeron Hurt, Naomi Komadina

Collaborators

Michael Parker, St Vincent's Institute of Medical Research

Sebastian Maurer-Stroh, Bioinformatics Institute (BII), A*STAR, National University of Singapore

Project overview

The Centre has several collaborations with external groups to use computer modelling to explore the structures of proteins of interest such as HA and NA. This analysis allows a better understanding of the molecular basis for changes that affect the efficacy of influenza vaccines and antiviral drugs.

Related publications 2010

Reference: 3

Antigenic cartography and molecular evolution of the influenza virus

Centre staff

Ian Barr, Aeron Hurt, Naomi Komadina

Collaborators

Derek Smith and Colin Russell, University of Cambridge, UK

Project overview

This project involves analysis of influenza viruses by antigenic cartography in combination with known amino acid changes in HA. The cartography system uses sophisticated computer algorithims to spatially plot each influenza virus in terms of its reactivity in an HI assay — analogous to a road map that interconnects towns and cities. Over the course of each year the virus strains form clusters that map differently over time, reflecting the changing nature of the influenza virus. Integration of these data with sequence data provides a thorough understanding of the reasons for antigenic drift, with the ultimate goal of predicting the direction of antigenic drift before it occurs.

Additional research collaborations

Centre staff members have also been involved in the following collaborations in 2010:

Wild bird avian influenza sequencing
Centre Staff: Aeron Hurt
Collaborators: Simone Warner, Victorian Government Department of Primary Industries
Edla Arzey, Elizabeth Macarthur Agricultural Institute (EMAI), New South Wales
2010 publication: Reference 13

Genetic analysis of equine influenza viruses from the Australian outbreak
Centre Staff: Aeron Hurt
Collaborators: Peter Kirkland, EMAI, New South Wales
2010 publication: Reference 20

Nanopatch influenza vaccine delivery model in ferrets
Centre Staff: Karen Laurie, Louise Carolan
Collaborators: Mark Kendall and Germain Fernando, The University of Queensland

NHMRC Program Grant: Understanding and controlling influenza (2010 - 2014)

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

Centre staff Anne Kelso, Patrick Reading, Karen Laurie, Aeron Hurt
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, Ludwig Institute for Cancer Research
Stephen Turner, The University of Melbourne
Lorena Brown, The University of Melbourne

Program overview

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, the Ludwig Institute, the School of Population Health (UM) and the CSIRO Australian Animal Health Laboratory.

2010 Highlights and developments

Anne Kelso established a small laboratory in the Department of Microbiology and Immunology at the University of Melbourne with research assistant Kim Charlton. The laboratory is working collaboratively with Stephen Turner and other Program members on the epigenetic regulation of $CD8^+$ T lymphocyte phenotype and function in order to understand mechanisms underlying cell-mediated immunity to influenza infection. Kim Charlton presented a poster on the work at the Annual Scientific Meeting of the Australasian Society for Immunology in Perth, 5–9 December.

A Program retreat held on 27 July was attended by approximately 45 people representing all of the research groups in the Program. Aeron Hurt, Anne Kelso and Patrick Reading presented talks at the retreat. Louise Carolan and Teagan Guarnaccia also participated.

A focus group meeting on determinants of influenza transmission was held at VIDRL on 14 December, at which Aeron Hurt and Karen Laurie gave presentations.

Related publications 2010

References: 11,34

Collaborative Agreements

The Centre is party to two collaborative research and development agreements with industry bodies. Like all potential collaborations with the commercial sector, these agreements underwent review by the Australian Government Advisory Committee before execution 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.

Cooperative Research and Development Agreement (CRADA) with Novartis Vaccines & Diagnostics (Marburg, Germany): Development and provision of influenza virus strains isolated on MDCK 33016PF cells for vaccine production (2008–2011)

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

Project overview

The suitability of a proprietary Novartis cell line (MDCK 33016PF) for influenza virus isolation and growth as a basis for cell-based vaccine manufacture is being evaluated. Some original clinical specimens are used to isolate viruses directly into the MDCK 33016PF cell line in parallel with egg isolation. These MDCK 33016PF isolates undergo analysis of their growth, antigenic and other properties.

2010 Highlights and developments

During the period 2008–2010, 150 clinical specimens were cultured in MDCK 33016PF cells, of which 125 (81%) produced isolates, well above the rate of isolation in eggs. The isolates comprised A(H1N1) seasonal, A(H1N1)pdm09, A(H3N2) and B viruses. Isolates were sent to Novartis in Marburg for further evaluation as potential vaccine candidates produced by the cell culture process.

Results of the work were presented in two posters at the Options for the Control of Influenza VII conference held in Hong Kong, 3–7 September.

As part of the collaboration, Dr Heidi Trusheim, Head of Technology at Novartis Behring in Marburg, Germany, visited the Centre on 9–10 September.

Agreement with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) (2008–2011)

Centre staff Chantal Baas, Joelle Dharmakumara, Robert Shaw, Anne Kelso, Ian Barr

Project overview

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

2010 Highlights and developments

A total of 52 egg isolates were obtained from 104 inoculations with original clinical specimens from various geographical locations, substantially exceeding numbers obtained in the years before the IFPMA project commenced. Isolation rates ranged from approximately 30% to 70% according to virus type/subtype. Suitable isolates were made available to other laboratories and industry for reassortment and assessment as vaccine candidates.

Research Funding

In addition to ongoing funding from the NHMRC Program Grant and Collaborative Agreements, the Centre was awarded funding for specific research purposes through other collaborations during 2010.

The Centre is a partner organisation in a $350,000 Linkage Infrastructure, Equipment and Facilities Grant awarded by the Australian Research Council on 1 December 2010 for an advanced flow cytometry facility at the Peter Doherty Institute.

