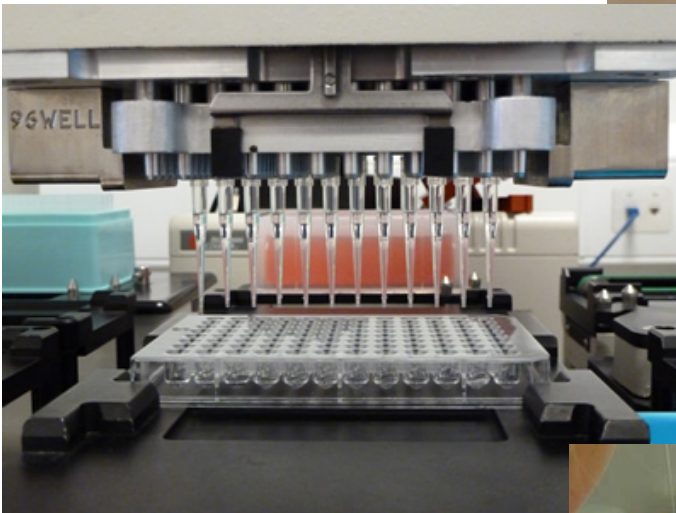
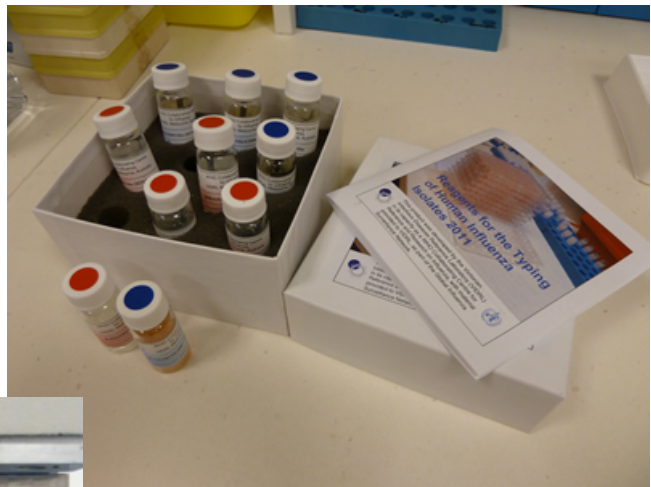




WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL

Annual Report 2011





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Contact information

WHO Collaborating Centre for Reference and Research on Influenza
10 Wreckyn Street, North Melbourne, VIC 3051, Australia
Tel: +61 3 9342 3900 Fax: +61 3 9342 3939
Email: whoflu@influenzacentre.org
Website: <http://www.influenzacentre.org>



About the Centre

The WHO Collaborating Centre for Reference and Research on Influenza at the Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne is part of the World Health Organisation Global Influenza Surveillance and Response System (WHO GISRS). The network was established in 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 2011-2015) are:

- i. to obtain, isolate and preserve representative viruses from outbreaks and sporadic cases of influenza, and characterise their antigenic and other relevant properties, including resistance to anti-influenza drugs;
- ii. to exchange information and new antigenic variants of influenza viruses with other WHO Collaborating Centres for Reference and Research on Influenza and with Essential Regulatory Laboratories;
- iii. to assist WHO in developing recommendations on viruses to be included in influenza vaccines;
- iv. to provide training and laboratory support to WHO National Influenza Centres and other laboratories, especially those in the developing world, in specialised techniques for diagnosis, isolation and characterisation of influenza viruses, according to their needs;
- v. to collect epidemiological information on the prevalence of influenza, especially in countries and areas in the Region;
- vi. to undertake research to improve the detection, prevention and treatment of influenza; and
- vii. to assist WHO and national health authorities in developing and implementing plans for responding to pandemic influenza.

Governance

The Centre is supported by the Australian Government Department of Health 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 2011

Prof Jim Bishop AO (Chair until May 2011)

Prof Chris Baggoley (Acting Chair from May 2011)

Dr Gary Lum AM, 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 (Director, Nossal Institute for Global Health) (until July 2011)

Prof Mike Richards (Director, Victorian Infectious Diseases Service, Royal Melbourne Hospital) (from December 2011)

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 Operations, Ambulatory and Primary Health Care, South East Sydney Local Health District)

Dr Heather Wellington (Consultant, Health Law Team, DLA Piper Australia)

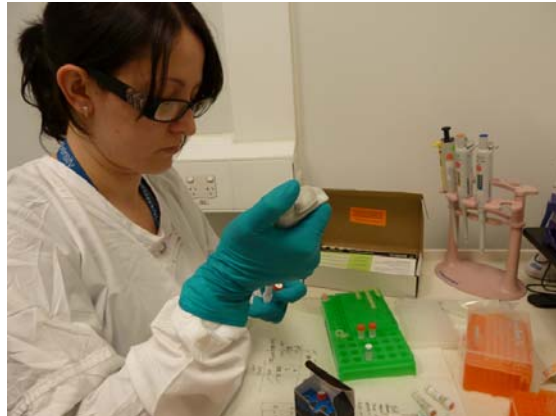
Dr Martyn Jeggo, observer (Director, Australian Animal Health Laboratory, CSIRO)

Highlights of 2011



Surveillance

The Centre received and processed 5001 samples from 15 countries during 2011. Of 4883 samples analysed, 34.5% were subtyped as A(H1N1)pdm09 and 32.6% were typed as influenza B.



Community transmission of antiviral drug-resistant A(H1N1)pdm09 viruses

The first documented occurrence of the sustained transmission of A(H1N1)pdm09 influenza viruses with oseltamivir resistance in the community was reported by the Centre in 2011 in the New England Journal of Medicine (Hurt AC et al., N Engl J Med 365(26): 2541-2).



Publications

Centre staff members were authors on 39 papers and publications in 2011, including 33 original research and surveillance papers. Three papers published by Centre staff members during the past five years were recognised by their respective publishers for their quality of research and/or high number of citations.



Director's Report

It is a pleasure to present the 2011 Report of the WHO Collaborating Centre for Reference and Research on Influenza at VIDRL. The Centre has continued to grow to meet the challenges of enhanced influenza surveillance since the 2009 pandemic and global interest in finding better ways to prevent and manage this significant viral disease. As you will see from the Report, we have also continued to increase our productivity, particularly in surveillance and research.

The annual rise in numbers of samples submitted to the Centre by WHO National Influenza Centres and other laboratories continued in 2011, with the exception of 2009, the year of the pandemic. Two years on from the 2009 H1N1 pandemic, viruses of the former pandemic lineage A(H1N1)pdm09 and type B viruses accounted for the majority of influenza viruses analysed at the Centre in 2011. The third group of human influenza viruses, those belonging to the subtype A(H3N2), were nevertheless prevalent in several countries which sent us samples. The great majority of viruses analysed at the Centre remained antigenically similar to the viruses represented in trivalent influenza vaccines used in the southern and northern hemispheres during 2011.

The value of enhanced and timely laboratory surveillance of influenza viruses was highlighted quite dramatically in the middle of the year when an unexpectedly high number of oseltamivir (Tamiflu)-resistant A(H1N1)pdm09 viruses was detected in samples from the Hunter New England Health District, in eastern Australia. Laboratory, public health and clinical colleagues there worked closely with Aeron Hurt and others in the Centre to test as many samples as possible and to collect clinical histories of patients from whom resistant viruses were isolated. This intense effort led to the recognition of a cluster of highly similar drug-resistant viruses, focussed around the city of Newcastle but detected as far away as Western Australia, in the period May – September 2011. Most importantly, all but one of the viruses came from community patients who had not received oseltamivir. Their genetic similarity suggested that they had originated from a common source, though whether or not they spread from an oseltamivir-treated patient remains unknown.

This was the largest cluster of such viruses detected since the emergence of the A(H1N1)pdm09 virus in early 2009. Its significance lies in the fact that these viruses spread readily in the absence of the drug, indicating that the mutation in the viral neuraminidase (histidine to tyrosine at position 275) which conferred resistance had not markedly impaired the “fitness” of the virus. The same mutation had been seen in the former seasonal A(H1N1) viruses which displaced their sensitive counterparts worldwide during 2007 – 2008.

Fortunately the Newcastle cluster died out, coincident with the end of the influenza season in temperate Australia, but it has provided a reminder of the capacity of influenza viruses to avoid our defences.

We were delighted that the Centre was redesignated as a WHO Collaborating Centre for Reference and Research on Influenza by the Western Pacific Regional Office of WHO in July 2011, for the period 2011 – 2015. The designation is based on a review of the Centre's performance in meeting its terms of reference.

The Centre welcomed several new staff members in 2011. Dr Lumin Xue and Jeff Butler joined us as research scientists to work with Aeron Hurt on externally funded projects – Lumin from CSL Limited where she worked in influenza vaccine production and Jeff from the Australian Animal Health Laboratory where he has been undertaking his PhD on A(H5N1) viruses. Dr Sheena Sullivan commenced as the Centre's first epidemiologist in October 2011; with a background in HIV epidemiology in China and PhD from the University of California Los Angeles, Sheena brings a new set of skills that will significantly enhance the Centre's capabilities in surveillance and research.

I would like to take the opportunity to thank all of the people and institutions who have supported the Centre's work throughout 2011. First, the contribution of the WHO National Influenza Centres and other laboratories which submitted viruses to the Centre in 2011 and assisted us in other ways must be highlighted as they have been critical in enabling us to meet our commitments to the WHO Global Influenza Surveillance and Response System. I would like to record the Centre's deep appreciation of the support of Professor Jim Bishop, Australia's Chief Medical Officer from 2009 until May 2011, and chair of our Australian Government Advisory Committee (AGAC) throughout that time. We are also very grateful to Professor Graham Brown for his wise counsel as a member of AGAC from 2007 until July 2011. Professor Chris Baggoley (Chief Medical Officer from August 2011) and other members of AGAC, colleagues in the Department of Health and Ageing, Dr Mike Catton and colleagues at VIDRL and our many research collaborators are warmly thanked for their work with the Centre. Finally I would like to thank the staff and students of the Centre for another highly productive year of surveillance and research work in 2011.

Professor Anne Kelso AO
Director





Surveillance

Introduction

The WHO Collaborating Centre at VIDRL in Melbourne is one of five Collaborating Centres in the world that conduct human influenza surveillance for WHO by analysing samples submitted by WHO National Influenza Centres and other laboratories. Most of the samples received at the Centre come from the Asia-Pacific region. Twice a year (once each for the northern and southern hemispheres) WHO makes recommendations on suitable influenza strains to be included in the next seasonal vaccine based on data and advice from the five Collaborating Centres and other experts.

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 there are three families of influenza viruses circulating in the human population — influenza A(H1N1), influenza A (H3N2) and influenza B.

Since the emergence of the pandemic A(H1N1) strain in 2009 [A(H1N1)pdm09], circulation of the previous seasonal A(H1N1) virus [A(H1N1) seasonal] has ceased.

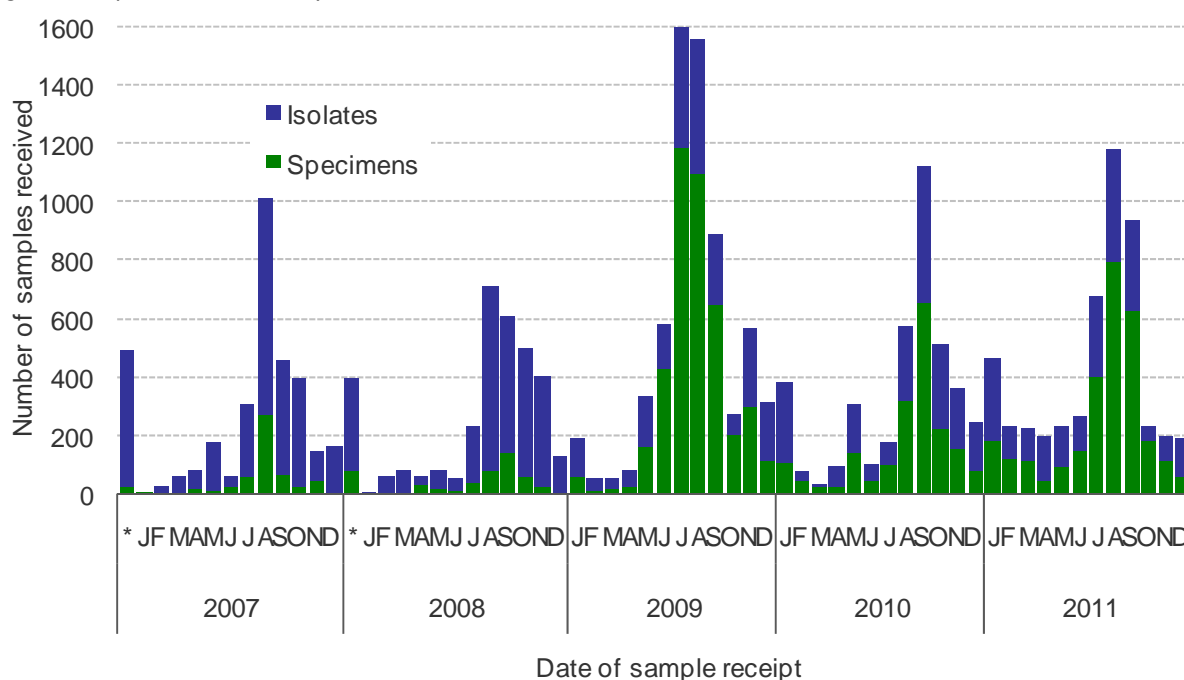
Receipt of Influenza Viruses

During 2011 the Centre received 5001 clinical specimens and virus isolates from 34 laboratories in 15 countries (Figures 1 and 2, Table 1). The number of samples received was higher than each of the previous five years, apart from 2009 when an unusually large number of samples (6570 samples) were received due to the pandemic (Figure 1). Of the 5001 samples received in 2011, 4883 (97.6%) samples were analysed by real-time reverse-transcription polymerase chain reaction (RT-PCR) reaction 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 younger than 5 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.

Figure 1. Samples received and analysed at the Centre, 2007-2011



* Samples received early in the indicated year but with sample dates from the preceding year. The method of recording receipt date was changed in 2009 to reflect more accurately the actual date that samples were received.



Figure 2. Geographic spread of influenza laboratories sending viruses to the Centre during 2011

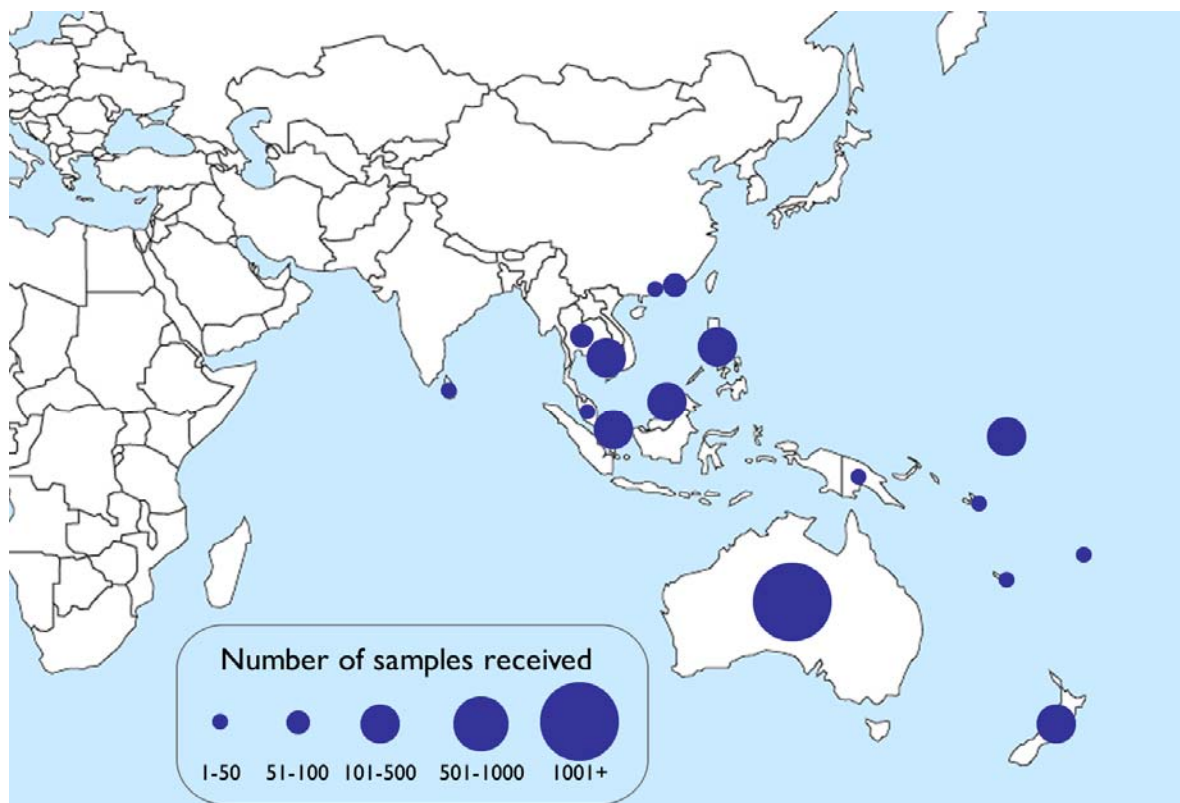


Figure 3. Age distribution of subjects from whom samples were received at the Centre in 2011

