

7th Australian Influenza Symposium

6-7 October 2011

Bio21 Molecular Science and Biotechnology Institute, Melbourne, Australia

Hosted by the
WHO Collaborating Centre for Reference and Research on Influenza, VIDRL

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Therapeutic Goods Administration
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Australian Government Department of Health and Ageing

Welcome

The WHO Collaborating Centre for Reference and Research on Influenza and the Therapeutic Goods Administration are delighted to welcome you to the 7th Australian Influenza Symposium.

We are very grateful for the ongoing support of the Department of Health and Ageing and the Therapeutic Goods Administration for this meeting.

The Organising Committee

WHO Collaborating Centre for Reference and Research on Influenza

- Dr Ian Barr
- Professor Anne Kelso
- Katie O'Bryan



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Day 1 Thurs 6 October		9:00am Opening and welcome	Ian Barr and Gary Grohmann
	Plenary Session 1	Chair: Anne Kelso, WHOCC	
9:05am		Peter Doherty	One world and pandemics
9:35am		Ben Cowling	Reflections on the 2009 pandemic H1N1 in Hong Kong
10:05am		Jeff Partridge	Manila Regional perspective on 2009 pandemic & ongoing influenza monitoring
10:35am		Gary Lum	Review of the Australian Health Sector Response to Pandemic (H1N1) 2009: Lessons Identified
11:05am		Morning Tea	
	Plenary Session 2	Chair: Jodie McVernon, School of Population Health, The University of Melbourne	
11:30am		Lance Jennings	Reviewing the deaths from pandemic influenza (H1N1) in New Zealand in 2009
11:55am		David Speers	Grave concerns about influenza - Respiratory virus findings from mortuary samples in WA
12:20pm		Allen Cheng	Severe influenza: epidemiology and influenza vaccine effectiveness in the 2011 season
12:45pm		Ian Barr	Devising a pandemic severity scale
1.10pm		General Discussion	
1:15pm		Lunch	
	Plenary Session 3	Chair: Simone Warner, Department of Primary Industries	
2:00pm		Peter Daniels	Veterinary surveillance/programs for influenza post the 2009 swine pandemic
2:25 pm		Frank Wong	Recent H5N1 activity and diversification in commercial poultry in the Southeast Asian region
2:45pm		Tiggy Grillo	National Avian Influenza Wild Bird Surveillance Program (Australia)
3:05 pm		Edla Arzey	The Influenza A/H10N7 in chickens and poultry abattoir workers in Australia.
3:25pm		Yi Mo Deng	Pandemic A(H1N1)2009 influenza in Australian swine
3:45pm		Afternoon Tea	
	Workshop 1 - Clinical & Research	Chairs: Karen Laurie, WHOCC & Julie McAuley, The University of Melbourne	
4:15pm		Geoff Higgins	Respiratory virus testing in the pandemic: which sample is best?
4:30pm		Emma Job	Examining the effect of additional glycosylation sites on the head of H1N1 2009 pandemic viruses
4:45pm		Katherine Kedzierska	Oseltamivir and influenza: inflammation-induced morbidity versus generation of anti-viral T cell immunity
5:00pm		Peter Mohr	A pandemic H1N1/09 virus with H274Y and D198G mutations emerges after <i>in vitro</i> passage in a combination of oseltamivir and zanamivir
5:15pm		Jeff Butler	Rapid mammalian adaption of H5N1 avian influenza virus following infection in ferrets
5:30pm		Joanna Cobbin	Viruses selected through classical reassortment have phenotypic characteristics directed by PB1 composition that impact on vaccine yields
5:45pm		Germain Fernando	Nanopatch targeted delivery of both influenza vaccine and adjuvant to skin synergistically drives enhanced antibody responses.
6:30pm		Dinner at the Leveson Hotel, North Melbourne	