Aeron Hurt is part of a collaboration with James McCaw and Jodie McVernon (Vaccine and Immunisation Research Group, Melbourne School of Population Health, The University of Melbourne) which was awarded funding from the University of Melbourne Faculty Research Grant Support Scheme in December 2010 for a project on mathematical models of influenza transmission.

Research Students

PhD candidates

Mr Aeron Hurt completed his PhD thesis in 2009 under the supervision of Dr Ian Barr and Ms Jenny Mosse (Monash University, Gippsland) and was awarded his doctorate in February 2010. His thesis investigated the emergence, incidence and characterisation of resistance to the neuraminidase inhibitor class of antiviral drugs amongst circulating human influenza viruses and highly pathogenic avian influenza viruses. In addition, he developed a novel methodology to compare the fitness of different viral strains in a ferret model, and used this method to examine the viral fitness of strains containing specific mutations of interest. Aeron was awarded the Monash University Mollie Holman Doctoral Medal in the Faculty of Science for the best doctoral thesis in 2010.

Ms Teagan Guarnaccia commenced her PhD candidature at the Centre on 9 March 2010. She is enrolled through the School of Applied Sciences and Engineering, Monash University, Gippsland, under the supervision of Dr Karen Laurie and Ms Jenny Mosse. Her project is entitled "Assessment of the immune response to influenza in the ferret model". The major aims of the project are:

1) To develop *ex vivo* assays to assess the cellular immune response in the ferret model,
2) To use the ferret model to examine the protectiveness of pre-existing immunity against newly emerging drifted strains of influenza *in vivo*, and
3) To determine if the A(H1N1)pdm09 virus will drift under immune pressure in the ferret model.

BSc (Honours) students

Two BSc (Honours) students completed research projects at the Centre in 2010. Both students achieved a grade of First Class Honours from their respective university departments.

Ms Karen Little (School of Applied Sciences and Engineering, Monash University, Gippsland) was supervised by Dr Aeron Hurt. Karen's project, titled "Investigating the effect of two amino acid residues on the susceptibility of influenza viruses to the neuraminidase inhibitors", involved the mutagenesis of two key NA residues, the subsequent generation of viruses by reverse genetics, and then functional analysis of the viruses to determine the impact of those mutations on neuraminidase inhibitor susceptibility, viral replication and stability.

Mr Scott Reddiex (Department of Microbiology and Immunology, The University Melbourne) was supervised by Dr Patrick Reading and Dr Yi-Mo Deng. His thesis was titled "The role of glycosylation on the hemagglutinin of the 2009 H1N1 pandemic influenza virus in modulating sensitivity to components of innate and adaptive immunity". Using reverse genetics techniques, Scott generated a panel of viruses with HA mutants of A(H1N1)pdm09 or A(H1N1) seasonal viruses with differing numbers of glycosylation sites. These viruses were used to investigate (i) sensitivity to mouse and human C-type lectins, (ii) sensitivity to neutralising antibodies raised to seasonal or pandemic H1N1 viruses, and (iii) virulence in mice. It was found that increased glycosylation of the head of HA increased sensitivity to C-type lectins but reduce susceptibility to antibody-mediated neutralisation. Viruses bearing a highly glycosylated HA were also attenuated in a mouse model of infection.

Masters students

Mr Hen-Yi Lin (Master of Infectious Diseases candidate, Marshall Centre for Infectious Diseases Research and Training, University of Western Australia) and Mr Khaled Al Lemailem (Master of Laboratory Medicine candidate, School of Medical Sciences, RMIT University) undertook projects at the Centre from February to May under the supervision of Dr Patrick Reading and Dr Aeron Hurt. They undertook practicum projects in the isolation and characterisation of human influenza viruses and were trained in a range of influenza surveillance techniques.

Communications and Advisory Activities

The Centre plays an active role in promoting and sharing influenza-related knowledge in the scientific and public health domains. Centre staff members participate in WHO meetings and workshops to support the ongoing work and growth of WHO GISN, as well as provide advice to the Australian Government in relation to influenza and infectious disease. Staff members also co-organise the Australian Influenza Symposium, publish peer-reviewed papers and present talks and posters in a wide variety of forums.

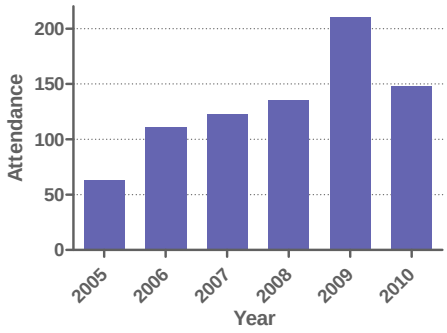
Australian Influenza Symposium

The 6th Australian Influenza Symposium was held at the John Curtin School of Medical Research, Australian National University, 7–8 October, co-hosted by the Centre and the Therapeutic Goods Administration (TGA). The organising committee was Anne Kelso, Ian Barr, Katie O'Bryan and Gary Grohmann (TGA).

The invited international speaker was Dr David Shay, from the Epidemiology and Prevention Branch of the Influenza Division of the US Centers for Disease Control and Prevention (CDC). Dr Shay gave two oral presentations, on pandemic influenza surveillance and on assessment of vaccine effectiveness, and was a highly engaged contributor to the Symposium.

Almost 150 people attended the symposium, including representatives from the biomedical, clinical, public health, government and industry sectors in several countries, including Australia, New Zealand, Singapore, USA and the United Kingdom. Attendance has risen considerably since the first Symposium was held in 2005. The exceptional attendance in 2009 probably reflected interest in the pandemic and staging in Melbourne for the first time. It is planned that future Symposia will alternate between Canberra and Melbourne.