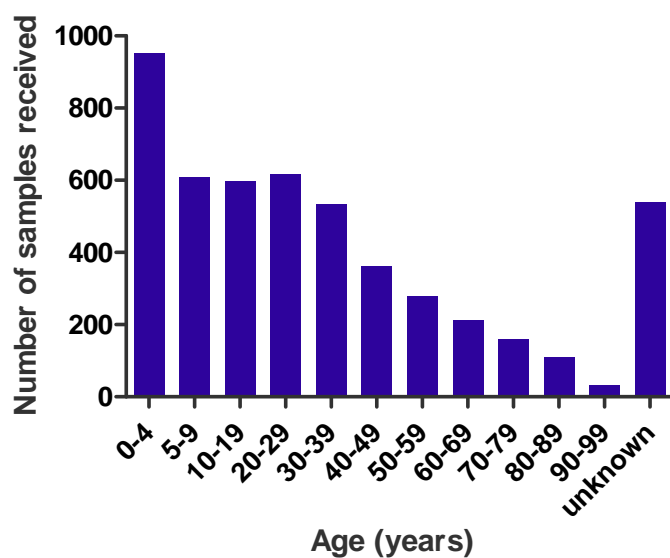
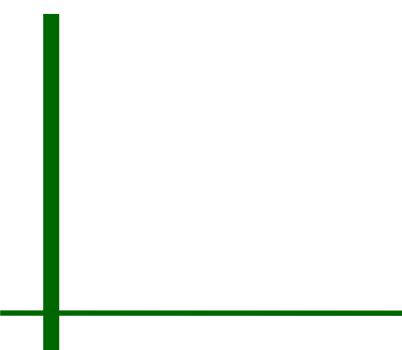




Table 1. Samples received at the Centre in 2011, by country, type and subtype

Country	Samples received		Samples tested	Samples testing positive by HI and/or RT-PCR assay				
	Specimens	Isolates		A(H1N1) pdm09	A (H3N2)	A (unsubtyped)	B	Mixed
AUSTRALASIA	2368	1669	3919	1344	769	449	1303	2
Australia	2362	1339	3583	1306	665	447	1111	2
New Zealand	6	330	336	38	104	2	192	0
SOUTH PACIFIC	215	0	215	21	56	26	34	1
Fiji	46	0	46	9	20	1	16	0
Nauru	111	0	111	0	28	5	10	1
New Caledonia	13	0	13	6	7	0	0	0
Papua New Guinea	31	0	31	5	1	18	7	0
Solomon Islands	14	0	14	1	0	2	1	0
SOUTH EAST ASIA	249	391	640	289	119	32	198	3
Brunei	94	20	114	95	1	15	1	3
Cambodia	94	66	160	46	22	0	92	0
Malaysia	9	13	22	6	13	0	3	0
Philippines	17	124	141	68	17	17	39	0
Singapore	30	108	138	60	46	0	32	0
Thailand	5	60	65	14	20	0	31	0
EAST ASIA	0	84	84	26	5	34	49	0
Hong Kong SAR	0	10	10	0	0	4	6	0
Macau SAR	0	74	74	26	5	30	43	0
SOUTH ASIA	25	0	25	5	0	10	10	0
Sri Lanka	25	0	25	5	0	10	10	0
TOTAL	2857	2144	4883	1685	949	551	1594	6





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 2011

A total of 4674 isolates that were received at the Centre in 2011 were analysed antigenically, of which 3269 (70%) produced a positive result. The majority of viruses were A(H1N1)pdm09 (39.1%) or influenza B (35.7%), with 25.0% typed as A(H3N2) (Figure 4). The relatively even distribution of subtypes was observed in isolates from most geographic regions, except for East Asia and South Asia, from where more B viruses were received than A viruses (Figure 5).

Figure 4. Influenza sub/types of isolates received in 2011 and analysed by HI assay

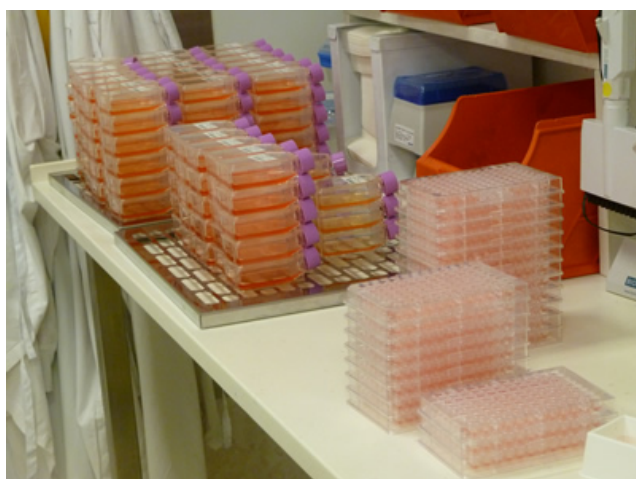
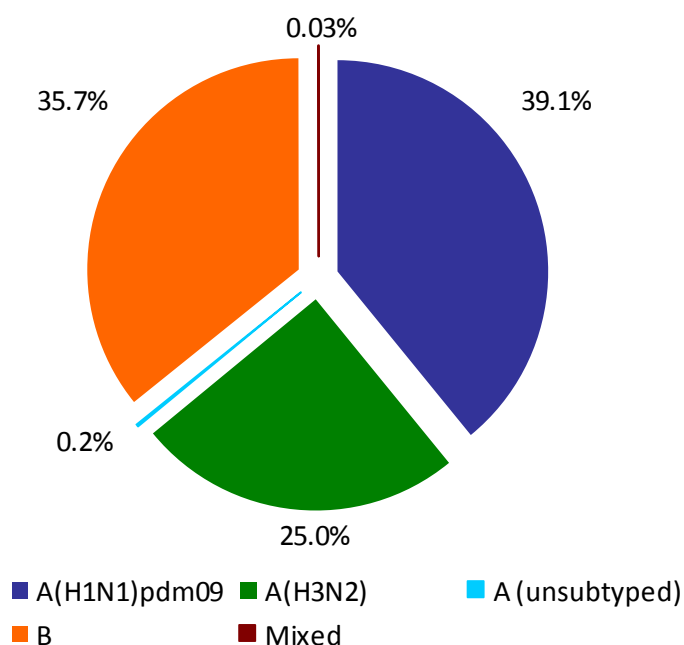
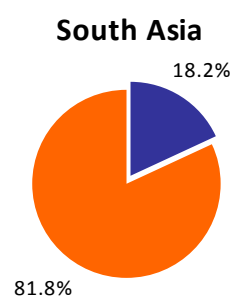
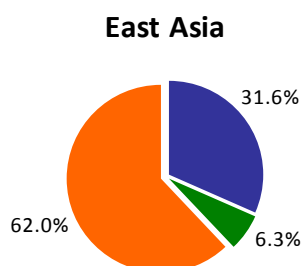
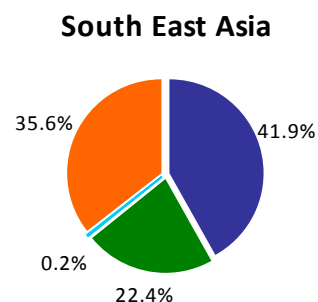
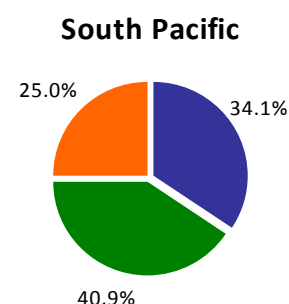
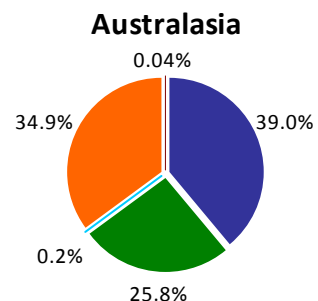


Figure 5. Influenza sub/types of isolates received from different world regions during 2011 as determined by antigenic analysis





Genetic Analysis of Influenza Viruses

Background

A subset of all influenza viruses analysed at the Centre undergo 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. Routine sequencing of the matrix protein (MP) and non-structural protein (NS) genes was also undertaken during 2011.

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

Sequencing 2011

The installation and implementation of an AB3500xL DNA capillary sequencer at the Centre in early 2011 has enabled in-house sequencing of samples, improving the efficiency of sample throughput and analysis of viruses, resulting in an increased number and greater range of genes being sequenced at the Centre.

In 2011, 496 HA, 492 NA, 332 MP and 213 NS genes of viruses received at the Centre were sequenced (Figure 6). In addition, 34 influenza A viruses were analysed by full genome sequencing (Figure 7) and 46 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 2011

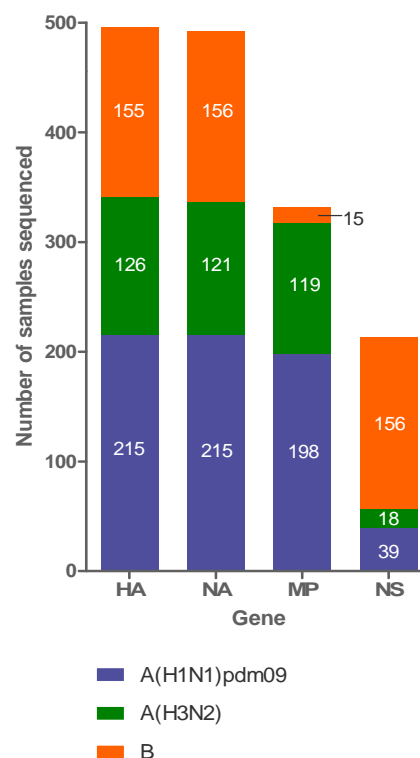


Figure 7. Geographic spread of submitting laboratories and numbers of viruses analysed by full genome sequencing at the Centre in 2011

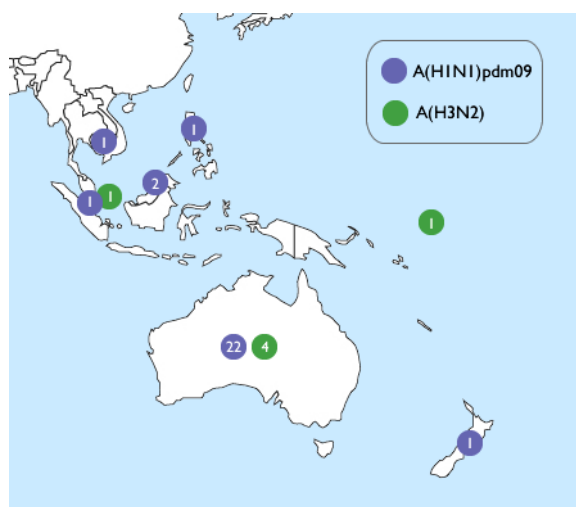
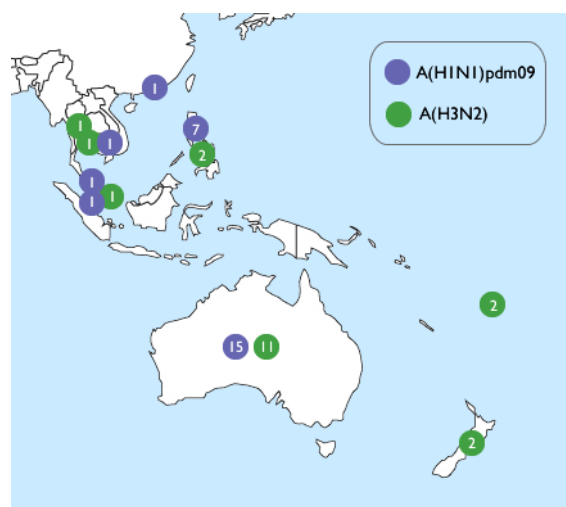


Figure 8. Geographic spread of submitting laboratories and numbers of viruses analysed by pyrosequencing at the Centre in 2011





Submission of Influenza Sequences to GISAID

Background

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

Sequences submitted in 2011

A total of 1241 gene sequences from 406 viruses were deposited with GISAID in 2011 (Table 2). The largest number of these sequences were of HA and NA genes, followed by MP and NS genes. Full genomes of 14 influenza viruses were also represented in the Centre's submissions (data not shown). 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 2011

Subtype \ Gene	HA	NA	MP	PB2	PB1	PA	NP	NS	Total
A(H1N1)pdm09	137	135	109	10	10	10	10	10	431
A(H3N2)	119	119	104	6	6	6	6	6	372
B	147	147	3	0	0	0	7	134	438
Total	403	401	216	16	16	16	23	150	1241



Surveillance Results by Influenza Subtype

Viruses were analysed by comparison with reference viruses recommended by WHO for the 2011 southern hemisphere and 2011-2012 northern hemisphere vaccines. Using the HI assay, viruses were identified as low-reactors if their titre with the reference antiserum was at least 8-fold lower than the titre of the reference virus. Results of sequencing analysis of the HA region of the haemagglutinin gene are also described in the following sections.

Influenza A(H1N1)pdm09

Antigenic analysis

A total of 1245 A(H1N1)pdm09 isolates were available for analysis by HI assay in 2011. The majority (83.1%) of these viruses displayed similar antigenic properties to the vaccine reference strain A/California/7/2009 (Table 3, Figure 9).

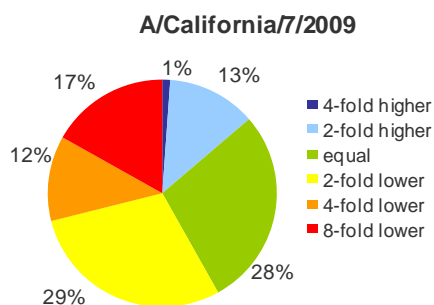
Haemagglutinin gene sequencing

Sequence analysis was performed on HA genes from 215 viruses indicated that circulating A(H1N1)pdm09 viruses sent to the Centre during 2011 were largely genetically similar to the vaccine reference strain A/California/7/2009 (Figure 10).

Table 3. Antigenic characterisation of A(H1N1)pdm09 viruses analysed at the Centre compared to the A/California.7/2009 reference virus

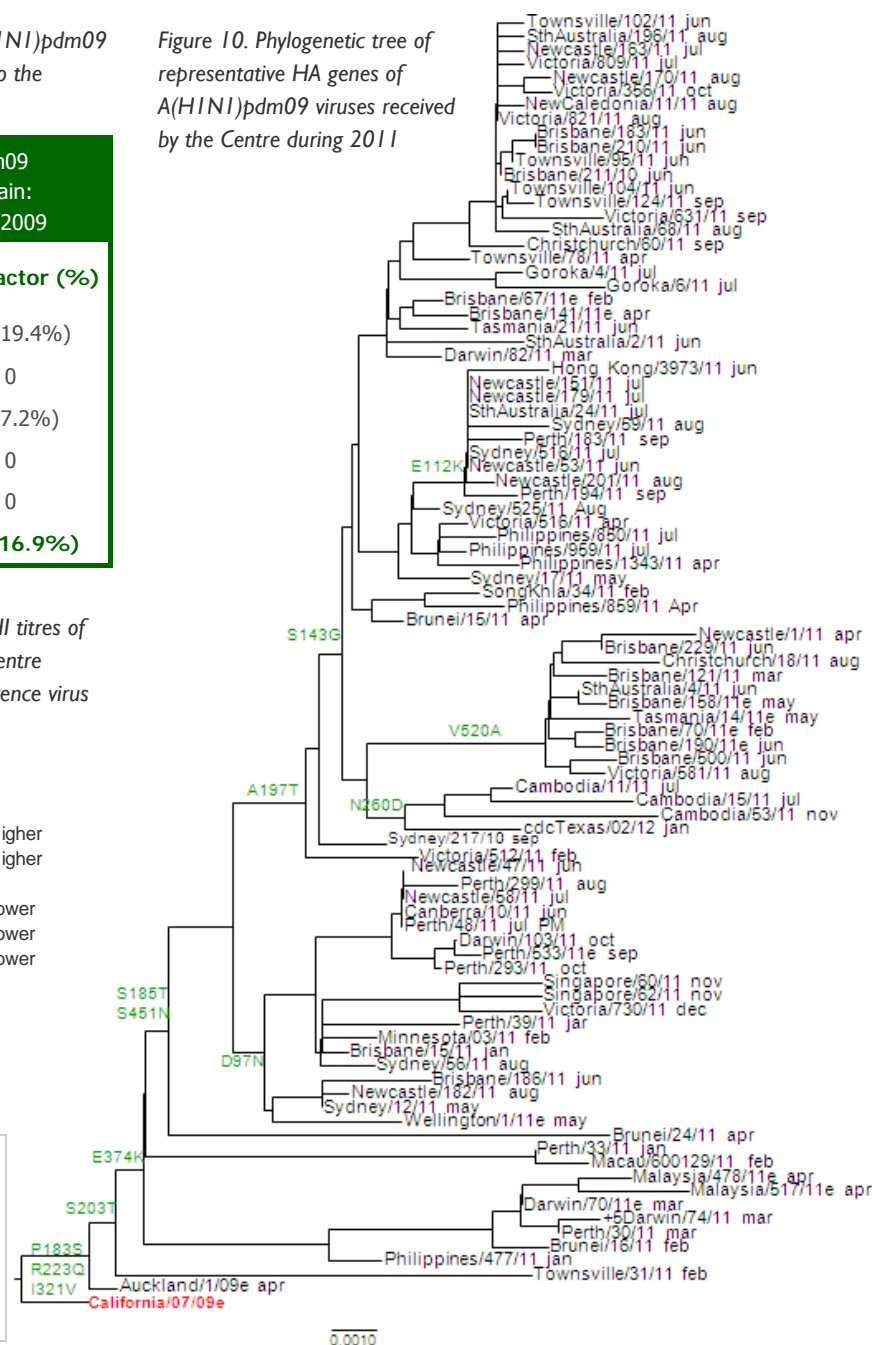
A(H1N1)pdm09 reference strain: A/California/7/2009		
Region	Like	Low reactor (%)
Australasia	813	196 (19.4%)
South Pacific	15	0
South East Asia	180	14 (7.2%)
East Asia	25	0
South Asia	2	0
Total	1035	210 (16.9%)

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



Legend
Vaccine Strain
 e: egg isolate
 Differences in amino acid sequence compared to 2011 consensus sequence
 Scale bar represents 0.1% nucleotide sequence difference between viruses

Figure 10. Phylogenetic tree of representative HA genes of A(H1N1)pdm09 viruses received by the Centre during 2011





Influenza A(H3N2)

Antigenic analysis

A total of 815 A(H3N2) subtype isolates were available for analysis by HI assay. No significant antigenic drift was observed, with only 5% of the viruses having a titre 8-fold lower than the A/Perth/16/2009 vaccine reference strain (Table 4, Figure 11).