Day 2 Fri 7 October		Chair: Robert Booy, NCIRS,CHW, Sydney	
8:00 am	Plenary Session 4	Mark Simmerman	Improving Influenza Control with Quadrivalent Influenza Vaccines
8:25am		Peter Richmond	Seasonal vaccine studies on the protection of seasonal vaccines against pandemic*
8:50am		Eugene Maraskovsky	Scientific investigations into febrile reactions observed in the paediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine
9:15am		Aeron Hurt	Widespread community transmission of oseltamivir-resistant A(H1N1)2009 influenza
9:35am		Simon Tucker	The discovery and development of the next generation influenza neuraminidase inhibitors: long-acting neuraminidase inhibitors for once-only treatment of influenza
10:00am		Morning Tea	
		Chairs: David Muscatello CER, NSW DoH and Peter Markey, CDC	
10:30 am	Workshop 2 - Epidemiology	Wei Zheng	What are the greatest contributors to short-term changes in all-cause mortality?
10:45 am		Dora Pearce	Can the SCCS method estimate influenza vaccination effectiveness in the elderly?
11:00 am		David Muscatello	Windows on influenza – lab confirmed influenza infections seen through admin databases
11:15 am		Andrea Schaffer	Impact of influenza on intensive care unit (ICU) admissions in NSW 2007-10
11:30 am		Craig Dalton	Flutracking.net: A syndromic perspective on influenza
11:45 am		Kathryn Glass	What was the reproduction number of pandemic H1N1 and how did it vary by age?
12:00 pm		George Milne	Pandemic Severity Determines Cost-Effectiveness of Interventions: Results from a Modelling and Economic Analysis
12:15pm		Ben Dewar	Hospital Capacity and Management Preparedness for Pandemic Influenza in Victoria
12:30pm		Lunch	
		Chair: Heath Kelly, VIDRL	
1:15pm	Roundtable discussion	Panelists: - Lorena Brown - Peter Richmond - Jodie McVernon - Robert Booy - Ben Cowling	<u>Childhood vaccination: where do we stand?</u> For discussion: Should we have a universal vaccination policy for children? Should there be a selective vaccination policy (eg risk groups)? Should we have a quadrivalent vaccine for kids? Should we use live attenuated vaccines for kids? etc.
		Chair: John Mathews, School of Population Health, The University of Melbourne	
2:00pm	Plenary Session 5	Jodie McVernon	Non-pharmaceutical interventions to reduce influenza transmission: lessons from the two most sparsely populated countries on Earth.
2:25pm		Ben Cowling	Influenza transmission in households
2:50pm		Tania Sorrell	Influenza Research In The Sydney Institute For Emerging Infections And Biosecurity
3:15pm		Closing remarks	
3:20pm		Conference concludes	

ABSTRACTS

Plenary Session 1

One world and pandemics

Peter Doherty

Department of Microbiology & Immunology, The University of Melbourne

Plenary Session 1

The 2009 pandemic and beyond: The Hong Kong experience

Benjamin J. Cowling

School of Public Health, The University of Hong Kong, Hong Kong

2009 pandemic influenza A (H1N1) emerged in early 2009 and rapidly spread around the world. In Hong Kong, community transmission was first identified in mid-June, and the government immediately proactively closed schools, kindergartens and childcare centers for 2 weeks initially as a mitigation measure. The closures were subsequently extended to the summer vacation. Influenza incidence continued to increase through the summer, and peaked after schools re-opened in September. Serologic surveillance suggested that around 15% of the population were infected with H1N1 during the first wave with high incidence in school-age children.

The academic community led a strong research response to pandemic H1N1 in Hong Kong, and I will reflect on some experiences and research findings from 2009, and discuss some implications for preparing for the next pandemic.

Plenary Session 1

Regional perspective of the 2009 pandemic and ongoing influenza monitoring

Jeffrey Partridge

Epidemiologist

Emerging Disease Surveillance and Response

WHO Western Pacific Regional Office

The availability of epidemiological and virological data across the Western Pacific Region during the influenza A(H1N1) 2009 pandemic is a testament to the great strides that have been made in terms of strengthening surveillance systems, including establishment of laboratory facilities for case confirmation.

Experiences and lessons learnt in the Region from the pandemic in terms of preparedness planning, surveillance, response, and communications have been documented for future planning and action. The Asia Pacific Strategy for Emerging Diseases (APSED) was launched in 2005 as a common strategic framework for countries and areas of the region to strengthen their capacity to manage and respond to emerging disease threats, including influenza pandemics, and meet IHR (2005) obligations. The current strategy, APSED (2010), will be implemented by building on the achievements of the original APSED and lessons learnt from the pandemic, while recognizing variations in existing capacity levels across countries.

Influenza remains a priority for WHO. Ongoing and future work includes supporting the strengthening of national and regional influenza laboratory and epidemiological surveillance and reporting, disease burden determination, revision of preparedness guidance, development of vaccine introduction policy, and research for public health policy development.

Plenary Session 1

Review of Australia's Health Sector Response to Pandemic (H1N1) 2009: Lessons Identified

Gary Lum

Assistant Secretary, Health Emergency Response Branch, Office of Health Protection, Department of Health and Ageing, Canberra ACT

The Department of Health and Ageing has undertaken a review of the Australian health sector's response to pandemic (H1N1) 2009 influenza. The Report is the result of extensive consultation with Australia's domestic stakeholders to ensure it accurately reviews the health sector response to the 2009 pandemic. It focuses on what was planned, what happened during the response, and identifies key issues and lessons to inform future pandemic planning in Australia.