Figure 18. Yearly attendance at the Australian Influenza Symposium



Engagement in WHO Activities

Event	Location; Date	Centre staff
WHO Consultation on the Composition of the Influenza Vaccines for the Northern Hemisphere 2010-2011	Geneva, Switzerland; 14–17 February	Ian Barr, Anne Kelso
6th WHO Meeting on Evaluation of Pandemic Influenza Prototype Vaccines in Clinical Trials	Geneva, Switzerland; 18–19 February	Ian Barr, Anne Kelso
4th Meeting of National Influenza Centres in the Western	Manila, Philippines;	Ian Barr, Aeron Hurt, Anne Kelso,
WHO Informal Consultation for Improving Influenza Vaccine Virus Selection	Geneva, Switzerland; 14–18 June	Ian Barr, Anne Kelso
WHO Technical Advisory Consultation on Pandemic Influenza A(H1N1)pdm09 Virus Resistance to Antivirals	Hong Kong; 8 September	Aeron Hurt
WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2011	Geneva, Switzerland; 26–29 September	Ian Barr, Anne Kelso
Meeting on the Development of a WHO Collaborating	Geneva, Switzerland;	Anne Kelso
Meeting with National Influenza Centres on Strengthening the WHO Global Influenza Surveillance Network (GISN)	Yasmine Hammamet, Tunisia; 30 November–3 December	Ian Barr
WHO Training Workshop on Influenza Sequencing and	Singapore;	Yi-Mo Deng

Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2010.

Ian Barr
Australian Influenza Vaccine Committee (Therapeutic Goods Administration)
Organising Committee, Australian Vaccine and Immunotherapeutics Development (AVID) Group
Public Health Laboratory Network (Department of Health and Ageing)

Aeron Hurt
Neuraminidase Inhibitor Susceptibility Network
Scientific Committee, Influenza Specialist Group
Steering Group, National Avian Influenza Wild Bird Surveillance Program

Anne Kelso
Australian Influenza Vaccine Committee (Therapeutic Goods Administration)
Board and Council of Governors, Florey Neuroscience Institutes
Board of Trustees, International Society for Influenza and other Respiratory Diseases (isirv)
Board, Telethon Institute for Child Health Research
Council, Nossal Institute for Global Health, The University of Melbourne
Council, Queensland University of Technology
Editorial Board, Immunology and Cell Biology
Editorial Board, Influenza and Other Respiratory Viruses
Editorial Board, International Immunology
Medical Advisory Board, Sylvia and Charles Viertel Charitable Foundation
Organizing Committee, Options for the Control of Influenza VII, Hong Kong, 2010
Project Control Group, Peter Doherty Institute for Infection and Immunity
Research Advisory Committee, Burnet Institute
Scientific Advisory Committee (chair), Telethon Institute for Child Health Research
Seasonal Influenza Surveillance Strategy Working Group (Department of Health and Ageing)
University Research and Innovation Committee, Queensland University of Technology

Naomi Komadina
Technical Committee (head), Global Initiative on Sharing All Influenza Data (GISAID) Development Team GISAID Database

Karen Laurie
Safety Committee, Victorian Infectious Diseases Reference Laboratory

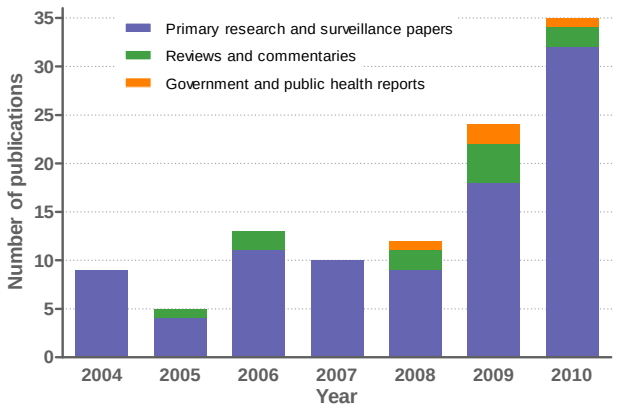
John Curtin Medical School of Research, Australian National University, venue of the 2010 Australian Influenza Symposium

Field-based reporters and surveillance staff in traditional dress attending the Colloquium on 40 Years of Pneumonia Research in Papua New Guinea, held in Goroka, PNG, 23–26 August

Publications and Reports

The Centre's research output continued to increase in 2010 with the publication of 34 original research papers and reviews in peer-reviewed journals and one report to government, the highest annual number of Centre publications to date.

Figure 19. Centre publications 2004-2010



Publication Highlights

Three papers published by Centre staff in recent years were recognised in 2010 by their respective publishers for their significant number of citations and/or website downloads.

Eurosurveillance:
Fifth most downloaded paper in 2010 (5434 downloads)

Barr IG, Cui L, **Komadina N**, Lee RT, Lin RT, **Deng Y**, **Caldwell N**, **Shaw R**, Maurer-Stroh S. A new pandemic influenza A(H1N1) genetic variant predominated in the winter 2010 influenza season in Australia, New Zealand and Singapore. EuroSurveill, 2010. 15(42). pii: 19692

Antiviral Research:
Fourth most cited paper 2006–2010
Top 10 most downloaded papers 2009–2010

Hurt AC, **Ernest J**, **Deng YM**, **Iannello P**, Besselaar TG, Birch C, Buchy P, Chittaganpitch M, Chiu SC, Dwyer D, Guigon A, Harrower B, Kei IP, Kok T, Lin C, McPhie K, Mohd A, Olveda R, Panayotou T, Rawlinson W, Scott L, Smith D, D'Souza H, **Komadina N**, **Shaw R**, **Kelso A**, **Barr IG**. Emergence and spread of oseltamivir-resistant A (H1N1) influenza viruses in Oceania, South East Asia and South Africa.(2009) Antiviral Research, 83 (1): 90-93.