Haemagglutinin gene sequencing

Sequencing of HA genes from 126 A(H3N2) viruses showed the continuing division of viruses into two genetically and antigenically related clades, one represented by the vaccine reference strain A/Perth/16/2009, and the second represented by A/Victoria/208/2009 (Figure 12). In comparison to 2010, a larger proportion of viruses fell into the latter group. The further emergence of a subgroup of A/Victoria/208/2009-like viruses, represented by A/Perth/10/2010, was also observed. However, these viruses still remain antigenically similar to A/Perth/16/2009.

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

Region	A(H3N2) reference strain: A/Perth/16/2009	
	Like	Low reactor (%)
Australasia	665	17 (2.5%)
South Pacific	16	2 (11.1%)
South East Asia	88	22 (20.0%)
East Asia	5	0
South Asia	0	0
Total	774	41 (5.0%)

Figure 11. Summary of fold differences in HI titres of A(H3N2) viruses analysed at the Centre compared to the A/Perth/16/2009 reference virus

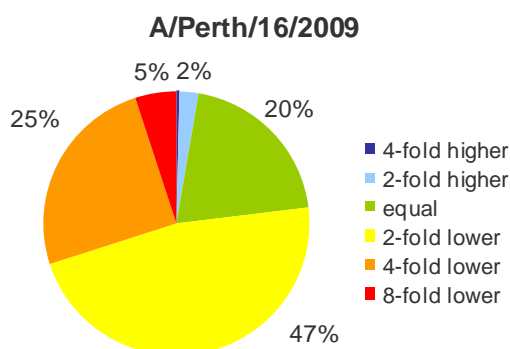
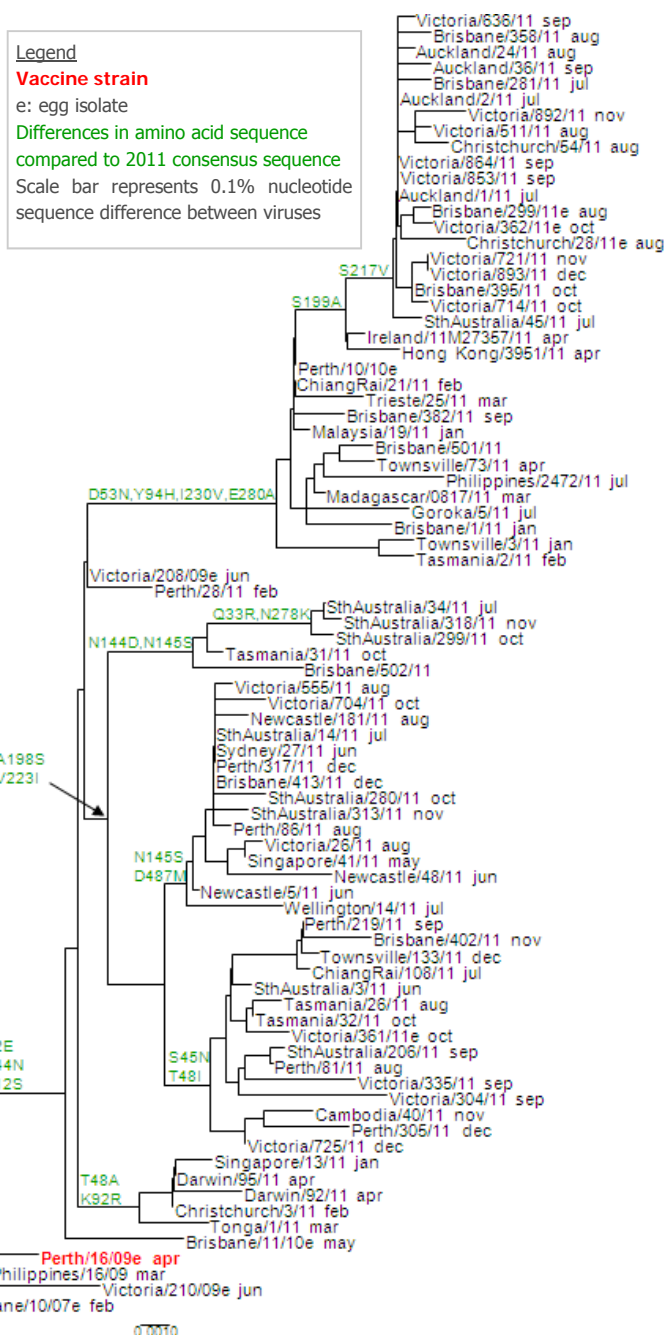


Figure 12. Phylogenetic tree of representative HA genes of A(H3N2) viruses received by the Centre during 2011





Influenza B

Antigenic analysis

There are currently two antigenically and genetically distinct lineages of influenza B virus in circulation, the B/Victoria/2/87 lineage (represented by the 2011 vaccine strain B/Brisbane/60/2008) and the B/Yamagata/16/88 lineage (represented by the former vaccine strain B/Florida/4/2006). Until 2001, B/Victoria lineage viruses had been restricted to Asia where they tended to alternate in predominance with the B/Yamagata lineage. In 2002 the B/Victoria lineage became the predominant influenza B lineage in most parts of the world. This trend was reversed in 2003 and 2004 when the B/Yamagata lineage predominated. Since then both lineages have co-circulated, with alternating cycles of predominance every few years.

Continuing a trend since 2009, during 2011 the B/Victoria lineage predominated amongst circulating influenza B viruses. Of the 1164 type B viruses received and analysed antigenically at the Centre in 2011, most were similar to B/Brisbane/60/2008 (Table 5, Figures 13 and 14).

Table 5. Antigenic characterisation of B viruses analysed at the Centre compared to the 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	817	95 (10.4%)	6	2 (25.0 %)
South Pacific	11	0	0	0
South East Asia	112	43 (27.7%)	2	15 (88.2%)
East Asia	42	0	2	5 (71.4%)
South Asia	7	0	0	2 (100%)
Total	989	138 (12.2%)	10	24 (70.6%)

* B/Victoria lineage virus

** B/Yamagata lineage virus

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

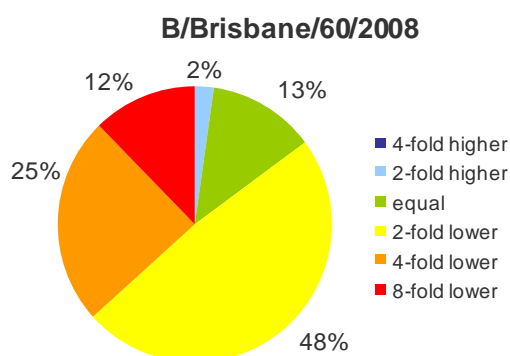
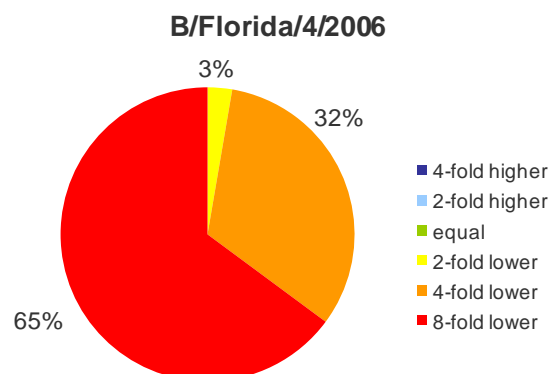
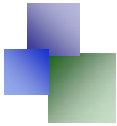


Figure 14. Summary of fold differences in HI titres of type B viruses analysed at the Centre compared to the B/Florida/4/2006 reference virus

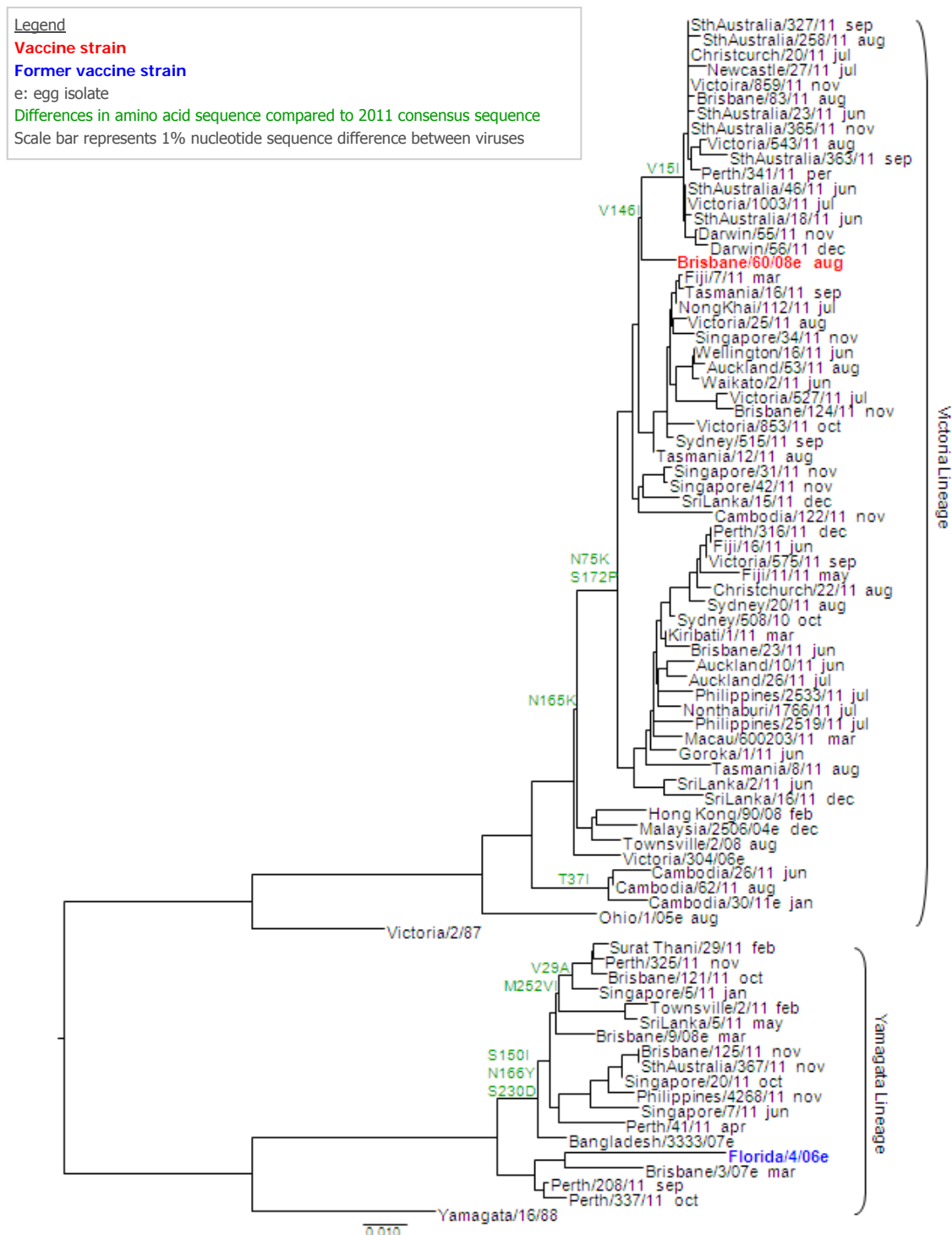




Haemagglutinin gene sequencing

A total of 155 HA genes from B viruses underwent sequence analysis and formed two distinct groups corresponding to the B/Brisbane/60/2008 and B/Florida/4/2006 lineages (Figure 15). The majority of B viruses fell into the B/Brisbane/60/2008 group; however, there was a noticeable increase in the number of B/Yamagata-lineage viruses received at the Centre during 2011.

Figure 15. Phylogenetic tree of representative HA genes of B viruses received by the Centre during 2011





Antiviral Drug Resistance Testing

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.

A(H1N1)pdm09 viruses are also screened by pyrosequencing to detect the mutation from histidine to tyrosine at position 275 (H275Y) in the N1 neuraminidase that reduces sensitivity 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 2011

NAI assays were used to analyse 3222 viruses assay for reduced sensitivity to zanamivir. All viruses were sensitive to zanamivir (data not shown).

A total of 3444 samples were analysed for reduced sensitivity to oseltamivir by NAI assay and/or pyrosequencing (Figure 16, Tables 6 and 7). The majority of currently circulating strains, including all influenza B (Table 7) and one mixed sample (data not shown), remained sensitive to oseltamivir. However, one A(H3N2) virus and small proportion of tested A(H1N1)pdm09 (3.4%) viruses showed highly reduced sensitivity to oseltamivir (Tables 6 and 7). Of particular interest was the identification of a geographic cluster of A(H1N1)pdm09 viruses from New South Wales (29 viruses) that had highly reduced sensitivity to oseltamivir (see box, p.18). A small number of viruses from other parts of Australia (Victoria, South Australia, Western Australia, Queensland), Brunei, Singapore and the Philippines were also found to be resistant to oseltamivir, and were all confirmed to carry the H275Y neuraminidase mutation. The oseltamivir resistant A(H3N2) virus was found to carry the E119V neuraminidase mutation that has previously been shown to confer resistance to oseltamivir.

Figure 16. Geographic spread of viruses received at the Centre during 2011 and screened for resistance to oseltamivir. Where applicable, the percentage (%) of viruses found to have highly reduced sensitivity is indicated.

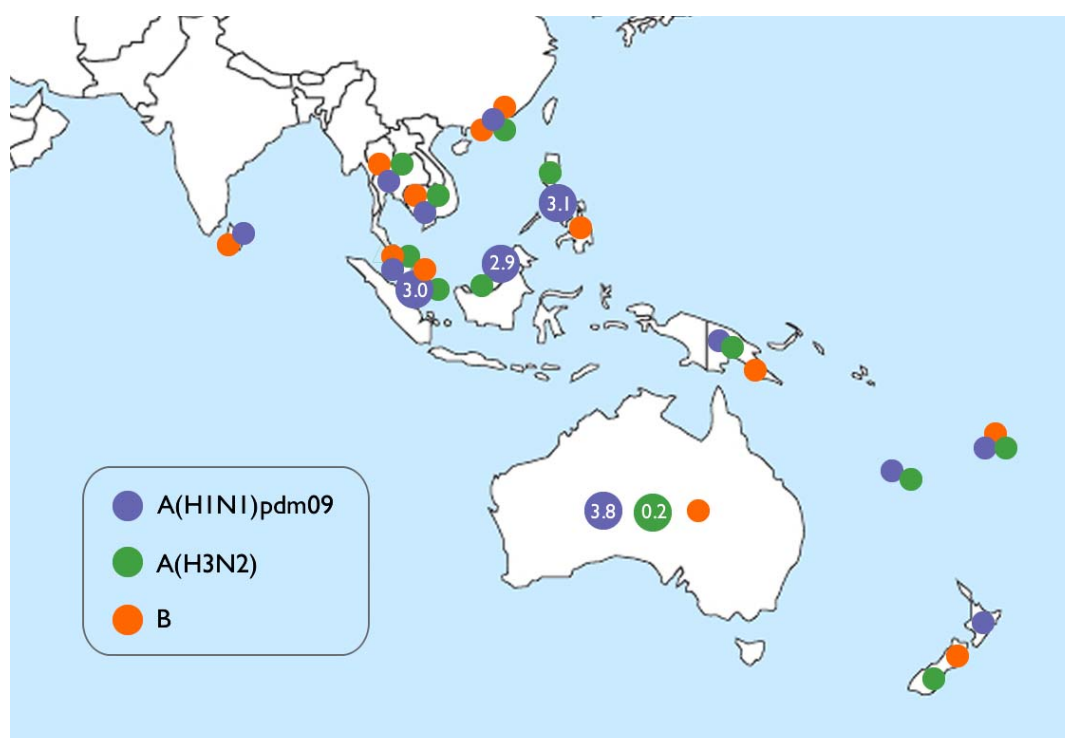




Table 6. Oseltamivir sensitivity in A(H1N1)pdm09 viruses received by the Centre in 2011

Country	Samples analysed by NAI assay		Samples analysed by pyrosequencing*		Total % with highly reduced sensitivity
	No. tested	No. with highly reduced sensitivity	No. tested	No. with highly reduced sensitivity	
Australasia					
Australia	966	25	207	20	3.8%
New Zealand	34	0	0	0	0
South Pacific					
Fiji	5	0	0	0	0
New Caledonia	5	0	0	0	0
Papua New Guinea	5	0	0	0	0
South East Asia					
Brunei	27	1	7	0	2.9%
Cambodia	35	0	0	0	0
Malaysia	6	0	0	0	0
Philippines	65	2	0	0	3.1%
Singapore	59	2	8	0	3.0%
Thailand	14	0	0	0	0
East Asia					
Hong Kong	0	0	0	0	0
Macau	25	0	0	0	0
South Asia					
Sri Lanka	2	0	0	0	0
TOTAL	1248	30	222	20	3.4%

* These viruses are distinct from those tested by NAI assay

Table 7. Oseltamivir sensitivity in A(H3N2) and Influenza B viruses received by the Centre in 2011

Country	A(H3N2) viruses analysed by NAI assay		Influenza B viruses analysed by NAI assay	
	No. tested	No. with highly reduced sensitivity (%)	No. tested	No. with highly reduced sensitivity (%)
Australasia				
Australia	584	1 (0.2%)	742	0
New Zealand	94	0	180	0
South Pacific				
Fiji	13	0	10	0
New Caledonia	4	0	0	0
Papua New Guinea	1	0	1	0
South East Asia				
Brunei	1	0	0	0
Cambodia	18	0	76	0
Malaysia	13	0	3	0
Philippines	17	0	35	0
Singapore	44	0	27	0
Thailand	17	0	30	0
East Asia				
Hong Kong	0	0	6	0
Macau	5	0	43	0
South Asia				
Sri Lanka	0	0	9	0
TOTAL	811	1 (0.1%)	1162	0

Emergence and Transmission of Oseltamivir-Resistant A(H1N1)pdm09 Viruses in the Community

Prior to 2011, the incidence of A(H1N1)pdm09 viruses with reduced sensitivity to oseltamivir was limited to a small number of isolated cases, usually in people who had received oseltamivir treatment. In 2011 the Centre and its collaborators found evidence of sustained transmission of oseltamivir-resistant A(H1N1)pdm09 viruses amongst untreated patients in the community. A cluster of resistant viruses was detected in the Hunter New England (HNE) region of New South Wales, centred around Newcastle during June–August 2011. A total of 26 oseltamivir-resistant viruses were from patients living within 50 km of Newcastle, and three others were within 500 km of Newcastle (Figure 17). Only one of these patients had been treated with oseltamivir prior to sample collection.