While the Report identifies what worked well, it focuses on identifying the issues that require further consideration to strengthen the planning, management and operational aspects of pandemic health response arrangements in Australia. The Report does not attempt to resolve these issues as they require further consultation and detailed evaluation. An implementation process will be developed jointly with state and territory health officials through the Australian Health Protection Committee. The outcomes of a number of recommendations will inform a review of the *Australian Health Management Plan for Pandemic Influenza 2009*.

The Report makes twenty-five recommendations that encompass the range of public health policies and actions relevant to a national health sector response to an influenza pandemic. This presentation will outline the key findings in each of the ten subject-specific chapters of the Report and its recommendations. The Report will be publicly available later this year.

Plenary Session 2

Reviewing the deaths from pandemic influenza (H1N1) in New Zealand in 2009

Lance C. Jennings

on behalf of PIMMRG.

Canterbury Health Laboratories and Pathology Department, University of Otago, Christchurch, New Zealand.

Background

Mortality from pandemic Influenza A(H1N1) 2009 differed from that due to seasonal influenza in previous seasons. In November 2009, the Minister of Health established the Pandemic Influenza Mortality Review Working Group (PIMMRG) to review all deaths associated with the pandemic in New Zealand.

Method

Cases were reported to EpiSurv (New Zealand's national notifiable disease surveillance database) (n=42) with six other cases identified via other sources. Another case was reported, however excluded as the death was outside New Zealand. Once identified, a full set of case notes was requested and all cases were summarised and then discussed at each meeting. Statistics were descriptive and rates and confidence intervals computed using population estimates where available.

Results

Forty-eight deaths were found to be caused by or associated with influenza A(H1N1) 2009 virus infection. The influenza mortality rate was 1.08/100,000 population. Eighty-five percent of those who died had associated conditions; the most common of these were respiratory illness, morbid obesity and substance abuse. Only thirty-nine percent of those who died presented with influenza-like illness. The age distribution of the influenza deaths was younger than in previous influenza seasons and there were more deaths in 2009 from influenza in those under the age of 65 than for the all the years from 1996 to 2008. One third of patients died at home, while 15% had no associated co-morbidity noted.

Conclusions

The intensity of this review was possibly not achievable in most countries affected by the A(H1N1) 2009 pandemic. The burden of mortality has largely fallen on a younger age group in New Zealand as in other countries. Further analysis will be needed to establish the significance of relative mortality rates. Never-the-less, as a result of this review recommendations have been made regarding the management of influenza which include public health messages, immunisation, recognition of patients at risk and access to antiviral agents.

Plenary Session 2

"Grave concerns about influenza" Influenza and other respiratory virus findings from mortuary samples in Western Australia 2007 - 2011

David Speers

Department of Microbiology, PathWest laboratory Medicine,
QEII Medical Centre

Respiratory virus testing by molecular detection and culture from respiratory tract specimens is an accepted component of clinical testing but is not routinely performed on post-mortem samples. PathWest is co-located with the state mortuary on the QEII Medical Centre site and performs the post-mortem microbiology. The Molecular Diagnostics section has been routinely performing virology PCR and culture on mortuary cases using a pre-determined age-based testing algorithm since 2003. This testing detected a cluster of childhood deaths in July 2007 where influenza A was found. Since then a more detailed microbiological examination has been performed from the samples obtained from childhood deaths. This has not detected further clusters during the ensuing influenza seasons and RSV was found to be the commonest respiratory virus.

A more extensive review of nearly 4,000 post-mortem virology samples from over 1,600 cases was therefore performed to investigate the prevalence of respiratory viruses from all age groups. Most respiratory tract samples were received in the winter months with a peak positivity rate of 55% in children and an overall positive rate of 8.3%. Influenza A was the commonest respiratory virus (3% of cases), followed by RSV. Only four of the 50 (8%) influenza cases were diagnosed ante-mortem according to the public pathology database. Almost all influenza cases occurred during the influenza seasons and the type of influenza found reflected the predominant types in the influenza season each year. The peak age of influenza cases was in the 50-54 age group, reflective of the age distribution of the cases, and 94% of detections were made from lung specimens which made up 86% of respiratory tract specimens. Of influenza cases with multiple respiratory tract specimens the majority (88%) of sites were positive. PCR testing for influenza was much more sensitive than culture, with culture contributing only one extra case.

Although routine testing of post-mortem respiratory tract specimens has an overall low yield for influenza, PCR testing of a lower respiratory tract specimen during the influenza season each year will detect additional cases that may have contributed to death with minimal additional workload and expense. The role of the influenza in the demise of the patient requires more investigation.