Antiviral Research:
Most cited paper 2006–2010

Hurt AC, Selleck P, **Komadina N**, **Shaw R**, Brown L, **Barr IG**. Susceptibility of highly pathogenic A(H5N1) avian influenza viruses to the neuraminidase inhibitors and adamantanes.(2007) Antiviral Research, 73 (3): 228-231.

Papers Published in 2010

1. Baker MG, Thornley CN, Mills C, Roberts S, Perera S, Peters J, **Kelso A**, **Barr I**, and Wilson N, Transmission of pandemic A/H1N1 2009 influenza on passenger aircraft: retrospective cohort study. *BMJ*, 2010. 340: c2424.
2. Bandaranayake D, Huang QS, Bissielo A, Wood T, Mackereth G, Baker MG, Beasley R, Reid S, Roberts S, Hope V, and **2009 H1N1 Serosurvey Investigation Team**, Risk factors and immunity in a nationally representative population following the 2009 influenza A(H1N1) pandemic. *PLoS One*, 2010. 5(10): e13211.
3. **Barr IG**, Cui L, **Komadina N**, Lee RT, Lin RT, **Deng Y**, **Caldwell N**, **Shaw R**, and Maurer-Stroh S, A new pandemic influenza A(H1N1) genetic variant predominated in the winter 2010 influenza season in Australia, New Zealand and Singapore. *Euro Surveill*, 2010. 15(42). pii: 19692
4. **Barr IG**, McCauley J, Cox N, Daniels R, Engelhardt OG, Fukuda K, Grohmann G, Hay A, **Kelso A**, Klimov A, Odagiri T, Smith D, Russell C, Tashiro M, Webby R, Wood J, Ye Z, and Zhang W, Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009-2010 northern hemisphere season. *Vaccine*, 2010. 28(5):1156-67.
5. Blyth CC, Foo H, van Hal SJ, **Hurt AC**, **Barr IG**, McPhie K, Armstrong PK, Rawlinson WD, Sheppeard V, Conaty S, Staff M, Dwyer DE, and World Youth Day 2008 Influenza Study Group, Influenza outbreaks during World Youth Day 2008 mass gathering. *Emerg Infect Dis*, 2010. 16(5):809-15.

Papers Published in 2010 (continued)

6. Blyth CC, **Kelso A**, McPhie KA, Ratnamohan VM, Catton M, Druce JD, Smith DW, Williams SH, Huang QS, Lopez L, Schoub BD, Venter M, and Dwyer DE, The impact of the pandemic influenza A(H1N1) 2009 virus on seasonal influenza A viruses in the southern hemisphere, 2009. *Euro Surveill*, 2010. 15(31). pii: 19631
7. Chen MI, **Barr IG**, Koh GC, Lee VJ, Lee CP, **Shaw R**, Lin C, Yap J, Cook AR, Tan BH, Loh JP, Barkham T, Chow VT, Lin RT, and Leo YS, Serological response in RT-PCR confirmed H1N1-2009 influenza A by hemagglutination inhibition and virus neutralization assays: an observational study. *PLoS One*, 2010. 5(8):e12474.
8. Chen MI, Lee VJ, **Barr I**, Lin C, Goh R, Lee C, Singh B, Tan J, Lim WY, Cook AR, Ang B, Chow A, Tan BH, Loh J, **Shaw R**, Chia KS, Lin RT, and Leo YS, Risk factors for pandemic (H1N1) 2009 virus seroconversion among hospital staff, Singapore. *Emerg Infect Dis*, 2010. 16(10):1554-61.
9. Chen MI, Lee VJ, Lim WY, **Barr IG**, Lin RT, Koh GC, Yap J, Cui L, Cook AR, **Laurie K**, Tan LW, Tan BH, Loh J, **Shaw R**, **Durrant C**, Chow VT, **Kelso A**, Chia KS, and Leo YS, 2009 influenza A(H1N1) seroconversion rates and risk factors among distinct adult cohorts in Singapore. *JAMA*, 2010. 303(14):1383-91.
10. Chidlow GR, Harnett GB, Williams SH, Tempone SS, Speers DJ, **Hurt AC**, **Deng YM**, and Smith DW, The detection of oseltamivir-resistant pandemic influenza A/H1N1 2009 viruses using a real-time RT-PCR assay. *J Virol Methods*, 2010. 169(1):47-51.
11. Gras S, Kedzierski L, Valkenburg SA, **Laurie K**, Liu YC, Denholm JT, Richards MJ, Rimmelzwaan GF, **Kelso A**, Doherty PC, Turner SJ, Rossjohn J, and Kedzierska K, Cross-reactive CD8+ T-cell immunity between the pandemic H1N1-2009 and H1N1-1918 influenza A viruses. *Proc Natl Acad Sci U S A*, 2010. 107(28):12599-604.
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14. **Hurt AC**, Lowther S, Middleton D, and **Barr IG**, Assessing the development of oseltamivir and zanamivir resistance in A (H5N1) influenza viruses using a ferret model. *Antiviral Res*, 2010. 87(3):361-6.
15. **Hurt AC**, **Nor'e SS**, McCaw JM, Fryer HR, Mosse J, McLean AR, and **Barr IG**, Assessing the viral fitness of oseltamivir-resistant influenza viruses in ferrets, using a competitive-mixtures model. *J Virol*, 2010. 84(18):9427-38.
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17. Kaczmarek M, Owen R, and **Barr IG**, Annual report of the National Influenza Surveillance Scheme, 2008. *Commun Dis Intell*, 2010. 34(1):8-22.
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20. Kirkland PD, Finlaison DS, Crispe E, and **Hurt AC**, Influenza virus transmission from horses to dogs, Australia. *Emerg Infect Dis*, 2010. 16(4):699-702.
21. Lam WY, Leung TF, Lee N, Cheung JL, Yeung AC, Ho YI, Chan RC, Fung KS, **Barr IG**, Hui DS, Sung JJ, and Chan PK, Development and comparison of molecular assays for the rapid detection of the pandemic influenza A (H1N1) 2009 virus. *J Med Virol*, 2010. 82(4):675-83.
22. **Laurie KL**, **Carolan LA**, Middleton D, Lowther S, **Kelso A**, and **Barr IG**, Multiple infections with seasonal influenza A virus induce cross-protective immunity against A(H1N1) pandemic influenza virus in a ferret model. *J Infect Dis*, 2010. 202(7):1011-20.
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35. Upham JP, Pickett D, Irimura T, Anders EM, and **Reading PC**, Macrophage receptors for influenza A virus: role of the macrophage galactose-type lectin and mannose receptor in viral entry. *J Virol*, 2010. 84(8):3730-7.