Sequence analysis revealed that the oseltamivir-resistant viruses, which all contained the H275Y neuraminidase mutation, formed a closely related, genetically distinct group, suggesting the spread of the strain from a single variant (Figure 18). Three other oseltamivir-resistant viruses, two from Sydney and one from Western Australia (collected in September), were also genetically related, suggesting the spread of the resistant viruses outside the Hunter New England region. The resistant strains were antigenically similar to the current A(H1N1)pdm09 vaccine strain A/California/7/2009.

This is the first documented occurrence of the sustained transmission of oseltamivir-resistant A(H1N1)pdm viruses in the community. Findings from the study were reported in the New England Journal of Medicine (Hurt AC et al., N Engl J Med 365 (26): 2541-2) and the Journal of Infectious Diseases (Hurt AC et al, J Infect Dis, submitted 2011, accepted February 2012).

Figure 17. Geographic distribution of oseltamivir-resistant viruses in the Hunter New England (HNE) region. (inset indicates the location in Australia)

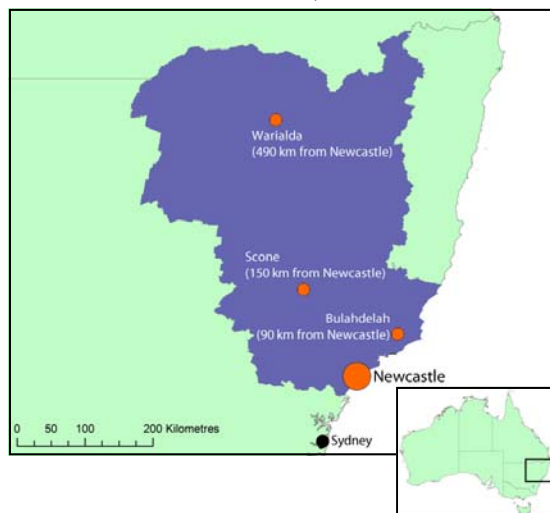
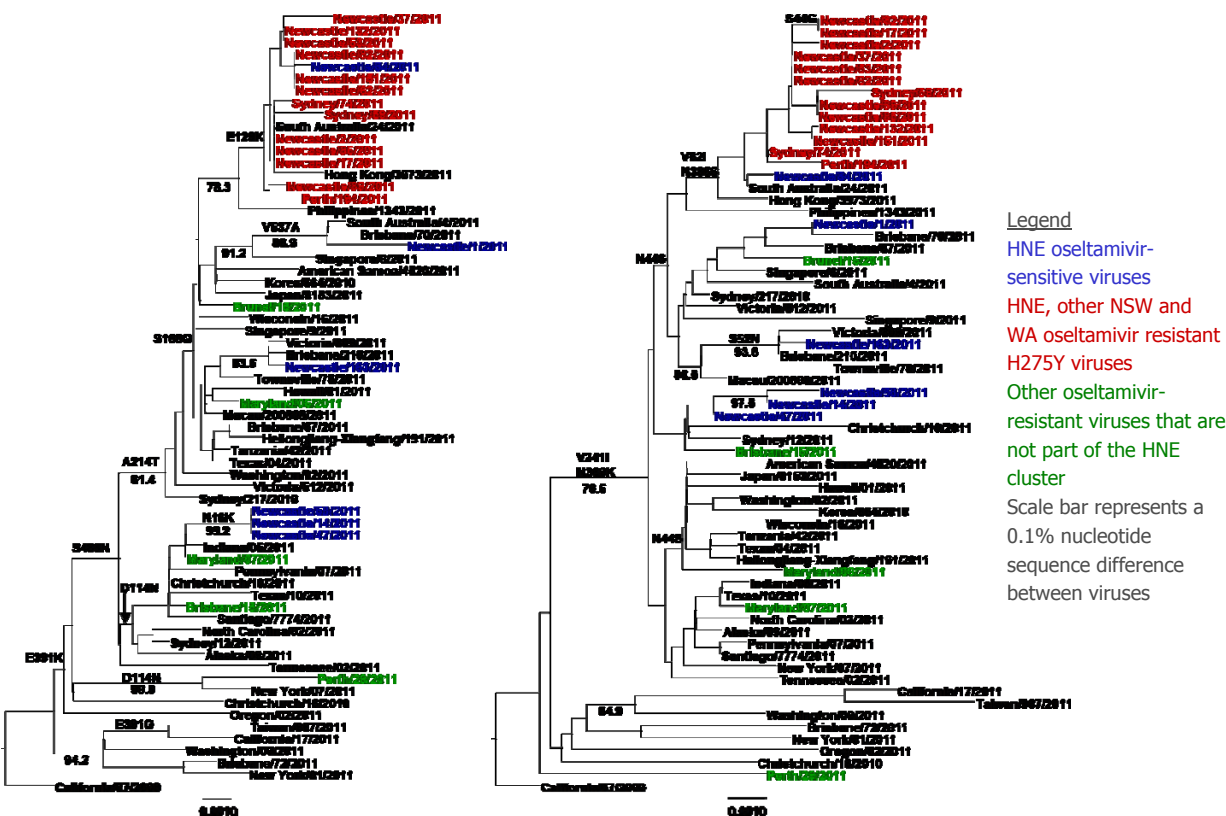


Figure 18. Phylogenetic analysis of HA (left) and NA (right) genes of oseltamivir-resistant viruses from the HNE region.





Resistance to Adamantanes

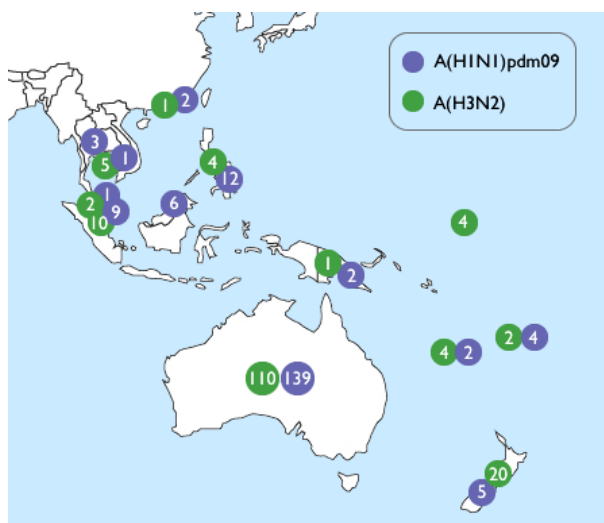
Background

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

Screening for adamantane resistance in 2011

Real-time PCR or sequencing was used to analyse 349 influenza A viruses, selected as representative of those submitted to the Centre during 2011 (Figure 19). Based on S31N analysis, all of the A(H1N1)pdm09 and A(H3N2) viruses that were tested were resistant to the adamantanes.

Figure 19. Geographic spread of viruses received at the Centre during 2011 and screened for adamantane resistance.



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 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. These panels are analysed using the HI assay against the current vaccine and representative influenza strains in preparation for the biannual WHO Consultations on the Composition of Influenza Vaccines. Serum panels from children, younger adults (20-64 years old) and older adults (≥ 65 years old) are assessed.

Serum panel analyses in 2011

In February the Centre analysed serum panels from recipients of seasonal trivalent influenza vaccines in Australia, China, Europe and Japan. In September, serum panels from Australia, USA and Japan were analysed. The 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 virus and most recent representative A(H1N1)pdm09, A(H3N2) and B/Victoria/2/87 lineage isolates, respectively. This indicated that influenza viruses circulating in the community during 2011 should be recognised by antibodies elicited by current vaccines. Titres were lower to some recent B/Yamagata/16/88 lineage isolates than to the current B/Victoria/2/87 lineage vaccine virus.

Table 8. Representative and vaccine candidate strains used for serological analyses during 2011

	February	September
Influenza A(H1N1)pdm09	A/California/7/2009*	A/California/7/2009*
	A/Christchurch/16/2010	A/Brisbane/70/2011
	A/Victoria/663/2010	A/South Australia/4/2011
	A/Perth/219/2010	A/Tasmania/14/2011
	A/Sri Lanka/21/2010	A/Minnesota/3/2011
Influenza A(H3N2)	A/Perth/16/2010*	A/Victoria/210/2009*
	A/Victoria/210/2009	A/Iowa/19/2010
	A/Victoria/563/2010	A/Sakai/20/2011
	A/Brisbane/220/2010	A/South Australia/3/2011
	A/Brisbane/11/2010	A/Sydney/27/2011
	A/Perth/10/2010	
	A/Rhode Island/1/2010	
Influenza B	B/Brisbane/60/2008^*	B/Brisbane/33/2008^
	B/Hiroshima/9/2010^	B/Cambodia/30/2011^
	B/Victoria/506/2010^	B/Shanghai-Jingan/1392/2011^
	B/Singapore/616/2008^	B/Victoria/500/2011^
	B/Fujian Gulou/1272/2008+	B/Sichuan-Angue/139/2011+
	B/Wisconsin/1/2010+	
	* Vaccine strain	^ B/Victoria-lineage viruses
		+ B/Yamagata-lineage viruses



Candidate Vaccine Strains

Background

The Centre collaborates closely with the other WHO Collaborating Centres and vaccine manufacturers to ensure the suitability of candidate strains for inclusion in seasonal vaccines. Regulatory requirements stipulate that viruses used to produce human vaccines are isolated and passaged only in embryonated hen's eggs or primary egg-derived cell cultures. Accordingly, the Centre undertakes primary isolation of selected viruses from clinical samples directly into eggs. These isolates are then analysed by HI assay and genetic sequencing.

Since 2009, the number of viruses isolated in eggs at the Centre has increased as a result of additional support received under a Letter of Agreement with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

Isolation of viruses in eggs in 2011

In 2011, 32 viruses were successfully isolated in eggs at the Centre, representing an overall isolation rate of 33% (Tables 9 and 10).

Table 9. Virus isolation in eggs at the Centre in 2011

Type/subtype	Isolates attempted	Isolates obtained	Success rate (%)
A(H1N1)pdm09	42	14	33
A(H3N2)	33	8	24
B	23	10	43
Total	98	32	33

Table 10. Potential candidate vaccine strains successfully isolated in eggs at the Centre in 2011

A(H1N1)pdm09	A(H3N2)	B
A/Brisbane/141/2011	A/Alaska/05/2010	B/Brisbane/40/2010
A/Brisbane/151/2011	A/Arizona/13/2010	B/Brisbane/41/2010
A/Brisbane/158/2011	A/Brisbane/299/2011	B/Cambodia/30/2011
A/Brisbane/190/2011	A/Christchurch/28/2011	B/Hong Kong/2205/2010
A/Brisbane/67/2011	A/Guadeloupe/202/2010	B/Hong Kong/2225/2010
A/Brisbane/70/2011	A/Iowa/19/2010	B/Hong Kong/2226/2010
A/Darwin/70/2011	A/Townsville/87/2010	B/Sydney/508/2010
A/Malaysia/478/2011	A/Victoria/362/2011	B/Sydney/509/2010
A/Malaysia/517/2011		B/Victoria/500/2011
A/Perth/533/2011		B/Victoria/512/2010
A/Tasmania/14/2011		
A/Townsville/126/2011		
A/Victoria/674/2011		
A/Wellington/1/2011		



Preparation and analysis of vaccine seed viruses

The Centre exchanges candidate vaccine viruses that have been isolated in eggs, as well as post-infection ferret antisera raised against these and other reference viruses, with the other WHO Collaborating Centres to enable direct comparison of strains isolated in the five centres. During 2011, 36 candidate vaccine viruses were received from other WHO Collaborating Centres and laboratories and then passaged in eggs at the Centre (Table 11).

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

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

Table 11. Potential candidate vaccine viruses received from other WHO Collaborating Centres during 2011

A(H1N1)pdm09	B
A/Kentucky/9/2010	B/Hiroshima/9/2010
A/Heilongjiang-Xiangfang/Swl191/2011	B/Georgia/28/2010
A/St Petersburg/100/2011	B/Bolivia/1526/2010
A/New York/9/2011	B/Washington/1/2010
A/Vorenezh/1/2011	NYMC bx41a(B/Wisconsin/1/2010)
A/Mexico/2208/2011	B/Guangdong-Luohu/1512/2010
A/Minnesota/3/2011	B/Fujian-Gulou/1790/2010
	B/Shanghai-Luwan/173/2011
	B/Sichuan-Anyua/139/2011
A(H3N2)	
A/Montana/5/2011	B/Hong Kong/591/2011
A/Minnesota/11/2010 (x-203)	B/Stockholm/3/2011
NYMC X-209 [HY A/IOWA/19/2010	B/St Petersburg/5/2011
NYMC X-209A [HY A/IOWA/19/2010	B/Stockholm/12/2011
A/Indiana/10/2011	B/Santiago/6025/2011
A/Minnesota/11/2010 X-203A	B/Nevada/3/2011
A/Minnesota11/2010	B/Shanghai-Jingan/1392/2011
A/Taiwan/851/2010	NYMC bx-39 (B/Hubei-Wujiagang/158/2009)
A/Rhode Island/1/2010 (X-199)	NYMC bx-43(B/Hong Kong/259/2010)
	NYMC bx-43a(B/Hong Kong/259/2010)
	NYMC bx-43b(B/Hong Kong/259/2010)



Preparation and Distribution of Diagnostic Reagents

Reagents for Antigenic Typing of Influenza Viruses

Each year the Centre prepares and distributes kits to regional and reference laboratories to enable influenza preliminary analysis and characterisation of influenza specimens prior to submission of samples to the Centre. The kits contain polyclonal sera, monoclonal antibodies and viral antigens for reference influenza strains. During 2011, 46 kits were sent to 23 laboratories in 15 countries. Each kit contained 10 mL each of the reference antigens A/Perth/16/2009, A/Brisbane/59/2007, A/California/7/2009, B/Florida/4/2006, B/Brisbane/60/2008, and homologous antisera.

Recipients of the 2011 Kit			
Australia	Institute of Medical and Veterinary Science, Adelaide, South Australia	Malaysia	Institute for Medical Research, Kuala Lumpur
	Queensland Health Scientific Services, Coopers Plains, Queensland	New Zealand	Institute of Environmental Science and Research, Wellington
	Westmead Hospital Westmead, New South Wales		University of Auckland, Auckland Auckland City Hospital, Auckland
	Flinders University, Adelaide, South Australia University of Queensland, Queensland	Philippines	Research Institute for Tropical Medicine, Muntinlupa City
Cambodia	Institut Pasteur du Cambodge, Phnom Penh	Singapore	Singapore General Hospital National Public Health Laboratory
Hong Kong, China	Hong Kong SAR Government Virus Unit	South Africa	National Institute for Communicable Diseases, Johannesburg
India	Manipal University, Karnataka	Sri Lanka	Medical Research Institute, Colombo
	University of Delhi, Delhi National Institute of Virology, Pune	Taiwan	National Cheng Kung University, Tainan
Kenya	Center for Virus Research Laboratories, Kenya Medical Research Institute, Nairobi	Thailand	National Institute of Health, Bangkok
Macau, China	Public Health Laboratory	Vietnam	Pasteur Institute, Ho Chi Minh City

Virus Panels for Analysis of Resistance to Antiviral Drugs

The Centre produces and distributes a panel of reference viruses on request to laboratories conducting NAI assays on behalf of the International Society for Influenza and other Respiratory Diseases (isirv) Antiviral Group. In 2011 panel kits were composed of 2 vials (250µL) of each the reference viruses listed in the table at right.