Plenary Session 2

Severe influenza: epidemiology and influenza vaccine effectiveness in the 2011 season

Allen Cheng, Paul Kelly, Tom Kotsimbos, Louis Irving, Simon Brown, Grant Waterer, Tony Korman, Mark Holmes, Sanjaya Senanayake, Deborah Friedman, Heath Kelly

Alfred Hospital, Monash University, ACT Health, Royal Melbourne Hospital, University of Melbourne, Royal Perth Hospital, University of Western Australia, Monash Medical Centre, The Canberra Hospital, Australian National University, Barwon Health, Deakin University, Victorian Infectious Diseases Reference Laboratory.

Background: The influenza vaccination programme aims to reduce mortality and morbidity due to influenza. However, there are relatively few studies that have examined vaccine effectiveness against hospitalisation from influenza. We present interim results from an Australian hospital-based sentinel surveillance system.

Methods: We have conducted hospital-based sentinel surveillance for patients hospitalized with PCR-confirmed influenza in the Influenza Complications Alert Network (FluCAN) since 2009; in 2011 the participating sites were The Alfred Hospital, the Royal Melbourne Hospital, Monash Medical Centre, Geelong Hospital (Victoria), Royal Adelaide Hospital (SA), The Canberra Hospital and Calvary Hospital (ACT) and the Royal Perth Hospital (WA). Vaccine effectiveness was estimated from the odds ratio of vaccination in cases compared to test-negative hospitalized control patients.

Results: From 1 May-19 September 2011, there were 155 admissions of adult patients to the sentinel hospitals with confirmed influenza. Influenza A was confirmed in 80% and influenza B in 20%. 77% of patients were aged <65 years but 72% had medical comorbidities. During the same period, 232 test negative control patients were enrolled; vaccination status was ascertained in 62% of cases and controls. Crude vaccine effectiveness was estimated at 74% (95% CI: 46, 87%) but after adjusting for age (>65 years) and the presence of medical comorbidities, adjusted VE was estimated at 67% (95% CI: 36, 85%).

Discussion: Although we cannot discount the possibility of ascertainment bias, this estimate is similar to previous community-based studies of VE against medically presented influenza and our previous study showing VE against hospitalisation with H1N1/09 influenza in the 2010 season. The 2011 trivalent seasonal influenza vaccine was moderately effective at reducing hospitalisation with PCR-confirmed influenza.

Plenary Session 2

Devising a pandemic severity scale

Ian Barr¹ and Heath Kelly²

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Like seasonal influenza epidemics, pandemics vary in their severity, with some having a low impact, such as pandemics in 1957 and 1968 and others, such as the 1918 pandemic having a high impact. Given this variation, it is important to determine the clinical severity of any new pandemic relatively early, so that the appropriate resources (both medical and non-medical) can be allocated for effective management of the pandemic without over or under reacting to the situation. In the most recent pandemic of 2009, the WHO was criticised for using its six pandemic phase system which did not incorporate a measurement of severity and relied mainly on the novelty of the virus and the degree of spread, to assign the phase. Many countries had tied their pandemic preparedness plans to the WHO phases but did not build in sufficiently flexible responses to these phases and hence may have over-reacted to the 2009 pandemic. Reviews of the pandemic from a number of countries now suggest that this pandemic was similar in severity to seasonal influenza, although with some important differences.

Several methods could be used to describe pandemic severity but many of these are not suited to developing countries where resources are limited. As the next pandemic will most likely begin in such a country, it would be optimal if these countries could provide an early and robust estimate of pandemic severity. One method that may be applicable is the FF100 or First Few Hundred, type of study. An FF100 study is a detailed case series that involves the intensive investigation of the first few hundred cases (typically 300-400 cases – preferably lab confirmed) and gathers subject information such as: the period of infection, symptoms, drug use, underlying medical conditions, medical interventions including GP visits, hospitalization and deaths. Only the UK undertook a formal FF100 study in 2009 although many other countries carried out similar early case studies. This early information though was generally not used expediently to better inform governments or modify existing pandemic plans.

A pandemic plan that has interventions matched to severity may improve both the public and professional confidence in the management of future pandemics.

Plenary Session 3

Veterinary surveillance programs for influenza with a public health focus

Peter Daniels, Gwenaëlle Dauphin and Keith Hamilton

OIE-FAO Global Network of Expertise on Animal Influenza (OFFLU)

<http://www.offlu.net/index.html>

During the last decade a much heightened awareness has developed of the potential of influenza infections in animals to cause serious disease in people. The H5N1 strain of avian influenza has been diagnosed in 564 human infections, 330 of which were fatal, as of August 2011. Fortunately this strain has not been contagious among people. However the pandemic H1N1 2009 strain infected humans globally. This virus, shown to have evolved by reassortant events involving viral genes seen variously in avian, human and pig populations, spread rapidly and in many countries has become the predominant H1 strain infecting people. Although there were some differences in the clinical presentation from seasonal influenza, in general terms the morbidity and mortality were of a similar order of magnitude. A major response to these events has been for human and animal health authorities to work much more closely to monitor influenza infections in animals and to analyse these for their potential threat to human health.