Oral Presentations

Centre staff members gave numerous oral presentations throughout the year, including educational lectures, research seminars, and presentations to government advisory meetings and international and national conferences.

Event **Location, Date**	**Centre Staff, *Presentation title***
AstraZeneca Respiratory Symposium Sydney, 31 January	Anne Kelso: *Learnings from the southern and northern hemisphere for H1N1 in Australia 2010.*
Influenza Specialist Group Scientific Conference Melbourne, 31 January–1 February	Ian Barr: *2009-2010 influenza season update.* Aeron Hurt: *Update on NA inhibitor resistance in circulating strains and preliminary results of ferret oseltamivir study.*
Pathology Update 2010, Royal College of Pathologists of Australasia	Anne Kelso: *Influenza – prevention and new prevention strategies.*
Multinational Influenza Seasonal Mortality Study (MISMS) Oceania Regional Influenza Meeting and Workshop	Ian Barr: *The small picture: Detection and significance of influenza species, reassortants and antiviral resistance in human clinical samples.*
Histology Group of Victoria One Day Seminar Melbourne, 20 March	Anne Kelso: *The influenza A(H1N1) 2009 pandemic in Australia.*

Oral Presentations (continued)

Event Location, Date	Centre Staff, *Presentation title*
World Congress of Internal Medicine Melbourne, 22–25 March	Anne Kelso: *The swine flu epidemic – an international perspective.*
Department of Microbiology and Immunology Seminar Series, The University of Melbourne Melbourne, 30 March	Aeron Hurt: *Antiviral drug resistance in seasonal and pandemic influenza viruses.*
4th Meeting of the National Influenza Centres in the Western Pacific Region Manila, Philippines, 3–6 May	Ian Barr: *Influenza Surveillance: A 2010 southern hemisphere perspective.* *Serosurvey of pandemic influenza H1N1 2009 infections in children and pregnant woman in WA.* *Development of candidate influenza vaccine strains.* Aeron Hurt: *Antiviral drug resistance in seasonal and pandemic influenza viruses.* Anne Kelso: *Analysis of influenza isolates at WHO Collaborating Centres.*
3rd Australasian Vaccines & Immunotherapeutics Development Meeting 2010 Melbourne, 5–7 May	Karen Laurie: *Protection against H1N1 pandemic influenza virus in a ferret model.*
The University of Melbourne Breadth Subject "Global health, security and sustainability" Melbourne, 10 May	Anne Kelso: *Influenza*.
Immunology Lecture Series, John Curtin School of Medical Research, Australian National University Canberra, 12 May	Patrick Reading: *Innate immunity to influenza virus.*
Australian National University Public Lecture Canberra, 13 May	Anne Kelso: *Pandemic influenza: an immunological challenge*.
The University of Melbourne BSc Honours Lecture Series 2010, Department of Microbiology and Immunology Melbourne, 14 May	Anne Kelso: *WHO Global Influenza Surveillance Network and its role in updating influenza virus vaccines.* Karen Laurie: *RNAi as a potential antiviral therapy for influenza.*
NHMRC Human Frontier Science Program Intergovernmental Conference Scientific Meeting Canberra, 27–28 May	Ian Barr: *Evolutional and epidemiological factors driving new epidemics of influenza*
Australasian Society for Infectious Diseases Annual Scientific Meeting Darwin, 28–29 May	Anne Kelso: *Emergence, epidemiology and evolution of pandemic (H1N1) 2009 influenza viruses.*
Peter MacCallum Cancer Centre Seminar Melbourne, 10 June	Anne Kelso: *Flu shifts backwards: the 2009 pandemic.*
Neuraminidase Inhibitor Susceptibility Network Scientific Meeting London, UK, 9–15 June	Aeron Hurt: *WHO Collaborating Centre, Melbourne—Antiviral susceptibility data update.*
WHO Informal Consultation for Improving Influenza Vaccine Virus Selection Geneva, Switzerland, 14–16 June	Anne Kelso: *The coordinated use of antigenic and genetic data in vaccine virus selection.*
Chief Medical Officer's Pandemic Debrief, Australian Government Department of Health and Ageing Canberra, 18 June	Anne Kelso: *Characterising the virus - how well did we do?*
Australian Society for Microbiology Virology Masterclass Adelaide, 2 July	Ian Barr: *Influenza*.