Recipients of the NAI assay panel in 2011

Institut für Virusdiagnostik, Friedrich-Loeffler-Institut, Germany
Naval Health Research Center, San Diego, USA
Innovation & Discovery Labs, Crucell, Netherlands
WHO National Influenza Centre, Kenya
ViroClinics, Netherlands
BioVent, Israel
WHO National Influenza Centre, Turkey

Reference virus	Amino acid residues of interest in NA protein	Sensitivity to antiviral drugs
A/Mississippi/3/01 (H1N1) wild-type (A/New Caledonia/20/99-like)	Histidine at position 275 (275H)	Susceptible to zanamivir Susceptible to oseltamivir carboxylate
A/Mississippi/3/01 (H1N1) resistant (A/New Caledonia/20/99-like)	Tyrosine at position 275 (275Y)	Susceptible to zanamivir Reduced susceptibility to oseltamivir carboxylate
A/Fukui/20/04 (H3N2) wild-type (A/Fujian/411/2002-like)	Glutamic acid at position 119 (119E)	Susceptible to zanamivir Susceptible to oseltamivir carboxylate
A/Fukui/20/04 (H3N2) resistant (A/Fujian/411/2002-like)	Valine acid at position 119 (119V)	Susceptible to zanamivir Reduced susceptibility to oseltamivir carboxylate



Recommendations on Influenza Vaccines

WHO Consultations on the Composition of Seasonal Influenza Vaccines

The antigenic, genetic, antiviral resistance and serological data generated from the Centre's surveillance activities are incorporated into detailed dossiers for use at the WHO Consultations on the Composition of Influenza Vaccines in February (for the northern hemisphere) and September (for the southern hemisphere).

The Centre Director and Deputy Director participate in preparatory teleconferences and then meet at the face-to-face Consultation with WHO, representatives from the other WHO Collaborating Centres and the four Essential Regulatory Laboratories (Center for Biologics Evaluation and Research, US Food and Drug Administration; 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 2011, WHO made the recommendations reported below. These recommendations were the same as those made in 2010, reflecting the findings that antigenic, genetic and human serological analyses detected little antigenic drift in any of the three vaccine virus types/subtypes during 2011.

WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2011–2012

Geneva, Switzerland, 14–16 February 2011

It is recommended that vaccines for use in the 2011–2012 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*.

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

WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2012

Geneva, Switzerland, 26–28 September 2011

It is recommended that vaccines for use in the 2012 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*.

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

Australian Seasonal Influenza Vaccine Recommendation

Whereas WHO makes recommendations on suitable viruses for inclusion in seasonal influenza vaccines, 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 5 October AIVC accepted the September WHO recommendation and decided that the Australian influenza vaccine for 2012 should contain the following:

- 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 and Regional Laboratories

Centre staff further support the GISRS surveillance network by providing training and advice to WHO National Influenza Centres (NICs) and other diagnostic laboratories, especially in the Asia-Pacific region. Strengthening technical capabilities and infrastructure for surveillance work in regional laboratories increases their capacity to detect and characterise circulating influenza viruses, and to identify viruses with pandemic potential.

In-House Training

During 2011 the Centre hosted several scientists who visited for training in a range of techniques for analysis and characterisation of influenza isolates. The Centre was pleased to welcome scientists not only from diagnostic laboratories, but also collaborating research laboratories.

Miss Siripaporn Phuygun (back) and Miss Thanutsapa Thanadachakul (front)

Thailand National Influenza Center, visited 28 February – 11 March

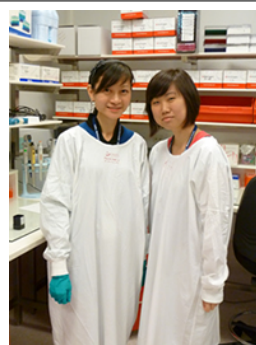
Trained in neuraminidase inhibition assays and phylogenetic analysis of influenza sequences.



Ms Michelle Chua (left) and Ms Huiling Guo (right)

Program of Emerging Infectious Diseases, Duke-NUS Graduate Medical School, Singapore visited 11–21 April

Trained in pyrosequencing techniques.



Mr Apaitia Vakacegu

Mataika House, Fiji, visited 22-26 August

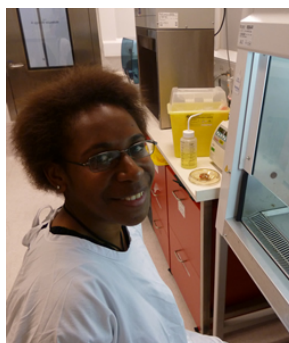
Trained in cell culture, virus isolation and molecular detection of influenza viruses.



Ms Marinjho Jonduo (left) and Ms Jacinta Kono (right)

Institute of Medical Research, Papua New Guinea, visited 29 August – 2 September

Trained in cell culture, virus isolation and molecular detection of influenza viruses.



Dr Jude Jayamaha

Medical Research Institute, Colombo, Sri Lanka, visited 5 September 2011 - 25 January 2012

Trained in cell culture, virus isolation and sequencing.





Other Training

The Centre's Educator, **Dr Patrick Reading**, participated as an influenza specialist in a Laboratory Management Course for Influenza, held in Johannesburg, 28 February – 4 March 2011, and organised by US CDC, the Association of Public Health Laboratories and the National Institute for Communicable Diseases. He gave presentations to 35 participants from African and Asian countries as part of a program on building the laboratory capability, capacity and biosafety of National Influenza Centres and other laboratories working toward NIC designation.

Naomi Komadina provided training via Skype to Professor Pagbajabyn Nymadawa and Mrs Enkhsaikhan Dashdondog from the National Influenza Center of Mongolia in the use of GISAID and other phylogenetic analysis tools, 22–31 March.

Dr Reading visited the Papua New Guinea Institute of Medical Research in Goroka with Dr Jeff Partridge (WPRO), Amanda Balish (CDC) and Alex Rosewell (WHO Office, Papua New Guinea) to discuss surveillance and laboratory testing capabilities, 26–30 June.

Dr Reading participated as an influenza specialist in a sub-regional workshop for influenza surveillance in the Pacific, held in Suva, Fiji, 26–29 September. He gave two presentations at the workshop, which was attended by laboratory scientists and epidemiologists from Fiji, Solomon Islands, Cook Islands, Samoa, Kiribati, Tonga and Vanuatu (pictured at right).



Staff Development

Laboratory Accreditation

The Centre maintains its PC3 facilities, regulatory approvals and technical expertise in preparedness to receive and characterize 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).

- National Association of Testing Authorities (NATA) Medical Testing Quality Managers' Forum, Melbourne, 14–15 September, attended by Katie O'Bryan and Tasoula Mastorakos.
- Medical Laboratory Quality Network (MLQN) Internal Auditors Course, Melbourne 10–11 October, attended by Tasoula Mastorakos.

Research



Centre staff are involved in several in-house and collaborative research projects. During 2011, the Centre's research focused on a range of projects areas as described below.

Research Projects

Viral fitness in ferret models

Centre staff Aeron Hurt, Ian Barr, Jeffrey Butler
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. Groups 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 cycles of transmission. The data are analysed by mathematical modelling to determine the relative fitness of one virus compared with another. The model has been applied to determining the fitness of neuraminidase inhibitor-resistant viruses and new antigenic variants. This project is supported by funding from the University of Melbourne Faculty Research Grant Support Scheme.

Related publications 2011 (see Centre Publications 2011, page 38)

Reference: 22

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.

Assessment of cytokine responses in ferrets

Centre staff Karen Laurie, Louise Carolan, Aeron Hurt, Jeffrey Butler, Patrick Reading
Collaborators Steve Rockman (CSL Limited)

Project overview

This study aims to assess cytokine responses in ferrets as markers of the early and late immune response.

Highlights and developments 2011

A number of cytokines can be identified reproducibly and in accordance with the literature for other animal models of infection with influenza or other viruses. Protocols have been developed and parameters have been optimised to enable the assay to be performed consistently and accurately.

Related publications 2011

Quantitation of mRNA cytokine levels in ferrets following influenza infection. (Poster, presented at the Keystone Symposia Conference: Pathogenesis of Influenza: Virus-Host Interactions, 23-28 May; and Fourth ESWI Influenza Conference, 11-13 September).



Assessment of antigenic drift in a ferret model

Centre staff and student Karen Laurie, Louise Carolan, Teagan Guarnaccia, Patrick Reading, Ian Barr, Anne Kelso

Collaborators Jenny Mosse (Monash University)

James McCaw, Stephen Price and Jodie McVernon (The University of Melbourne)

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

Project overview

As a core part of its surveillance activities, the Centre traces the antigenic drift of influenza viruses to monitor how well the current influenza vaccine matches circulating influenza strains. Interestingly, to date the A(H1N1)pdm09 influenza virus has not shown significant drift. In this project a model of antigenic drift has been developed by passaging influenza virus through multiple cycles of infection in immunised and naïve ferrets. It is hoped that this model will provide insights into why and how antigenic drift occurs in influenza viruses circulating in the human population.

Highlights and developments 2011

An antigenic drift variant that no longer matches the current influenza vaccine has been detected in the ferret model. This virus is not as fit as the wild type strain when passaged through immunised ferrets, yet is of equal fitness when passaged through naïve ferrets. Attempts to isolate a pure population of the HA mutant virus in conventional cell and egg cultures were unsuccessful. Difficulty in culturing this virus highlights a potential problem for future surveillance of human A(H1N1)pdm09 influenza viruses, and vaccine virus selection. Novel isolation techniques are being explored. Results from this project were presented by Teagan Guarnaccia at the NHMRC Program on Understanding and Controlling Influenza Student Seminar Series: Influenza virology and pathogenesis session.

Related publications 2011

Does the A(H1N1)pdm virus drift under immune pressure in the ferret model? (Poster, presented at the Monash University Gippsland Postgraduate Research Poster Competition).

Seroprevalence surveys to assess human population immunity to the 2009 pandemic H1N1 and other influenza outbreaks

Centre staff Karen Laurie, Louise Carolan

Collaborators Jodie McVernon (The University of Melbourne)

Stephen Lambert (Queensland Children's Medical Research Institute, The University of Queensland, and Queensland Children's Health Services, Queensland Health Immunisation Program, Brisbane, Australia)

Helen Faddy, Catherine Hyland and Hugh Capper (Australian Red Cross Blood Service)

Brenda White and Amanda di Carlo (The Royal Children's Hospital)

Project overview

This project assesses the continuing immunity to the A(H1N1)pdm09 virus in the Australian adult community and has now been extended to encompass children in Melbourne and Queensland. The project also explores the potential use of serosurveys to assess unseasonal outbreaks of influenza in the community (as observed in Queensland and the Northern Territory in early 2011).

Highlights and developments 2011

Serology studies were conducted to assess whether an unseasonal outbreak of influenza in the northern states of Australia in early 2011 was due a lack of immunity to the circulating viruses prior to the outbreak. Results from adult samples were inconclusive, and the study is now focused on obtaining and analysing collections from children to ascertain whether the burden of infection (and/or lack of cross-reactive immunity) fell primarily on the young.

Related publications 2011

Investigations of the seroprevalence status of Australians against pandemic and seasonal influenza from 2008-11. (Poster, presented at Fourth ESWI Influenza Conference, 11-13 September).



Serological studies to assess vaccine immunogenicity in paediatric oncology patients

Centre staff Karen Laurie, Louise Carolan
Collaborators Ushma Wadia (Princess Margaret Hospital, Western Australia)

Project overview

This study project has followed a cohort of children since 2009 to assess the serological response to influenza vaccines in children undergoing cancer therapy. 130 patients have been recruited over 3 years and the final groups of patients will be assessed in early 2012.

Highlights and developments 2011

The study has come to a close in 2011 and results should be available in early 2012.

Vaccine effectiveness

Centre staff Sheena Sullivan
Collaborators Heath Kelly and Kristina Grant (Epidemiology Unit, VIDRL)
James Fielding (National Centre for Epidemiology & Population Health, Australian National University)

Project overview

The WHO recommendation for the influenza vaccine is issued 5-6 months prior to the release of the influenza vaccine, leaving insufficient time to test vaccine efficacy and safety. The epidemiology group at VIDRL has a long-running influenza sentinel surveillance system that collects information on patients with influenza-like illness including their vaccination history and laboratory-confirmed influenza. Vaccine effectiveness in the community can be estimated from the data using a test-negative design. This project is using data collected from 2007 to 2011 to estimate vaccine effectiveness and will include sensitivity analyses to explore the validity of the epidemiological methods using causal graph theory.

Understanding the representativeness of influenza virus samples sent to the Centre

Centre staff Sheena Sullivan

Project overview

It is important to understand whether the influenza viruses evaluated by the Centre are representative of the viruses circulating during a season. While it is infeasible to ensure equal representation of each virus strain, it is possible to estimate the proportion of samples received among laboratory-confirmed cases. This study will attempt to understand whether viruses received by the Centre are representative of those reported to National Notifiable Diseases Surveillance System in terms of type/subtype and the demographic, geographic and temporal distribution of infections

Molecular analysis and structural modelling of influenza proteins

Centre staff Ian Barr, Yi-Mo Deng, Aeron Hurt, Naomi Komadina
Collaborators Sebastian Maurer-Stroh (Bioinformatics Institute (BII), A*STAR, National University of Singapore)
Michael Parker (St Vincent's Institute of Medical Research)

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.



Antigenic cartography and molecular evolution of the influenza virus

Centre staff Ian Barr, Aeron Hurt, Naomi Komadina, Lumin Xue
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 algorithms 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 insight into the reasons for antigenic drift, with the ultimate goal of predicting the direction of antigenic drift before it occurs.

Early recognition and response to influenza infection

Centre staff Patrick Reading
Collaborators Alberto Mantovani (Istituto 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 characterises 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 prior to the emergence 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.

Highlights and developments 2011

This research resulted in twelve publications during 2011, of which Dr Reading was senior author on nine. He presented several research talks at conferences and institutes during the year, including presentations at a Keystone Symposium (Pathogenesis of Influenza: Virus-Host interactions, Hong Kong, 23-28 May) and as an invited speaker at the Australian Virology Society Scientific Meeting (Kingscliff, NSW, 4-8 December). In 2011, his PhD student Michelle Tate was awarded The Chancellor's Award for Excellence in the PhD Thesis (The University of Melbourne), The Dean's Prize for Excellence in the PhD Thesis (Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne) and a Commendation in The Premier's Award for Health and Medical Research. Miss Wy Ching Ng commenced her PhD in March 2011 under the supervision of Dr Reading.

Related publications 2011

References: 19, 28-35



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

Chief Investigators

Anne Kelso, Patrick Reading, Karen Laurie, Aeron Hurt
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:

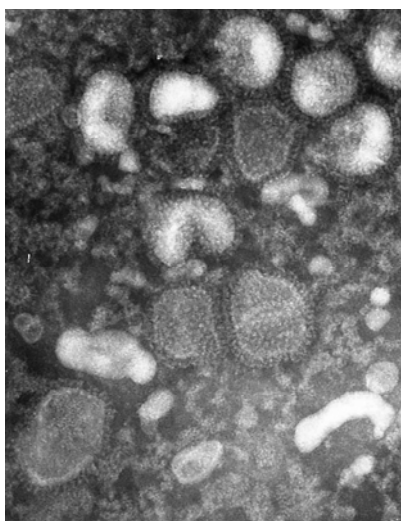
- to understand fundamental mechanisms that establish maximum effective cellular immunity to influenza A viruses
- to build the foundations for clinical application of strategies to induce cellular immunity to these viruses.

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.

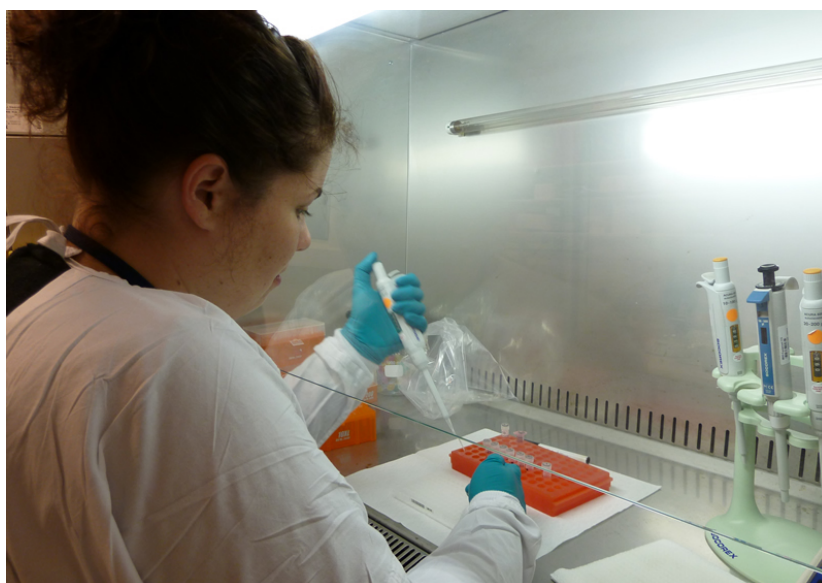
Highlights and developments 2011

Dr Bridie Day and Kim Charlton, working in the Department of Microbiology and Immunology under the supervision of Anne Kelso, have continued investigating the regulation of CD8 co-receptor expression in T lymphocytes. Changes in CpG methylation in and around the CD8 α gene are associated with changes in CD8 expression levels during development of CD8 T cells in the thymus and following IL-4-mediated CD8 down-regulation on cytotoxic T lymphocytes. This epigenetic regulation may contribute to the heritability of the CD8-low state in IL-4-exposed cells, lowering their sensitivity to antigen activation.