OFFLU is a formal partnership between the two global animal health agencies, the World Organization for Animal Health (OIE) and the Animal Production and Health Division of the Food and Agriculture Organization of the United Nations (FAO) to maintain an active network of expertise on animal influenza. The OFFLU vision is that the animal health community will provide early recognition and characterisation of emerging influenza viral strains in animal populations, and effective management of known infections, thereby better managing the risk to human health and promoting global food security, animal health and welfare, and other community benefits derived from domestic animals and wildlife. It specifically has as one of its objectives to collaborate with the WHO influenza network on issues relating to the animal-human interface, including early preparation of human vaccines.

To this end OFFLU has entered into a formal agreement for the next three years with the Global Influenza Program of WHO to provide animal health data to the twice yearly meetings of the WHO vaccine strain selection process. Epidemiologic, molecular and antigenic information regarding H5N1 strains received by the animal health reference centres is collated. In this way every effort is made to mitigate the risk of H5 N1 becoming an even greater public health problem.

Historically surveillance for influenza viruses in pigs has been neglected since such infections are widely disseminated on most continents, are not associated with a comparatively high economic cost and consequently influenza in swine has not been an OIE listed disease. OFFLU is coordinating an international group of experts in swine influenza to develop a surveillance strategy, but the limitations should be noted. Collection and laboratory processing of specimens is uncoordinated and inadequate so isolates will most likely be obtained opportunistically, with the results of their analyses shared on a voluntary basis. Furthermore the determinants of transmission of influenza viruses from pigs to humans are unknown, so putative genetic markers that would indicate the need for concern are not able to be monitored. Influenza surveillance in pigs can provide information about changes in influenza viruses circulating in pigs to detect novel influenza viruses and to identify those viruses that can be used for research.

Plenary Session 3

National Avian Influenza Wild Bird Surveillance Program (Australia)

Tiggy Grillo

Projects Coordinator

Australian Wildlife Health Network

In 2006, the National Avian Influenza Wild Bird (NAIWB) Steering Group was established to ensure national coordination and collaboration of wild bird surveillance for avian influenza in wild birds. The Australian Wildlife Health Network (AWHN) supports the NAIWB Steering Group and coordinates the wild bird surveillance program.

National wild bird surveillance projects are conducted Australia-wide, with national funding together with in-kind support from jurisdictional agencies and representative institutes. Surveillance activities target a combination of targeted risk-based (live, healthy or hunter-killed wild birds) and general (wild bird mortality / morbidity events) surveillance. This presentation will discuss the implications and outcomes of the NAIWB surveillance.

Plenary Session 3

Recent H5N1 activity and diversification in commercial poultry in the Southeast Asian region

Frank Wong¹, Paul Selleck¹, Chris Morrissy¹, John Allen¹, Peter Daniels^{1,2}

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² OIE-FAO Global Network of Expertise on Animal Influenzas (OFFLU).

H5N1 highly pathogenic avian influenza viruses continue to circulate in poultry and cause disease. Since 2003, H5N1 has caused the deaths of more than 400 million domestic poultry and an estimated \$20 billion of economic damage globally. H5N1 is recognized as endemic in five countries including Bangladesh, China, Egypt, Indonesia, and Viet Nam.

Reported HPAI outbreaks in poultry and wild birds have progressively increased since its lowest incidence in mid-2008 to almost 800 cases recorded between 2010-2011. In the Southeast Asian region, significant outbreaks in poultry have occurred in Cambodia, Indonesia, Myanmar, and Viet Nam over 2011 to date. More than 300 HPAI samples from Indonesia have been received by AAHL for characterization through OFFLU, from which 240 viable H5N1 viruses have been isolated. All Indonesian H5N1 viruses belonged to clade 2.1 with the majority in clade 2.1.3, an established and expanding lineage currently restricted to that country. Furthermore through our international AI reference lab activities, we have received and characterized H5N1 viruses recently submitted from Viet Nam (clade 1, clade 2.3.2, and clade 2.3.4), and 2010-2011 H5N1 outbreak viruses from Lao PDR (clade 2.3.4) and Myanmar (clades 2.3.2 and 2.3.4).