Oral Presentations (continued)

Event **Location, Date**	**Centre Staff, *Presentation Title***
Australian Society for Microbiology Annual Scientific Meeting and Exhibition Sydney, 4–8 July	Yi-Mo Deng: *Pyrosequencing, a powerful tool for rapid sequencing.*
NHMRC Program on Understanding and Controlling Influenza Retreat Melbourne, 27 July	Aeron Hurt: *Investigating the effectiveness of neuraminidase inhibitor treatment in ferrets and the impact of resistance on viral fitness.* Anne Kelso: *Why lymphocytes matter.* Patrick Reading: *Innate recognition of influenza viruses.*
Monash University Undergraduate Immunology Lecture Melbourne, 30 July	Ian Barr: *Influenza: a disease worth controlling.*
Melbourne Conversations "Climate Change, New Diseases and Parasites: What might it mean for Melbourne?" Melbourne, 17 August	Anne Kelso: *Influenza*
Burnet Institute Seminar Series Melbourne, 18 August	Patrick Reading: *Recognition and response of macrophages and dendritic cells to influenza virus.*
Colloquium on 40 Years of Pneumonia Research in Papua New Guinea Goroka, Papua New Guinea, 23–26 August	Anne Kelso: *Influenza in the Pacific; also a session panellist*
Department of Microbiology Seminar Series, Monash University Melbourne, 2 September	Patrick Reading: *Recognition of influenza virus by components of the innate immune system.*
Options for the Control of Influenza VII Hong Kong, 3–7 September	Ian Barr: *Multiple infections with seasonal influenza A viruses induces cross-protective immunity against A (H1N1) pandemic influenza virus in a ferret model.* Naomi Komadina: *Global Initiative of Sharing Avian Influenza Data.* Patrick Reading: *Macrophage and dendritic cell receptors for influenza A viruses.*
Neuraminidase Inhibitor Susceptibility Network Meeting Hong Kong, 5 September	Aeron Hurt: *Neuraminidase inhibitor resistance update from Asia-Pacific region.*
Laboratory meeting at Department of Microbiology and Immunology, The University of Melbourne Melbourne, 22 September	Karen Laurie: *Protection against A(H1N1) pandemic influenza virus in a ferret model.*
6th Australian Influenza Symposium Canberra, 7–8 October	Karen Laurie: *Protection against H1N1 pandemic influenza virus in a ferret model.* Patrick Reading: *Pandemic H1N1 influenza A viruses are resistant to the antiviral activities of innate immune proteins of the collectin and pentraxin superfamilies*.
Regional Workshop "LabNet" 2010 Suva, Fiji, 1–5 November	Patrick Reading: *The role of reference laboratories in laboratory-based influenza surveillance.* *The strengths and weaknesses of different methods used for laboratory-based surveillance of influenza virus.*
Seasonal Influenza Surveillance Strategy Working Group, Department of Health and Ageing Canberra, 4 November	Anne Kelso: *Influenza surveillance in 2010 at the WHO Collaborating Centre.*

Oral Presentations (continued)

Event Location, Date	Centre Staff, *Presentation Title*
Antivirals Congress Amsterdam, Netherlands, 7–9 November	Ian Barr: *Assessing the viral fitness of oseltamivir-resistant influenza viruses in ferrets; also plenary session chair*
Australian Health and Medical Research Congress Melbourne, 16–18 November	Aeron Hurt: *Assessing the viral fitness of oseltamivir-resistant influenza viruses in ferrets using a competitive mixtures model.* Anne Kelso: *The 2009 H1N1 influenza pandemic: what happened in 2010?* Karen Laurie: *Protection against H1N1 pandemic influenza virus in a ferret model.*
NHMRC Program on Understanding and Controlling Influenza Focus Group Meeting Melbourne, 14 December	Aeron Hurt: *Ferret transmission models to assess viral fitness.* Karen Laurie: *Assessing cross-protection in ferret models*
Innate Immunity at the Mucosal Barrier Adelaide, 12–14 December	Patrick Reading: *Early host defences that can limit influenza virus infection*
WHO Training Workshop on Influenza Sequencing Singapore, 13–17 December	Yi-Mo Deng: *Submission of data to a public database.* *Overview of case definition, sample collection, RNA Extraction, RT-PCR, elements of primer design.*

Other Conference and Meeting Participation

In addition to the oral presentations listed, Centre staff members also participated in the following conferences as attendees and/or poster presenters.

Event, location and date	Centre staff involved
Influenza Specialist Group Scientific Conference Melbourne, 31 January–1 February	Anne Kelso, Naomi Komadina
Immune Correlates of Protection against Influenza Miami, USA, 1–3 March	Anne Kelso (session chair)
Multinational Influenza Seasonal Mortality Study (MISMS) Oceania Regional Influenza Meeting and Workshop Melbourne, 15–16 March	Yi-Mo Deng, Aeron Hurt, Anne Kelso, Naomi Komadina, Karen Laurie
Swine Origin H1N1 Virus: The First Pandemic of the 21st Century Conference Atlanta, USA, 18–20 April	Chantal Baas, Karen Laurie (poster)
Colloquium on 40 Years of Pneumonia Research in Papua New Guinea Goroka, Papua New Guinea, 23–26 August	Patrick Reading
Global Initiative on Sharing All Influenza Data (GISAID) Data Database Technical Committee Workshop Hong Kong, 1–2 September	Naomi Komadina (meeting chair)
Options for the Control of Influenza VII Hong Kong, 3–7 September	Ian Barr (poster, plenary session and workshop chair), Yi-Mo Deng (poster), Aeron Hurt (poster), Pina Iannello (poster), Anne Kelso (organising committee, plenary session and workshop chair), Heidi Peck (poster)
Australian Health and Medical Research Congress Melbourne, 16–18 November	Louise Carolan, Joelle Dharmakumara
40th Annual Scientific Meeting of the Australasian Society for Immunology Perth, 5–9 December	Anne Kelso (symposium chair), Patrick Reading (poster)

Poster Presentations 2010

Centre staff contributed to the authorship and presentation of several posters at conferences in 2010.