A Program retreat held on 3-4 November was attended by 62 people representing all of the research groups in the Program. Teagan Guarnaccia, Anne Kelso, Karen Laurie and Patrick Reading presented talks. Louise Carolan also participated. A focus group meeting on early immune responses held at the University of Melbourne on 5 May was convened by Patrick Reading.



Viruses grown at the Centre as viewed by electron microscopy. Image courtesy of Ross Hamilton (CSL Limited).





Additional research collaborations

Centre staff members have also been involved in the following collaborations in 2011:

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)

Genetic analysis of equine influenza viruses from the Australian outbreak

Centre staff and student: Aeron Hurt, Chisha Sikazwe

Collaborators: Peter Kirkland (EMAI, New South Wales)

Role of permissive mutations in neuraminidase

Centre staff: Aeron Hurt, Jeffrey Butler

Collaborators: Jesse Bloom (Fred Hutchinson Cancer Research Center, USA)

Novel amino acid mutations confer neuraminidase inhibitor resistance

Centre staff: Aeron Hurt, Jeffrey Butler

Collaborators: Rod Daniels (National Institute Medical Research, UK)

Development of serological studies for the investigation of influenza outbreaks

Centre staff: Karen Laurie

Collaborators: Patricia Huston (Public Health Agency of Canada, Canada), Steven Riley (Imperial College, UK), Jacqueline Katz (Centers for Disease Control and Prevention, USA), Donald Willison (Public Health Ontario, Canada), John Tam (Initiative for Vaccine Research, World Health Organisation, Switzerland), Anthony Mounts (Global Influenza Programme, World Health Organisation, Switzerland), Elizabeth Miller (Health Protection Agency, UK), Katja Hoschler (Health Protection Agency, UK), Kaat Vandemaele (Influenza Programme, World Health Organisation, Switzerland), Eeva Broberg (European Centre for Disease Prevention and Control, Sweden), Maria Van Kerkhove (Imperial College, UK), Angus Nicoll (European Centre for Disease Prevention and Control, Sweden)

Research Funding

During 2011 Centre staff members were awarded funding for specific research projects:

Patrick Reading is a chief investigator in two research projects that were awarded grants by the National Health and Medical Research Council. The grants will be administered by The University of Melbourne and the work will be undertaken in the Department of Microbiology and Immunology at the University.

- *Soluble inhibitors of influenza virus in the airways fluids of mice, ferrets and humans*, 1 January 2012–31 December 2014
- *Cell surface lectin receptors for attachment and entry of influenza viruses into cells of the innate immune system*, 1 January 2012–31 December 2014, co-investigator Sarah Londrigan (The University of Melbourne)

Patrick Reading is a co-investigator with Paul King (Monash University) and Kumar Visvanathanon (Monash Medical Centre) in a research project titled "*Effect of airway inflammation on innate immune responses to influenza*", which was awarded funding for 2012 by the Monash University Faculty of Medicine, Nursing and Health Sciences Strategic Grant Scheme.

Aeron Hurt is part of a collaboration with James McCaw and Jodie McVernon (The University of Melbourne) which was awarded funding from the University of Melbourne Faculty Research Grant Support Scheme for 2012 to continue work on a project on mathematical models of influenza transmission and fitness.



Collaborative Agreements

The Centre is party to two collaborative research and development agreements with industry bodies. As with all potential collaborations with the commercial sector, these agreements have undergone review by the Australian Government Advisory Committee 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, Scott Reddiex, Robert Shaw, Anne Kelso, Ian Barr

Project overview

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

Highlights and developments 2011

During 2011, 99 clinical specimens were cultured in MDCK 33016PF cells, of which 75 (76%) produced isolates. As in previous years, this was much higher than the rate of isolation in eggs. The isolates, which comprised A(H1N1)pdm09, A(H3N2) and B viruses, were sent to Novartis in Marburg for further evaluation as potential vaccine candidates produced by cell culture.

Heidi Peck visited the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA, on 18-19 October, to meet and discuss the project with other collaborators participating in the CRADA. On 21 October, Heidi Peck gave an oral presentation at the CRADA technical meeting held at the Novartis FCC facility in Holly Springs, which was also attended by Ian Barr.

Related publications 2011

Reference: 25

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

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

Project overview

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

Highlights and developments 2011

A total of 32 egg isolates were obtained from 98 inoculations with original clinical specimens from various geographical locations. Isolation rates varied from 24% to 43% according to virus type/subtype. Suitable isolates were made available to other laboratories and industry for reassortment and assessment as vaccine candidates.



Research Students

PhD Candidate

Ms Teagan Guarnaccia, who commenced her PhD candidature at the Centre in 2010, was confirmed as a candidate on 14 April by the School of Applied Sciences and Engineering, Monash University, Gippsland. She has continued her project entitled "Analysis of the contribution of immune pressure on antigenic drift of influenza A viruses", under the supervision of Dr Karen Laurie and Ms Jenny Mosse (Monash University, Gippsland).

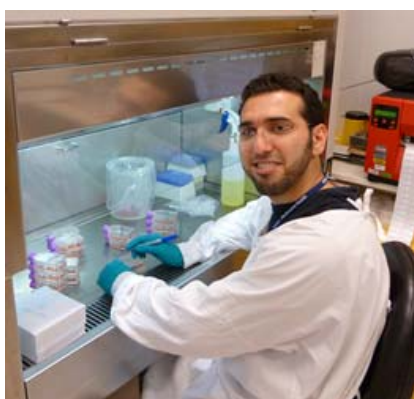
During 2011 Teagan gave two oral presentations, at the NHMRC Program on Understanding and Controlling Influenza Student Seminar Series: Influenza virology and pathogenesis session (Australian Animal Health Laboratory, Geelong, 15 July) and at the Immunology Group of Victoria Conference (Geelong, 22–23 September). She also presented a poster at the Monash University Gippsland Postgraduate Research Poster Competition, for which she was awarded first prize and gave a short presentation at the award ceremony.

Masters Students

The Centre hosted two Masters students for their practical projects from March to May.

Mr Almohanad Alkayyal (Master of Laboratory Medicine candidate, RMIT University, Melbourne; *pictured left*) received a high distinction for his project on investigation of recent changes in binding and growth characteristics of influenza A(H3N2) viruses, supervised by Dr Ian Barr.

Mr Chisha Sikazwe (Master of Infectious Diseases, University of Western Australia, Perth; *pictured right*) received a distinction for his project on genetic analysis of equine influenza viruses from the 2007 outbreak in Australia, supervised by Dr Aeron Hurt.



Ms Lucia Reh, Masters graduate from the Swiss Federal Institute of Technology (ETH) in Zurich, visited the Centre from September to December. Supervised by Dr Aeron Hurt and Mr Jeffrey Butler, she conducted a research project that involved cloning the entire genome of influenza A viruses into a specialised plasmid and characterization of the resultant viruses.



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 GISRS, as well as provide advice to the Australian Government in relation to influenza. Staff members also organise the Australian Influenza Symposium, publish peer-reviewed papers and present talks and posters in diverse forums.

Australian Influenza Symposium

The 7th Australian Influenza Symposium was hosted by the Centre and held on 6–7 October at the Bio21 Molecular Science and Biotechnology Institute in Melbourne. The organising committee was Anne Kelso, Ian Barr and Katie O'Bryan.

The Symposium was attended by 140 people, with broad representation across research, government, health care and commercial sectors, and from several different countries, including Australia, New Zealand, Hong Kong, Sri Lanka and the Philippines.

Delegates enjoyed presentations by two invited international speakers — Dr Jeffrey Partridge from the WHO Western Pacific Regional Office and Dr Ben Cowling from the School of Public Health at The University of Hong Kong. Dr Partridge spoke about the development of a strategic framework in the Western Pacific Region for surveying and responding to influenza outbreaks. Dr Cowling gave two presentations that described the response to, and transmission patterns of, the 2009 influenza pandemic in Hong Kong. He also participated in a roundtable discussion on childhood vaccination.

The majority of staff members from the Centre attended the conference. Ian Barr, Yi-Mo Deng and Aeron Hurt presented talks, and Anne Kelso and Karen Laurie chaired sessions.

The 2012 Symposium will be held in Canberra.





Engagement in WHO Activities

Event Location, Date	Centre staff involved
WHO Consultation on the Composition of Influenza Vaccines for the Northern Hemisphere 2011-2012 Geneva, Switzerland, 14–16 February	Ian Barr, Anne Kelso
7th WHO Meeting on Evaluation of Pandemic Influenza Vaccines in Clinical Trials Geneva, Switzerland, 17 February	Ian Barr, Anne Kelso
WPRO/China MOH Regional Meeting on Reviewing and Strengthening Pandemic Influenza Preparedness and Response Beijing, China, 14–16 March	Anne Kelso
5th Meeting of National Influenza Centres in the Western Pacific and South-East Asia Regions Vientiane, Lao PDR, 7–10 June	Ian Barr, Aeron Hurt, Anne Kelso (plenary session chair, poster session facilitator), Naomi Komadina, Patrick Reading
WHO Working Group on PCR Protocols for the Detection of Subtype Influenza A Viruses Geneva, Switzerland, 15–16 June	Patrick Reading
WHO Consultation on the Composition of Influenza Vaccines for the Southern Hemisphere 2012 Geneva, Switzerland, 26–28 September	Ian Barr, Anne Kelso
WHO Meeting with Delegation from Ministry of Health of Brazil Geneva, Switzerland, 29 September	Anne Kelso
WHO Meeting of Expert Group for GISRS on Surveillance for Antiviral Susceptibility Rio de Janeiro, Brazil, 11 November	Aeron Hurt (planning committee, chair)
WHO Regional Forum of Collaborating and Reference Centres on Emerging Infectious Diseases and Zoonoses Sapporo, Japan, 5–6 December	Aeron Hurt (discussion chair)
2nd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection Geneva, Switzerland, 7–9 December	Anne Kelso

Right: The designation ceremony for the new WHO Collaborating Centre for Reference and Research on Influenza in Beijing. Pictured are the Directors of the WHO Collaborating Centres in Atlanta, London, Melbourne and Tokyo; Prof Yuanji Guo (Former Director of the Chinese National Influenza Center); Dr Wenqing Zhang (Global Influenza Programme, WHO Headquarters); and staff of the new Centre.





Committees and Advisory Groups

Centre staff members served on the following governing boards, committees and advisory groups during 2011.

Ian Barr

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

Aeron Hurt

Influenza Specialist Group, *Scientific Committee*
International Society for Influenza and other Respiratory Virus Diseases (isirv) Antiviral Group, *Committee member*
National Avian Influenza Wild Bird Surveillance Program, *Steering Group*
WHO Expert Group for GISRS on surveillance of antiviral susceptibility, *Chair*

Anne Kelso

Australasian Society for Immunology Annual Scientific Meeting 2012, *Scientific Advisory Board*
Australian Influenza Vaccine Committee (Therapeutic Goods Administration)
Burnet Institute, *Research Advisory Committee*
Florey Neuroscience Institutes, *Board and Council of Governors*
Immunology and Cell Biology, *Editorial Board*
Influenza and Other Respiratory Viruses, *Editorial Board*
Influenza Surveillance Strategy Working Group (Australian Government Department of Health and Ageing)
International Immunology, *Editorial Board*
International Society for Influenza and other Respiratory Virus Diseases (isirv), *Board of Trustees*
Nossal Institute for Global Health (The University of Melbourne), *Advisory Council*
Options for the Control of Influenza VIII, Cape Town, 2013, *Scientific Committee*
Peter Doherty Institute for Infection and Immunity, *Project Control Group and Collocation Group*
Queensland University of Technology, *Council and University Research and Innovation Committee*
Telethon Institute for Child Health Research, *Board, Scientific Advisory Committee (Chair), Recruitment and Selection Committees for appointment of the new Director*
WHO/OIE/FAO H5N1 Evolution Working Group

Naomi Komadina

Global Initiative on Sharing All Influenza Data (GISAID) Development Team, GISAID Database, *Technical Committee (Head)*

Karen Laurie

2nd International Influenza Seroepidemiology Expert Meeting, Stockholm, Sweden, *Steering Committee*
Victorian Infectious Diseases Reference Laboratory, *Safety Committee*

Patrick Reading

Australasian Virology Society Meeting 2011, Kingscliff NSW, *Organising Committee*
24th International Lectin Meeting (Interlec24), Brisbane, *Scientific Organising Committee*

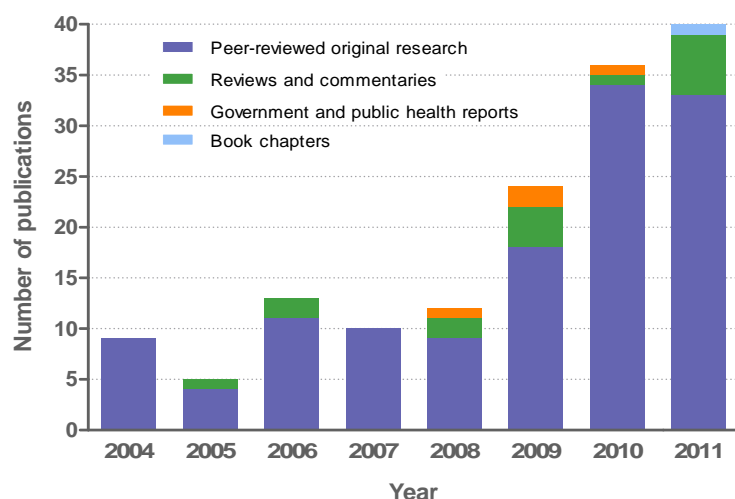


Publications and Reports

Publication Highlights

The Centre continued to build its research profile in 2011 with the publication of 39 original research papers and reviews, as well as one book chapter, the highest annual number of Centre publications to date (Figure 20).

Figure 20. Centre publications 2004-2011



Of especial note was the publication of a paper in the New England Journal of Medicine, describing the detection and analysis of the largest community-transmitted cluster of oseltamivir-resistant A(H1N1)pdm09 reported to date (see page 18).

Hurt AC, Hardie K, Wilson NJ, Deng YM, Osbourn M, Gehrig N and Kelso A. (2011) Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza. *N Engl J Med*, 365(26): 2541-2

Three papers published by Centre staff were recognised in 2011 by their respective publishers for their high quality of research published and/or number of citations (Centre authors underlined).

Immunology and Cell Biology *Runner up, Publication of the Year 2010*

Reading PC, Whitney PG, Pickett DL, Tate MD and Brooks AG. (2010) Influenza viruses differ in ability to infect macrophages and to induce a local inflammatory response following intraperitoneal injection of mice. *Immunol Cell Biol*, 88(6): 641-650.

Antiviral Research *Most cited paper 2007-2011*

Hurt AC, Selleck P, Komadina N, Shaw R, Brown L and Barr IG. (2007) Susceptibility of highly pathogenic A(H5N1) avian influenza viruses to the neuraminidase inhibitors and adamantanes. *Antiviral Res*, 73(3): 228-31.

Antiviral Research *Third most cited paper 2007-2011*

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 and Barr IG. (2009) Emergence and spread of oseltamivir-resistant A(H1N1) influenza viruses in Oceania, South East Asia and South Africa. *Antiviral Res*, 83(1): 90-3.