All of these recently circulating viruses belonged to endemic H5N1 lineages that are undergoing continuing diversification, and subject of current clade revisions by the WHO/OIE/FAO H5N1 Evolution Working Group. The genetic and antigenic relationships among these viruses and their apparent evolution will be presented.

Plenary Session 3

The Influenza A/H10N7 in chickens and poultry abattoir workers in Australia.

George Arzey¹, Peter D Kirkland¹, **Edla Arzey^{1*}**, Melinda Frost¹, Patrick Maywood², Stephen Conaty², Aeron C Hurt³, Yi-Mo Deng³, Pina Iannello³, Ian G Barr³, Dominic Dwyer⁴, Mahla Ratnamohan⁴, Kenneth McPhie⁴ and Paul Selleck⁵.

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In commercial chickens, influenza A infections are most frequently due to viruses from the H5 and H7 subtypes. Such infections in chickens are notifiable internationally because of the propensity of H5 or H7 virus strains, often initially of low pathogenicity, to mutate and give rise to “high pathogenicity” strains which cause severe disease. Occasionally people have been infected after contact with infected birds, the most notable being with A/H5N1 viruses and, infrequently, an A/H7 or A/H9 virus.

In March 2010, a chicken farm in New South Wales experienced a slight increase in mortality and a 15% drop in egg production over a period of several days. Autopsy of dead birds revealed swollen kidneys and various degrees of visceral gout. No respiratory signs were evident. Cloacal and tracheal swabs were collected from 20 birds and submitted to the laboratory for testing. All samples were positive in an influenza A real time reverse transcriptase PCR (qRT-PCR). Subsequent testing in both H5- and H7-specific qRT-PCR assays gave negative results.

An influenza A typing microarray assay allowed rapid identification of the virus to an H10N7 subtype. This virus was readily isolated in both embryonated chicken eggs and in cell culture. Several segments of the genome of this virus have been fully sequenced, allowing confirmation of the virus as a ‘low pathogenicity’ strain and providing an insight into the phylogeny of the virus. Serology with both an influenza A pan reactive blocking ELISA and HI tests confirmed widespread infection in birds in all sheds on the farm.

A few weeks later, a number of workers at the poultry abattoir receiving apparently healthy birds from the farm developed conjunctivitis and some experienced a systemic illness consistent with influenza. Conjunctival swabs from 2 people gave positive results in the influenza A qRT-PCR. The microarray assay detected RNA from an H10 virus in one of these samples.

This presentation will review the use of the diagnostic aspects of this investigation, characteristics of the H10N7 virus and epidemiological studies that have been undertaken on the affected and neighbouring farms in an effort to identify the source of the virus.

Plenary Session 3

Pandemic A(H1N1)2009 influenza in Australian swine

Yi-Mo Deng¹, Pina Iannello¹, Ina Smith², James Watson², Peter Daniels², Naomi Komadina¹, Ian Barr^{1,3}, Bruce Harrower⁴, Vittoria Stevens², Frank Wong²

¹ WHO Collaborating Centre for Reference and Research on Influenza, VIDRL, Melbourne, Victoria, Australia;

² CSIRO Australian Animal Health Laboratory, Geelong, Victoria, Australia;

³ School of Applied Sciences, Monash University, Churchill, Victoria, Australia;

⁴ Virology, Queensland Health Scientific Service, Brisbane, Queensland, Australia

The A(H1N1)2009 influenza virus which caused influenza pandemic in 2009 consists of genetic components derived from avian, human and swine influenza viruses. Apart from infecting humans globally, it was also found to infect farmed pigs in many countries, including Australia. Since July 2009 pigs from four separate farms from different states were infected with A(H1N1)2009 virus. This was the first time that influenza virus has been detected in Australian swine herds. Genetic analysis from viruses isolated from these outbreaks revealed that these viruses from pigs were very similar to the human A(H1N1)2009 virus but were distinct from each other, indicating that separate infections had occurred presumably via human sources.

At the Queensland outbreak, two staff working in the same piggery with close contacts with the sick pigs showed ILI symptoms a few days after the pigs became sick. Sequence analysis of the A(H1N1)2009 virus HA genes from the two staff showed that they were infected with different H1N1pdm virus strains, with each identical to one of the two virus strains isolated from the pigs. This indicates that the two staff were probably infected by different pigs with slightly different strains of the H1N1pdm virus. Following full genome analysis on one human and one pig virus isolate as well as pyrosequencing reassortment analysis on ten viruses isolated from pigs, no reassortment between human seasonal A(H1N1) or A(H3N2) viruses or other swine influenza viruses were detected. No genetic markers for resistance to oseltamivir or zanamivir were detected in any samples however all A(H1N1)2009 viruses retained their resistance to the adamantane class of antiviral drugs.