Conference	Poster Title and Authors (Centre staff highlighted in bold)
Swine Origin H1N1 Virus: The First Pandemic of the 21st Century Conference, Atlanta, USA, 18–20 April	Protection against H1N1 pandemic influenza virus in a ferret model. **Laurie K**, **Carolan L**, Middleton D, Lowther S, **Kelso A, Barr I**
Options for the Control of Influenza VII, Hong Kong 3–7 September	GISAID - a global initiative on sharing all influenza data. Buech J, Roomp K, Bach G, Steinbrueck L, Beer M, Gregory V, **Komadina N**, Lan Y, Monne I, Smith C, Fujisaki S, Bogner P, Lengauer T Human antibody responses following RT-PCR confirmed H1N1-2009 influenza A infection: implications for serodiagnosis and understanding heterotypic cross-immunity. Chen MI, **Barr IG**, Koh GC, Lee VJ, Lee CP, Chow VT, Lin RT, Leo YS Quantitation of H275Y mutant viruses by pyrosequencing in pandemic (H1N1)2009 infected patients. **Deng YM**, **Caldwell N**, **Hurt A**, Chidlow G, Williams S, Smith D, **Kelso A**, **Barr I** No reassortment in pandemic (H1N1) 2009 viruses isolated from swine in Australia. **Deng YM**, **Iannello P**, Smith I, Watson J, Daniels P, **Komadina N**, **Barr I**, Harrower B, Wong F Investigating the effectiveness of oseltamivir treatment or prophylaxis in preventing or reducing pandemic A (H1N1) infection in ferrets. **Hurt AC**, Lowther S, McCaw JM, McVernon J, **Kelso A**, Middleton D, **Barr IG** Assessing the viral fitness of oseltamivir-resistant influenza viruses in ferrets using a competitive mixtures model. **Hurt AC**, **Nore S**, McCaw JM, Fryer HR, Mosse J, McLean AR, **Barr IG** The long pentraxin PTX3 is a soluble protein of the innate immune system that mediates potent antiviral activity against influenza viruses in vitro and in vivo. Job ER, Bottazzi B, Brooks AG, Mantovani A, **Reading PC** A mathematical framework for estimating influenza virus transmission fitness and inoculum size using data from a competitive mixtures animal model. McCaw JM, Arinaminpathy N, **Hurt AC**, McVernon J, McLean AR Seroprevalance of antibody to influenza A (H1N1) 2009 in Australian blood donors - before and after the 2009 influenza season, and prior to the 2010 southern hemisphere winter. McVernon J, **Laurie K**, Nolan T, Owen R, Irving D, Capper H, Hyland C, Faddy H, **Carolan L**, **Barr I**, **Kelso A** Evaluation of growth, genetic, and antigenic characteristics of pandemic H1N1 viruses isolated and passaged in qualified MDCK suspension cells (MDCK33016PF) and embryonated hen eggs. **Peck H**, **Dodin J**, **Baas C**, **Shaw R**, Lenz-Bauer C, Trusheim H, Roth B, Blayer S, Tsai T, **Barr I** Memory B cell responses to H1N1 pandemic influenza in a longitudinal cohort study. Santoso D, Goy K, Hearps A, Edouard V, Elliott J, Crowe S, **Barr I**, French R Co-infecting viruses in pandemic H1N1 and seasonal influenza positive human respiratory samples.
40th Annual Scientific Meeting of the Australasian Society for Immunology, Perth 5–9 December	Recognition of influenza A viruses by macrophage and dendritic cell receptors. Londrigan SL, Tate MD, Turville S, **Deng Y**, Brooks AG, **Reading PC**

Website

The Centre has undertaken a complete redesign of its website during 2010. The design company Nuttshell Graphics was engaged to develop a new Centre website image. Dr Michelle Chow was appointed in November as Communications and Administration Officer to develop, deploy and regularly update the new website, amongst other responsibilities.