Centre Publications 2011

1. **Barr I** and Selleck P. (2011) Influenza - our constant companion. *Microbiol Aus*, 32(1): 2-3.
2. Brown L, Cobbin J, Middleton D, **Barr I**, Zeng W and Jackson D. (2011) Universal vaccination: is this premature with current vaccine approaches? *Influenza Other Respi Viruses*, 5(Suppl. 1): 2-53.
3. Buch J, Roomp K, Bach G, Steinbruck L, Beer M, Gregory V, **Komadina N**, Lan Y, Monne I, Smith C, Fujisaki S, Bogner P and Lengauer L. (2011) GISAID - a global initiative on sharing all influenza data. *Influenza Other Respi Viruses*, 5(Suppl. 1): 416-424.
4. Crispe E, Finlaison DS, **Hurt AC** and Kirkland PD. (2011) Infection of dogs with equine influenza virus: evidence for transmission from horses during the Australian outbreak. *Aust Vet J*, 89 Suppl 1: 27-8.
5. **Deng YM**, **Caldwell N** and **Barr IG**. (2011) Rapid detection and subtyping of human influenza A viruses and reassortants by pyrosequencing. *PLoS One*, 6(8): e23400.
6. **Deng YM**, **Caldwell N**, **Hurt A**, Shaw T, **Kelso A**, Chidlow G, Williams S, Smith D and **Barr I**. (2011) A comparison of pyrosequencing and neuraminidase inhibition assays for the detection of oseltamivir-resistant pandemic influenza A (H1N1) 2009 viruses. *Antiviral Res*, 90(1): 87-91.
7. Dowse GK and **Barr I**. (2011) What serosurveillance studies tell us about the 2009 influenza pandemic. *Microbiol Aus*, 32(1): 18-21.
8. Dowse GK, Smith DW, Kelly H, **Barr I**, **Laurie KL**, Jones AR, Keil AD and Effler P. (2011) Incidence of pandemic (H1N1) 2009 influenza infection in children and pregnant women during the 2009 influenza season in Western Australia - a seroprevalence study. *Med J Aust*, 194(2): 68-72.
9. Eisen DP, Marshall C, Dean MM, Sasadeusz J, Richards M, Buising K, Cheng A, Johnson PD, **Barr IG** and McBryde ES. (2011) No association between mannose-binding lectin deficiency and H1N1 2009 infection observed during the first season of this novel pandemic influenza virus. *Hum Immunol*, 72(11): 1091-4.
10. Haller W, Buttery J, **Laurie K**, Beyerle K, Hardikar W and Alex G. (2011) Immune response to pandemic H1N1 2009 influenza a vaccination in pediatric liver transplant recipients. *Liver Transpl*, 17(8): 914-20.
11. **Hurt A**. (2011) Antiviral drug resistance in seasonal and pandemic influenza. *Microbiol Aus*, 32(1): 26-28.
12. **Hurt A**, **Deng Y**, **Ernest J**, **Caldwell N**, **Leang L**, **Iannello P**, **Komadina N**, **Shaw R**, Smith D, Dwyer D, Tramontana A, Lin R, Freeman K, **Kelso A** and **Barr I**. (2011) Oseltamivir-resistant influenza viruses circulating during the first year of the influenza A(H1N1)2009 pandemic in the Asia-Pacific region, March 2009 to March 2010. *Euro Surveill*, 16(3): pii: 19770.
13. **Hurt AC**, Hardie K, Wilson NJ, **Deng YM**, Osbourn M, Gehrig N and **Kelso A**. (2011) Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza. *N Engl J Med*, 365(26): 2541-2.
14. **Hurt AC**, Lee RT, **Leang SK**, Cui L, **Deng YM**, Phuah SP, **Caldwell N**, Freeman K, **Komadina N**, Smith D, Speers D, **Kelso A**, Lin RT, Maurer-Stroh S and **Barr IG**. (2011) Increased detection in Australia and Singapore of a novel influenza A(H1N1)2009 variant with reduced oseltamivir and zanamivir sensitivity due to a S247N neuraminidase mutation. *Euro Surveill*, 16(23): pii: 19884.
15. Kelly H, **Peck HA**, **Laurie KL**, Wu P, Nishiura H and Cowling BJ. (2011) The age-specific cumulative incidence of infection with pandemic influenza H1N1 2009 was similar in various countries prior to vaccination. *PLoS One*, 6(8): e21828.
16. **Kelso A**. (2011) *Influenza, in Health*, Sykes, H, Editor. 2011, Future Leaders: Sydney, Australia. pp.45-64.
17. Lee VJ, Chen MI, Yap J, Ong J, Lim WY, Lin RT, **Barr I**, Ong JB, Mak TM, Goh LG, Leo YS, Kelly PM and Cook AR. (2011) Comparability of different methods for estimating influenza infection rates over a single epidemic wave. *Am J Epidemiol*, 174(4): 468-78.
18. Lim WY, Chen CH, Ma Y, Chen MI, Lee VJ, Cook AR, Tan LW, Flores Tabo N, Jr., **Barr I**, Cui L, Lin RT, Leo YS and Chia KS. (2011) Risk factors for pandemic (H1N1) 2009 seroconversion among adults, Singapore, 2009. *Emerg Infect Dis*, 17(8): 1455-62.
19. Londrigan SL, Turville SG, Tate MD, **Deng YM**, Brooks AG and **Reading PC**. (2011) N-linked glycosylation facilitates sialic acid-independent attachment and entry of influenza A viruses into cells expressing DC-SIGN or L-SIGN. *J Virol*, 85(6): 2990-3000.
20. Mardani J, Calder L, **Laurie K**, **Barr I**, **Kelso A** and Jones N. (2011) Limited novel influenza A (H1N1) 09 infection in travelling high-school tour group. *Influenza Other Respi Viruses*, 5(1): 47-51.
21. Marshall C, **Kelso A**, McBryde E, **Barr IG**, Eisen DP, Sasadeusz J, Buising K, Cheng AC, Johnson P and Richards M. (2011) Pandemic (H1N1) 2009 risk for frontline health care workers. *Emerg Infect Dis*, 17(6): 1000-6.



Centre Publications 2011 (continued)

22. McCaw JM, Arinaminpathy N, **Hurt AC**, McVernon J and McLean AR. (2011) A mathematical framework for estimating pathogen transmission fitness and inoculum size using data from a competitive mixtures animal model. *PLoS Comput Biol*, 7(4): e1002026.
23. McVernon J, **Laurie K**, **Barr I**, **Kelso A**, Skeljo M and Nolan T. (2011) Absence of cross-reactive antibodies to influenza A (H1N1)2009 before and after vaccination with 2009 Southern Hemisphere seasonal trivalent influenza vaccine in children aged 6 months-9 years: a prospective study. *Influenza Other Respi Viruses*, 5(1): 7-11.
24. McVernon J, **Laurie K**, Nolan T, Owen R, Irving D, Capper H, Hyland C, Faddy H, **Carolann L**, **Barr I** and **Kelso A**. (2011) Seroprevalence 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. *Influenza Other Respi Viruses*, 5(Suppl. 1): 175-178.
25. **Peck H**, **Dodin J**, **Baas C**, **Shaw R**, Lenz-Bauer C, Trusheim H, Roth B, Blayer S, Tsai T and **Barr I**. (2011) Evaluation of growth, genetic, and antigenic characteristics of pandemic H1N1 viruses isolated and passaged in qualified MDCK suspension cells (MDCK33016PF) and embryonated hen eggs. *Influenza Other Respi Viruses*, 5(Suppl. 1): 328-394.
26. Rosewell A, Dagina R, Murhekar M, Ropa B, Posanai E, Dutta S, **Barr I**, Mola G, Zwi A and Macintyre CR. (2011) Concurrent influenza and shigellosis outbreaks, Papua New Guinea, 2009. *Emerg Infect Dis*, 17(4): 756-758.
27. Roth B, **Peck H**, Schwarz K, **Dodin J**, Horn V, Trusheim H, Blayer S, Tsai T and **Barr I**. (2011) Co-infecting viruses in pandemic H1N1 and seasonal influenza positive human respiratory samples. *Influenza Other Respi Viruses*, 5(Suppl. 1): 416-424.
28. Short KR, Diavatopoulos DA, Thornton R, Pedersen J, Strugnell RA, Wise AK, **Reading PC** and Wijburg OL. (2011) Influenza virus induces bacterial and nonbacterial otitis media. *J Infect Dis*, 204(12): 1857-65.
29. Tate MD, Brooks AG and **Reading PC**. (2011) Correlation between sialic acid expression and infection of murine macrophages by different strains of influenza virus. *Microbes Infect*, 13(2): 202-7.
30. Tate MD, Brooks AG and **Reading PC**. (2011) Receptor specificity of the influenza virus hemagglutinin modulates sensitivity to soluble collectins of the innate immune system and virulence in mice. *Virology*, 413(1):128-38.
31. Tate MD, Brooks AG and **Reading PC**. (2011) Specific sites of N-linked glycosylation on the hemagglutinin of H1N1 subtype influenza A virus determine sensitivity to inhibitors of the innate immune system and virulence in mice. *J Immunol*, 187(4): 1884-94.
32. Tate MD, Brooks AG and **Reading PC**. (2011) Inhibition of lectin-mediated innate host defences in vivo modulates disease severity during influenza virus infection. *Immunol Cell Biol*, 89(3): 482-91.
33. Tate MD, Ioannidis LJ, Croker B, Brown LE, Brooks AG and **Reading PC**. (2011) The role of neutrophils during mild and severe influenza virus infections of mice. *PLoS One*, 6(3): e17618.
34. Tate MD, Job ER, Brooks AG and **Reading PC**. (2011) Glycosylation of the hemagglutinin modulates the sensitivity of H3N2 influenza viruses to innate proteins in airway secretions and virulence in mice. *Virology*, 413(1): 84-92.
35. Tate MD, Schilter HC, Brooks AG and **Reading PC**. (2011) Responses of mouse airway epithelial cells and alveolar macrophages to virulent and avirulent strains of influenza a virus. *Viral Immunol*, 24(2): 77-88.
36. Teo J, Di Pietro P, San Biagio F, Capozzoli M, **Deng YM**, **Barr I**, **Caldwell N**, Ong KL, Sato M, Tan R and Lin R. (2011) VereFlu: an integrated multiplex RT-PCR and microarray assay for rapid detection and identification of human influenza A and B viruses using lab-on-chip technology. *Arch Virol*, 156(8): 1371-8.
37. Tong SY, Dakh F, **Hurt AC**, **Deng YM**, Freeman K, Fagan PK, **Barr IG** and Giffard PM. (2011) Rapid detection of the H275Y oseltamivir resistance mutation in influenza A/H1N1 2009 by single base pair RT-PCR and high-resolution melting. *PLoS One*, 6(6): e21446.
38. Trauer JM, **Laurie KL**, McDonnell J, **Kelso A** and Markey PG. (2011) Differential effects of pandemic (H1N1) 2009 on remote and indigenous groups, Northern Territory, Australia, 2009. *Emerg Infect Dis*, 17(9): 1615-23.
39. Valkenburg SA, **Laurie K**, **Kelso A**, Turner SJ, Doherty PC and Kedzierska K. (2011) T-cell immunity against the A(H1N1) 2009 pandemic virus. *Microbiol Aus*, 32(1): 22-25.
40. Wong FY and **Deng Y**. (2011) Pandemic H1N1 2009 influenza in pigs in Australia. *Microbiol Aus*, 32(1): 39-41.



Oral Presentations

Centre staff members gave oral presentations at many different events during 2011, including national and international conferences, WHO meetings, government advisory meetings, educational lectures and research seminars.

Event Location, Date	Centre Staff Member, <i>Presentation Title</i>
National Institute for Biological Standards and Control (NIBSC) London, UK, 1 February	Ian Barr: <i>Melbourne WHO CC; Analysis of influenza viruses from September 2010 - January 2011</i>
University of Melbourne Immunology Summer Camp 2011 for Selected Students from Tsinghua University, Beijing Melbourne, 2 February	Anne Kelso: <i>Immunology and the WHO's Global Influenza Programme.</i>
Influenza Specialist Group Annual Scientific Meeting Melbourne, 6–7 February	Aeron Hurt: <i>What's new in antivirals for influenza.</i> Ian Barr: <i>Flu epidemiology update.</i>
International Meeting on Influenza Seroprevalence Studies Ottawa, Canada, 9–10 February	Karen Laurie: <i>Early serological studies for influenza.</i>
Mini-symposium on Influenza Surveillance and Vaccine Selection Bioinformatics Institute, Singapore, 21 February	Ian Barr: <i>How the WHO influenza vaccine formulation recommendation is made.</i>
Peter Doherty Institute for Infection and Immunity Seminar Series Melbourne, 24 February	Anne Kelso: <i>The WHO Collaborating Centre for Influenza as a partner in the Doherty Institute.</i>
CDC Laboratory Management Course for Influenza Johannesburg, South Africa, 28 February – 4 March	Patrick Reading: <i>WHO Requirements for becoming a NIC Laboratory.</i> Patrick Reading: <i>Basic cell culture laboratory requirements and methods for respiratory viruses.</i> Patrick Reading: <i>EQA programs for influenza PCR.</i> Patrick Reading: <i>An introduction to FluNet.</i>
WPRO/China MOH Regional Meeting on Reviewing and Strengthening Pandemic Influenza Preparedness and Response Beijing, China, 14–16 March	Anne Kelso: <i>Epidemiology of the pandemic in Australia.</i>
Communicable Disease Control Conference Canberra, 4–6 April	Heidi Peck: <i>The cumulative incidence of pandemic influenza infection.</i>
Monash Infectious Diseases Society Seminar Series Melbourne, 15 April	Anne Kelso: <i>Post-pandemic influenza: has anything changed?</i>
Queensland Health Brisbane, 20 April	Anne Kelso: <i>How diagnostic and reference laboratories contribute to global influenza surveillance and vaccine development.</i>
3rd Australia-China Biomedical Research Conference Melbourne, 28–30 April	Anne Kelso: <i>Influenza in 2011: what has happened to the H1N1 pandemic virus?</i>
Public Lecture, International Day of Immunology Melbourne, 29 April	Anne Kelso: <i>The continuing challenge of influenza.</i>
Lecture to 3rd year university students, University of Melbourne Breadth Subject "Global health, security and sustainability" Melbourne, 11 May	Anne Kelso: <i>Influenza.</i>



Oral Presentations (continued)

Event Location, Date	Centre Staff Member, <i>Presentation Title</i>
IFCC-WorldLab-EuroMedLab Berlin 2011 (21st International Congress of Clinical Chemistry and Laboratory Medicine) Berlin, Germany, 15–19 May	Anne Kelso: <i>The 2009 influenza pandemic - The experience in the southern hemisphere.</i>
Keystone Symposia Conference: Pathogenesis of Influenza: Virus-Host Interactions Hong Kong, 23–28 May	Patrick Reading: <i>Glycosylation as a target for recognition of influenza virus by the innate immune system.</i>
5th Meeting of National Influenza Centres in the Western Pacific and South-East Asia Regions Vientiane, Lao PDR, 7–10 June	Aeron Hurt: <i>What should be taken into consideration when establishing antiviral resistance surveillance?</i> Anne Kelso and Patrick Reading: <i>A Collaborating Centre perspective on the three Cs: collaboration, communication and capacity building.</i>
Neuraminidase Inhibitor Susceptibility Network Meeting London, UK, 15–22 June	Aeron Hurt: <i>Antiviral surveillance in the Asia-Pacific region; The NISN virus reference panel.</i>
Visit to the Centre by a Delegation from the Singapore Ministry of Health Melbourne, 15 June	Aeron Hurt: <i>Antiviral surveillance in the Asia-Pacific region.</i> Anne Kelso: <i>Overview of the WHO Collaborating Centre for Reference and Research on Influenza.</i> Karen Laurie: <i>A(H1N1)pdm09 serological studies at the WHO CC for Reference and Research on Influenza</i>
WHO Working Group on PCR Protocols for the Detection of Subtype Influenza A Viruses Geneva, Switzerland, 15–16 June	Patrick Reading: <i>Influenza surveillance at WHO CC.</i> Patrick Reading: <i>A regional perspective on influenza surveillance.</i>
Australian Society for Microbiology Annual Scientific Meeting Hobart, 4–8 July	Ian Barr: <i>What's happened since the 2009 influenza pandemic?</i>
NHMRC Program on Understanding and Controlling Influenza Student Seminar Series: Influenza virology and pathogenesis session Australian Animal Health Laboratory, Geelong, 15 July	Teagan Guarnaccia: <i>Does the A(H1N1)pdm virus drift under immune pressure in the ferret model?</i>
National Institute for Biological Standards and Control (NIBSC) London, UK, 19 July	Ian Barr: <i>Melbourne WHO CC: Analysis of influenza viruses from January 2011 - July 2011</i>
Melbourne School of Population Health Seminar Series, The University of Melbourne Melbourne, 20 July	Anne Kelso: <i>Influenza pandemics, policy and politics.</i>
4 th Sino-Australian Meeting on Infectious Diseases Melbourne, 25 July	Anne Kelso: <i>Post-pandemic influenza: what has happened since the last Sino-Australian Meeting in 2009?</i>
24th International Lectin Meeting (Interlec24) Brisbane, 27–29 July	Patrick Reading: <i>How mammalian lectins limit influenza virus infection.</i>
Immunology Group of Victoria Conference Geelong, 22–23 September	Teagan Guarnaccia: <i>Does the A(H1N1)pdm virus drift under immune pressure in the ferret model?</i>
Sub-Regional Workshop for Influenza Surveillance in the Pacific Suva, Fiji, 26–29 September	Patrick Reading: <i>The role of reference laboratories in influenza surveillance in Pacific Island Countries and Territories.</i> Patrick Reading: <i>Specimen collection, transport and testing.</i>



Oral Presentations (continued)