These cases highlight the ability of the A(H1N1)2009 viruses to easily cross between humans and pigs, and pig-to-human infection underlying the importance of ongoing monitoring of swine throughout the world for novel influenza infections that may infect man.

Workshop 1 - Clinical & Research

Respiratory virus testing in the pandemic: which sample was best?

Mark Turra¹, Patricia Haahes¹, Katina D'Onise² Geoffrey Higgins¹

¹ Institute of Medical and Veterinary Science

² Communicable Diseases Control Branch Dept of Health, Adelaide South Australia

There is little empirical evidence to support the superiority of one sample site over another with regards to respiratory viruses. We have investigated the effect of sample type and age on positivity rates using the results of high volume of testing during the influenza pandemic. Between May 2009 to July 2010 45,674 respiratory specimens from general practice (77.4 %), emergency department (4.6%) and hospital patients (18.0%) were tested.

All samples were tested in parallel in separate PCR reactions for influenza A (matrix gene), pandemic (H1N1) 2009 (haemagglutinin), RSV, and adenovirus. Samples received included nasal swabs (58.4%), unspecified (20.6%), throat swabs (12.6%), NPAs (4.2%) and sputum (3.0%). Influenza A was detected in 18.5% of samples.

The influenza A matrix PCR assay was positive in 14.5% of samples, the pandemic (H1N1) 2009 assay in 16.9% and both assays in 13.0%. Pandemic (H1N1) 2009 influenza was most common (14.3% of positives) in the 15-20 year age group and was more frequently detected in nasal swabs (18.2%) than throat swabs (15.7%) ($p < 0.001$). However, the earliest PCR crossing thresholds (Ct) were seen in NPAs and sputum samples. An analysis to determine the effect of age, sample type, and health care provider type on positivity rates and Ct values will be presented.

Workshop 1 - Clinical & Research

Examining the effect of additional glycosylation sites on the head of H1N1 2009 pandemic viruses

Emma R. Job^{*}, Yi-Mo Deng[†], Scott Reddiex[†], Michelle D. Tate^{*}, Louise A. Carolan[†], Karen L. Laurie[†], Andrew G. Brooks^{*} and Patrick C. Reading^{*,†}

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As influenza viruses circulate within the human population they gradually increase the number of glycosylation sites upon the head of their hemagglutinin (HA). Acquisition of glycosylation sites on the head of the HA has been proposed as an effective mechanism for promoting antigenic drift. When the H1N1 pandemic (pdm) virus first arose within the human population, it displayed one potential glycosylation site on the HA, at Asn₁₀₄. This is in contrast to recent seasonal H1N1 strains, which carry 3-4 potential sites. As a result of extensive infection and widespread vaccination in 2009/2010, neutralizing antibodies to H1N1 pdm viruses have now been elicited in a large proportion of the human population. Analysis of HA sequences of >2000 H1N1 pdm virus samples (submitted to NCBI in 2010) indicate the presence of >30 strains with 1-2 additional glycosylation sites on the head of HA (Asn₁₃₆ and Asn₁₇₉, alone or in combination), consistent with addition of glycosylation to HA to evade antibody-mediated neutralization and promote virus survival in the human population. Using site-directed mutagenesis, we have added Asn₁₃₆ and/or Asn₁₇₉ to the HA of an 'early' H1N1 pdm virus strain to determine if glycosylation modulates sensitivity to (i) innate immune proteins (collectins and pentraxins) and (ii) adaptive humoral responses (i.e. do glycans mask antigenic epitopes?).

To date we have shown that addition of Asn₁₃₆ and/or Asn₁₇₉ does not alter sensitivity to the antiviral activities of collectins however the addition of Asn₁₃₆ reduces sensitivity to neutralization by antisera elicited to the parental H1N1 pdm virus. The decrease in neutralization due to the addition of Asn₁₃₆ is also observed in a human isolate, A/Townsville/2010. Current studies are focused on use of these viruses to compare virulence in mouse and ferret models of influenza infection. Moreover, we will use vaccination to induce antibody-mediated immunity to early H1N1 pdm viruses in mice and ferrets (or to type B viruses as a control) and challenge with glycosylation mutant viruses to determine if the presence of additional glycosylated sites on the viral HA can provide protection *in vivo* against pre-existing antibody responses.

Workshop 1 - Clinical & Research

Oseltamivir and influenza: inflammation-induced morbidity versus generation of anti-viral T cell immunity

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Immune CD8⁺ T cells directed towards conserved viral regions elicit broad immunity against different influenza A viruses, both seasonal and pandemic. Such pre-existing T cell pools can promote more rapid virus elimination and enhanced host recovery following infection with a newly emerged virus. During the A/H1N1 2009 influenza pandemic, the neuraminidase inhibitor oseltamivir (Tamiflu®) was the most common antiviral drug prescribed for both therapy and prophylaxis. However, it remained unclear how oseltamivir treatment affected influenza virus replication and morbidity in relation to establishment of cross-strain protective T cell immunity.