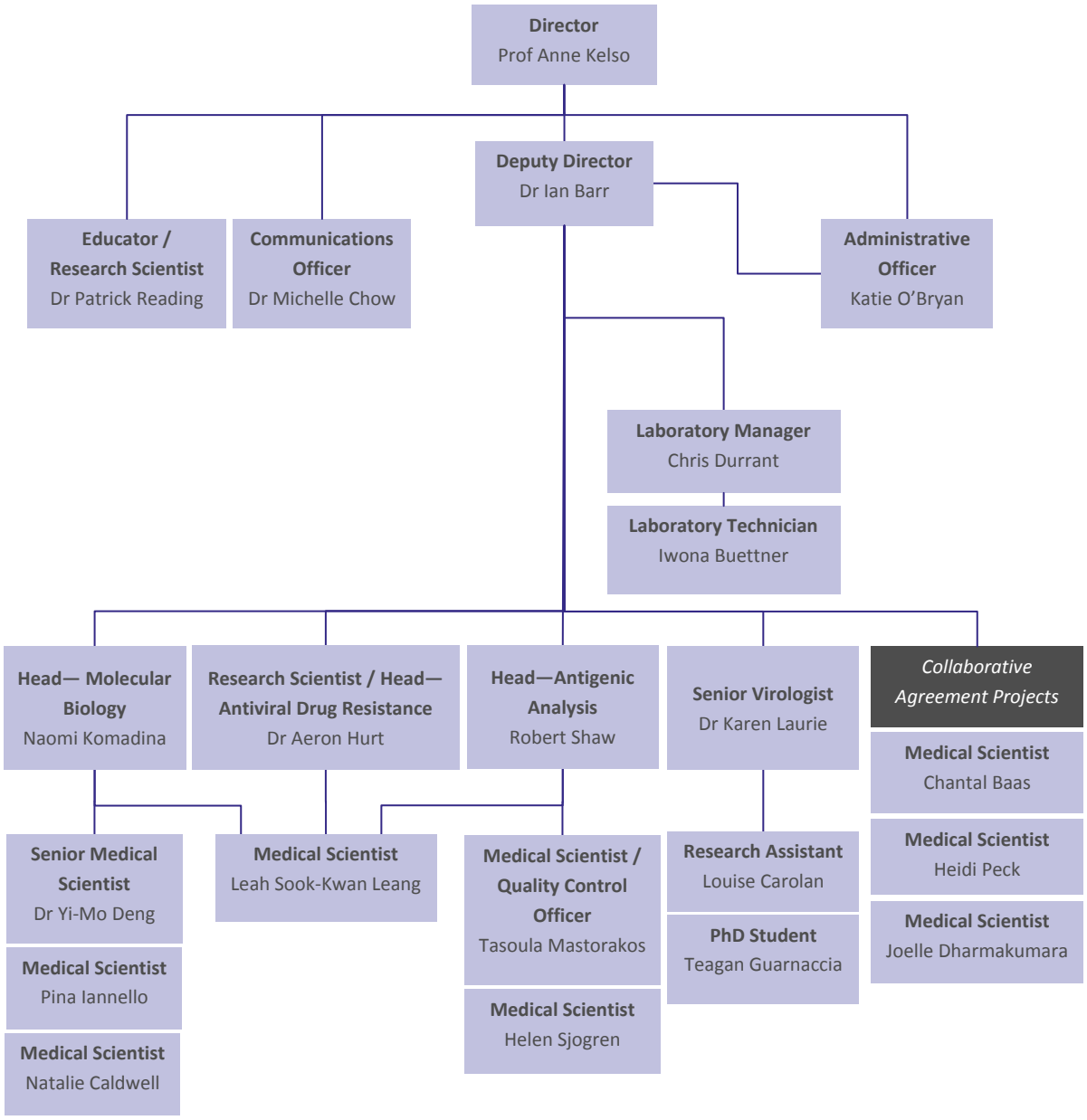
The new website will be launched in early 2011. It is anticipated that it will provide useful information about influenza, surveillance activities and data, ongoing research and relevant resources to other members of the global influenza surveillance community, as well as the general public.

Visitors to the Centre

During 2010 the following people visited the Centre for a variety of purposes, including collaborative discussions, technical training and laboratory studies.

12 January	Dr Steven Tong: Researcher, Menzies School of Health Research and Specialist in Infectious Diseases at Royal Darwin Hospital
14 January	Associate Professor Raymond Lin: Head and Senior Consultant, National Public Health Laboratory, Ministry of Health, Singapore
18 March	Professor Jim Bishop: Chief Medical Officer, Department of Health and Ageing; Chair, Australian Government Advisory Committee
31 May–9 June	Dr Vijaykrishna Dhanasekeran: Program in Emerging Infectious Diseases, Duke-NUS Graduate Medical School, Singapore, *presented a workshop on phylogenetics*
12–23 July	Professor Jen-Ren Wang: Professor and Chair, Department of Medical Laboratory Science and Biotechnology, National Cheng Kung University, Tainan, Taiwan
9–10 September	Dr Heidi Trusheim: Head of Technology at Novartis Behring in Marburg, Germany
4–5 October	Dr David Shay: Epidemiology and Prevention Branch, US Centers for Disease Control and Prevention (CDC), USA, *gave a seminar at VIDRL*
11–15 October	Associate Professor Gavin Smith: Program in Emerging Infectious Diseases, Duke-NUS Graduate Medical School, Singapore
15–19 November	Dr Mark Chen, Ms Serene Chew, Ms Yen Ling Jessie Tan, Ms Pei Ling Loh, Ms Dollyn Li Ying Quek: National Public Health Laboratory, Singapore, *conducted laboratory studies for serosurveys on immunity to pandemic influenza in Singapore*
17 November	Dr Jackie Katz: Chief, Immunology and Pathogenesis Branch of the Influenza Division, National Center for Immunization and Respiratory Diseases, CDC, USA
13–17 December	Dr Mark Chen, Ms Serene Chew: National Public Health Laboratory, Singapore Mr Joe Kwan Yap: Tan Tock Seng Hospital, Singapore Mrs Meng Chee Phoon, Ms Yan Wu, Ms Hsu Jung Pu: National University of Singapore, *conducted laboratory studies for serosurveys on immunity to pandemic influenza in Singapore*

Management and Staff



Staff Changes 2010

Ms Joanne Ernest, who completed her BSc(Hons) project at the Centre in 2008 and was then employed as a Medical Scientist, left the Centre in February to commence her PhD at La Trobe University.

In April Ms Ernest was replaced by Ms Leah Sook-Kwan Leang, with her time divided between all three divisions (Molecular Biology, Antiviral Drug Resistance, Antigenic Analysis) of surveillance activities. Ms Leang completed her BSc(Hons) project at the Centre in 2004.

Ms Iwona Buettner was appointed as Laboratory Technician in April, improving laboratory, procurement and logistics systems within the Centre.

In November, Dr Michelle Chow was appointed as Communications and Administration Officer to assume responsibilities related to reporting on Centre activities in several different forums.