Event Location, Date	Centre Staff Member, <i>Presentation Title</i>
Vietnam Antiviral Resistance Surveillance Workshop Hanoi, Vietnam, 26–30 September	<p>Aeron Hurt: <i>Why is antiviral testing necessary?</i></p> <p>Aeron Hurt: <i>What should be considered when establishing antiviral resistance testing?</i></p> <p>Aeron Hurt: <i>Neuraminidase inhibition assays.</i></p> <p>Aeron Hurt: <i>Pyrosequencing for the detection of antiviral resistance mutations.</i></p> <p>Aeron Hurt: <i>What's new in influenza antivirals?</i></p> <p>Aeron Hurt: <i>Data storage and quality control of neuraminidase.</i></p>
WHO Meeting with a Delegation from the Ministry of Health of Brazil Geneva, Switzerland, 29 September	Anne Kelso: <i>WHO Collaborating Centre for Reference and Research on Influenza at VIDRL: a southern hemisphere perspective.</i>
7th Australian Influenza Symposium Melbourne, 6–7 October	<p>Aeron Hurt: <i>Widespread community transmission of oseltamivir-resistant A(H1N1)2009 influenza.</i></p> <p>Ian Barr: <i>Devising a pandemic severity scale.</i></p> <p>Yi-Mo Deng: <i>Pandemic A(H1N1)2009 influenza in Australian swine.</i></p>
Phylogenetics for Infectious Diseases Workshop Singapore, 10–14 October	Yi-Mo Deng: <i>Pyrosequencing and phylogenetics for influenza surveillance.</i>
Friedrich Loeffler Institute Greifswald, Germany, 14–15 October	Ian Barr: <i>WHO CC for Reference and Research in Influenza – Melbourne, Australia.</i>
Careers Development Workshop, Burnet Student Symposium Melbourne, 14 October	Patrick Reading: <i>Developing a career that combines research and public health interests - a balancing act.</i>
Novartis CRADA technical meeting Novartis FCC facility, Holly Springs, USA, 20 October	Heidi Peck: <i>NVD-WHO CC Melbourne cell culture CRADA: Technical Review.</i>
Laboratory meeting at the Department of Microbiology and Immunology, The University of Melbourne Melbourne, 26 October	Karen Laurie: <i>Serological surveys of human population responses to the H1N1 2009 virus.</i>
National Health and Medical Research Council (NHMRC) Program on Understanding and Controlling Influenza Program Retreat Melbourne, 3–4 November 2011	<p>Anne Kelso: <i>A perspective from the WHO Collaborating Centre for Influenza.</i></p> <p>Karen Laurie: <i>Serological surveys of human population responses to the H1N1 2009 virus.</i></p> <p>Patrick Reading: <i>Recognition of influenza virus by innate immune defences - modulating early inflammation and disease.</i></p> <p>Patrick Reading: <i>How early immune events shape CD8 T cell responses.</i></p> <p>Teagan Guarnaccia: <i>Antigenic drift in the ferret model.</i></p>



Oral Presentations (continued)

Event Location, Date	Centre Staff Member, <i>Presentation Title</i>
Influenza Antivirals: Efficacy and Resistance Rio de Janeiro, Brazil, 8–10 November	Aeron Hurt: <i>Widespread community transmission of oseltamivir-resistant A(H1N1)2009 influenza.</i> Aeron Hurt: <i>ISIRV-AVG virus reference panel.</i>
WHO Meeting of Expert Group for GISRS on Surveillance for Antiviral Susceptibility Rio de Janeiro, Brazil, 11 November	Aeron Hurt: <i>Overview of progress made by expert group.</i> Aeron Hurt: <i>Current GISRS capacity for antiviral surveillance.</i> Aeron Hurt: <i>Priority mutations for NIC screening.</i> Aeron Hurt: <i>NIC surveillance for adamantane susceptibility.</i> Aeron Hurt: <i>Pros and cons of genotypic assays and suggestions to NICs.</i>
5th International Congress of the Asia Pacific Society of Infection Control Melbourne, 8–11 November	Anne Kelso: <i>World Health Organisation Global Influenza Surveillance and Response System (GISRS) – regional analysis of human influenza viruses.</i>
Meeting of the Influenza Surveillance Strategy Working Group, Department of Health and Ageing Canberra, 21–22 November	Anne Kelso and Sheena Sullivan: <i>Regional influenza surveillance in 2011 at the WHO Collaborating Centre.</i>
Visit to VICNISS by a Delegation from the Health Department of Sichuan Province, China Melbourne, 28 November 2011	Anne Kelso: <i>WHO Collaborating Centre for Reference and Research on Influenza.</i>
Second International Influenza Seroepidemiology Expert Meeting Stockholm, Sweden, 4–8 December	Karen Laurie: <i>Influenza serological studies to inform public health action: best practices to optimise timing, quality and reporting.</i>
Australasian Virology Society Meeting 2011 Kingscliff, NSW, 4–8 December	Yi-Mo Deng: <i>Genetic analysis of oseltamivir-resistant A(H1N1) 2009 pandemic influenza viruses from a community outbreak in Newcastle, Australia.</i> Patrick Reading: <i>Recognition of influenza viruses by cells and proteins of the innate immune system.</i>
CSL Limited Pfizer Animal Ethics Committee Melbourne, 5 December	Karen Laurie: <i>Using the ferret model in influenza research - key outcomes.</i>
2nd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection Geneva, Switzerland, 7–9 December	Anne Kelso: <i>Improving quality and timeliness of surveillance for vaccine virus selection.</i>



Poster Presentations 2011

Centre staff contributed to the authorship and presentation of several posters at conferences and meetings in 2011. Teagan Guarnaccia was awarded first prize in the Monash University Gippsland Postgraduate Research Poster Competition (marked with asterisk)

Event Location, Date	Poster Title and Authors (Centre staff highlighted in bold, presenting author underlined)
Keystone Symposia Conference: Pathogenesis of Influenza: Virus-Host Interactions Hong Kong, 23–28 May	Quantitation of mRNA cytokine levels in ferrets following influenza infection. <u>Carolán LA</u> , Rockman S, Hurt A , Kelso A , Barr IG and Laurie KL Specific sites of N-linked glycosylation on the hemagglutinin of H1N1 subtype influenza A virus determine sensitivity to inhibitors of the innate immune system and virulence in mice. Tate MD, Brooks AG, <u>Reading PC</u>
4th Sino-Australian Meeting on Infectious Diseases Melbourne, 25 July	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 Quantitation of mRNA cytokine levels in ferrets following influenza infection. Carolán LA , Rockman S, Hurt A , Kelso A , Barr IG and Laurie KL Genetic analysis of two influenza A(H1) swine viruses isolated from humans in Thailand and the Philippines. Komadina N , Roque V, Thawatsupha P, Rimando-Magalong J, Waicharoen S, Bomasang E, Sawanpanyalert P, Rivera M, Iannello P , Hurt AC and Barr IG Does the A(H1N1)pdm virus drift under immune pressure in the ferret model? Guarnaccia T , Carolán L , Barr I , Kelso A , Mosse J, Laurie K
Fourth ESWI Influenza Conference Malta, 11–13 September	Detection of a novel A(H1N1)2009 influenza variant with reduced oseltamivir and zanamivir sensitivity. Hurt AC , Lee RTC, Leang SK , Cui L, Deng YM , Phuah SP, Caldwell N , Freeman K, Komadina N , Smith D, Speers D, Kelso A , Lin RTP, Maurer-Stroh S, Barr IG Quantitation of cytokine mRNA levels in ferrets following influenza infection. Carolán LA , Rockman S, Hurt A , Kelso A , Barr IG and <u>Laurie KL</u> Investigations of the seroprevalence status of Australians against pandemic and seasonal influenza from 2008-11. <u>Laurie KL</u> , McVernon J, Carolán LA , Nolan T, Owen R, Irving D, Capper H, Hyland C, Faddy H, Lambert S, Barr IG , Kelso A
Monash University Gippsland Postgraduate Research Poster Competition Gippsland, 13 September	*Does the A(H1N1)pdm virus drift under immune pressure in the ferret model? <u>Guarnaccia T</u> , Carolán L , Barr I , Kelso A , Mosse J, Laurie K
Neuraminidase Inhibitor Susceptibility Network Meeting Rio de Janeiro, Brazil, 8–10 November	The GISAID EpiFlu Influenza Database-Tool for sharing and analysing influenza data. Brytting M, Pohlmann A, Bush J, Beer M, Gregory V, Setaiwati V, Lan Y, Monne I, Smith C, Fujisaki S, Komadina N , Bogner P
Australasian Virology Society Meeting 2011 Kingscliff, NSW, 4–8 December	Rapid detection and subtyping of human influenza A viruses and reassortants by pyrosequencing. <u>Caldwell N</u> , Deng YM , Barr IG
WHO Regional Forum of Collaborating and Reference Centres on Emerging Infectious Diseases and Zoonoses Sapporo, Japan, 5–6 December	WHO Collaborating Centre for Influenza, Melbourne – its role, training and research. <u>Hurt AC</u>



Other Conference and Meeting Participation

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

Event, Location, Date	Centre staff involvement
Influenza Specialist Group Annual Scientific Meeting Melbourne, 6–7 February	Anne Kelso
One Health Congress Melbourne, 14–16 February	Aeron Hurt
Communicable Disease Control Conference Canberra, 4–6 April	Ian Barr
4 th Sino-Australian Meeting on Infectious Diseases Melbourne 25 July	Anne Kelso (session chair), Pina Iannello, Karen Laurie, Lumin Xue
GISAID Symposium—Breaking through influenza information walls Bonn, Germany, 11–12 October	Ian Barr, Naomi Komadina (Chair, GISAID Database Technical Committee (DTC) Annual Meeting)
US Department of Health and Human Services and CDC Influenza Risk Assessment Algorithm Tool Meeting Washington DC, USA, 18–19 October	Ian Barr
Australasian Virology Society Meeting 2011 Kingscliff, NSW, 4–8 December	Ian Barr, Patrick Reading (organising committee)
Second International Influenza Seroepidemiology Expert Meeting Stockholm, Sweden, 4–8 December	Karen Laurie (steering committee)
Australasian Society for Immunology Annual Meeting Adelaide, 11–15 December	Anne Kelso (plenary session chair)



Community Engagement

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

Anne Kelso

"Your Body at War", The Voice (newspaper for The University of Melbourne), feature article interview, April edition, <http://www.voice.unimelb.edu.au/volume-7/number-4/your-body-war>;

Einstein A Go-Go, 3RRR radio, radio interview, 17 April

ABC Radio News, radio interview, 28 April

International Day of Immunology in Melbourne, public seminar presentation, 29 April

"Flu shot may prevent pre-term births", ABC Science Online, interview 1 June

Medical Observer, online video interview, 22 July

Ian Barr:

6:30 with George Negus, Channel 10 television 27 April

"Scientists find mutant swine flu strain", ABC TV News, 14 June

The Australian, newspaper interview, 3 September

Centre staff wrote the following commentaries for the website *The Conversation*, an online forum from the university and research sector:

Anne Kelso

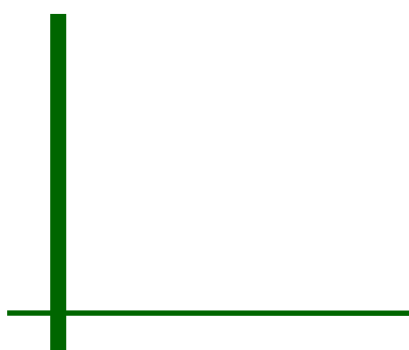
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| 4 May | What we learnt from the 2009 swine-flu pandemic"
http://theconversation.edu.au/what-we-learnt-from-the-2009-swine-flu-pandemic-948 |
| 18 September | New theory on why CSL's flu vaccine caused febrile convulsions in children"
http://theconversation.edu.au/new-theory-on-why-csls-flu-vaccine-caused-febrile-convulsions-in-children-3426 |

Ian Barr

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| 3 August | Don't hold your breath for universal pandemic flu vaccine"
http://theconversation.edu.au/dont-hold-your-breath-for-universal-pandemic-flu-vaccine-2595 |
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Aeron Hurt

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| 30 August | Marvellous mutants: how nimble flu viruses outsmart drugs"
http://theconversation.edu.au/marvellous-mutants-how-nimble-flu-viruses-outsmart-drugs-1981 ; |
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Visitors to the Centre

The Centre welcomed the following visitors during 2011:

- 3 February Dr Annette Fox, Immunologist, Oxford University Clinical Research Unit, Hanoi, Vietnam, *presented a seminar, met with staff at the Centre and collaborators from the School of Population Health at The University of Melbourne*
- 15 February Dr Takeshi Kasai, Director, Health Security and Emergencies, WHO Regional Office for the Western Pacific (WPRO), Manila, Philippines
- 15 February Dr Gyanendra Gongal, Scientist, WHO Regional Office for South-East Asia (SEARO), New Delhi, India
- 15 June Delegation from the Singapore Ministry of Health:
Prof Raymond Lin (Head of National Public Health Laboratory)
Prof Chew Suok Kai (Deputy Director of Medical Services (Public Health Group))
Mr Chua Soy Tee (Deputy Director, Emergency Preparedness and Response Division)
Ms Lee Chime (Assistant Director, Emergency Preparedness and Response Division)
- 18 October Prof Chris Baggoey, Chief Medical Officer, Chair Australian Government Advisory Committee, Department of Health and Ageing
- 17 November Dr Theodore Tsai, Senior VP, Scientific Affairs, Novartis Vaccines, Boston, USA, *presented a seminar*
- 14 December Delegation from China CDC:
Dr Guizhen Wu (Director, Laboratory Management Office)
Prof Mifang Liang (Professor, National Institute for Viral Disease Control and Prevention)
Dr Chihong Zhao (Deputy Director, Laboratory Management Office)
Dr Yan Liu (Office of Laboratory Management)



Visit from Singapore Ministry of Health delegation: from L to R: Ian Barr, Karen Laurie, Ms Lee Chime, Mr Chua Soy Tee, Prof Chew Suok Kai, Prof Raymond Lin, Anne Kelso, Aeron Hurt.



Dr Takeshi Kasai (left) and Dr Gyanendra Gongal (right) with Aeron Hurt (centre)

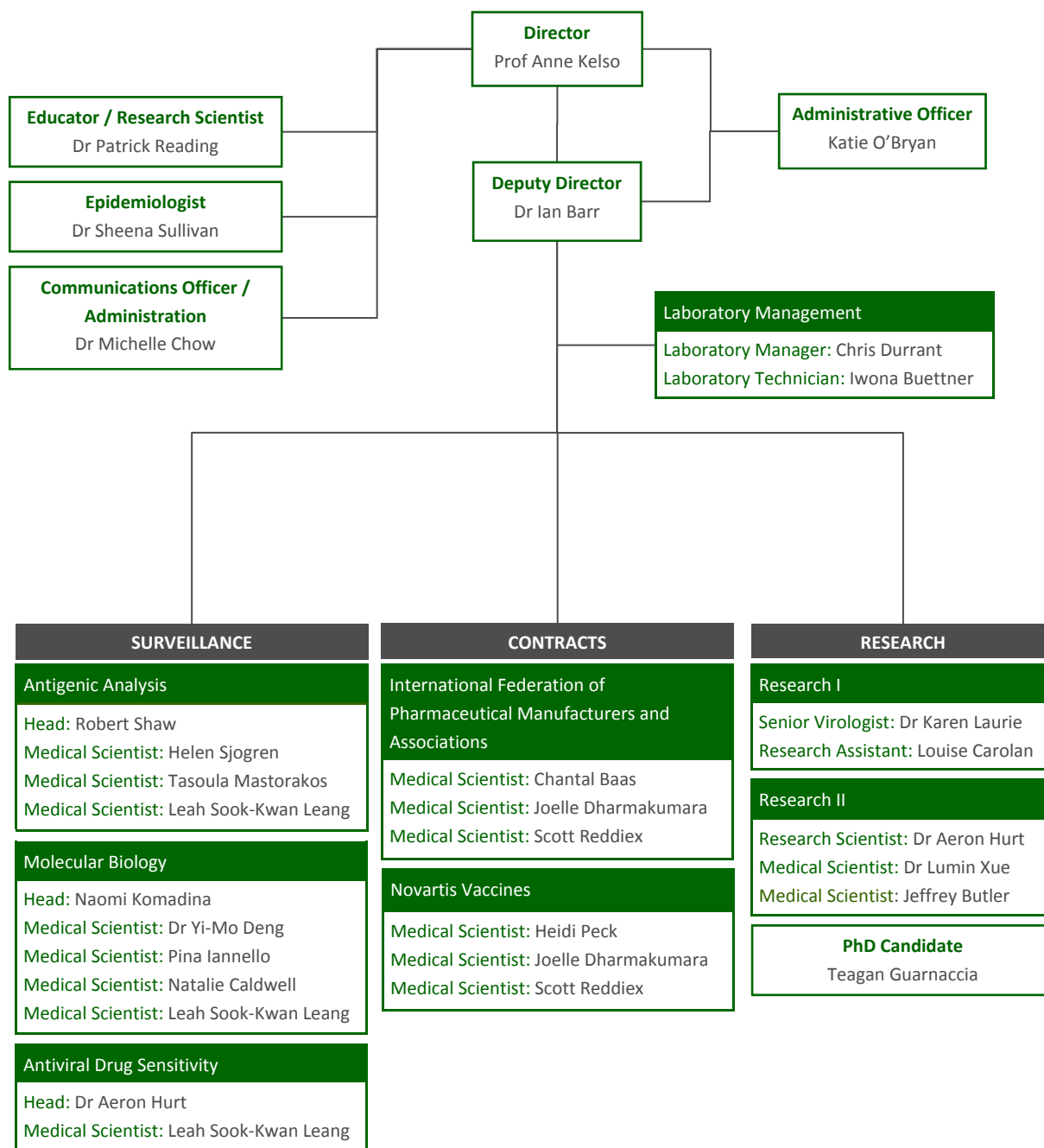
Website

Following a complete redesign during 2010, the new Centre website was launched in March 2011. NICs, government bodies and Centre collaborators were notified of the new website and responded with very positive feedback. During the period from March to December 2011, the website was viewed by 3879 unique visitors from 98 different countries. The vast majority of visits to the website came from Australia, followed by the United States.





Management and Staff



Staff Changes 2011

Dr Lumin Xue and Mr Jeffrey Butler joined the Centre as Medical Scientists in June to undertake research related to human antibody responses to influenza and antiviral drug sensitivity.

Mr Scott Reddiex joined the Centre in September to fill the role left by Mrs Joelle Dharmakumara who went on maternity leave in May. Mr Reddiex completed his BBiomedSci(Hons) project at the Centre in 2010.

Dr Sheena Sullivan was appointed as the Epidemiologist for the Centre in October.