Using influenza A virus infection of B6 mice, we dissected the effects of oseltamivir treatment on viral replication, animal morbidity, inflammatory processes and establishment of immunological T cell memory. Our study found that prophylactic oseltamivir treatment prior and during influenza infection led to a rapid decrease in morbidity and accelerated clearance of the influenza virus from the site of infection. Oseltamivir also reduced innate immune responses, the extent of inflammation and, ultimately, the magnitude of effector T cell responses. Strikingly, however, the short- and long-term memory CD8⁺ T cell pools established during this drug-reduced effector phase were similar to those found for untreated, influenza-infected animals. Importantly, the memory CD8⁺ T cells generated during this 'interrupted' influenza virus infection were fully functional and could be recalled to the same extent as those established following the normal infection.

In summary, our study provides evidence that long-term memory T cell pools can be generated during an oseltamivir-interrupted influenza infection. Thus, in the case of an unpredicted influenza pandemic, while prophylactic oseltamivir treatment may limit virus growth and reduce disease severity, the capacity to generate memory T cells specific for the newly emerged virus is not compromised. These findings have implications for both vaccine development and drug therapy.

Workshop 1 - Clinical & Research

A pandemic H1N1/09 virus with H274Y and D198G mutations emerges after *in vitro* passage in a combination of oseltamivir and zanamivir

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The emergence of the H274Y (H275Y) mutation in N1 subtypes of influenza either spontaneously or as a result of oseltamivir exposure is well documented. This mutation confers high level resistance to oseltamivir and also cross-resistance to peramivir. However, mutations in the NA conferring high level resistance to zanamivir remain extremely rare. It has been proposed that dual oseltamivir and zanamivir therapy may prevent emergence of resistance.

Our aim was to passage a pandemic H1N1/09 virus in the presence of zanamivir or zanamivir and oseltamivir to determine whether we would select resistant viruses with zanamivir treatment alone, and whether dual zanamivir and oseltamivir treatment could prevent the emergence of the H274Y mutation. A pandemic H1N1/09 virus was passaged in increasing concentrations of zanamivir for 12 passages, from 1 nM to 1 μ M. For dual treatment both inhibitors were increased from 1 nM to 10 nM over 5 passages and then zanamivir remained constant while the oseltamivir was increased further to 500 μ M for a total of 12 passages. Viruses were evaluated for altered drug susceptibility in enzyme inhibition assays and plaque reduction assays and for replication in cell culture and red cell binding and elution assays. A virus was selected after 6 passages in zanamivir which had an N146S NA mutation and a G172E (G158E H3 numbering) HA mutation. The NA mutation only reduced the IC₅₀ by around 2-fold in enzyme inhibition assays, and the HA mutation led to altered receptor binding to red cells resulting in both drug dependence and a 10-fold reduced susceptibility in the plaque reduction assay. A virus was selected after 4 passages in the dual drug treatment with a D198G mutation, which conferred around 5-10-fold reduced susceptibility to zanamivir, oseltamivir and peramivir. This amino acid is known to affect the interactions of R152 with the N-acetyl group of the sugar ring, so mutations at this site confer reduced susceptibility to all NAIs. A virus with both the D198G and H274Y was selected by the 12th passage in the dual treatment passaging. This had an IC₅₀ in the enzyme inhibition assay of more than 10,000 nM to oseltamivir, significantly higher than the H274Y alone in other N1 viruses. Replication of all mutant viruses was less than wild type in MDCK cells.

Thus although we did not see the emergence of a virus with a mutation in the NA conferring high level resistance to zanamivir, zanamivir at 10 nM was not able to prevent the emergence of the H274Y mutation in the presence of oseltamivir.

Workshop 1 - Clinical & Research

Rapid mammalian adaptation of H5N1 avian influenza virus following infection in ferrets

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H5N1 avian influenza viruses continue to cause human infections with a mortality rate of up to 60%. We previously determined that two different H5N1 viruses, both of which were 100% lethal in poultry, produced vastly different pathogenicity phenotypes in ferrets, which are a relevant small animal model of human influenza infection.

The human H5N1 isolate A/Vietnam/1203/2004 (A/Viet) caused a highly pathogenic systemic infection with rapid onset, whereas the avian H5N1 isolate, A/Chicken/Laos-Xaythiani/26/2006 (A/Laos), demonstrated a relatively attenuated phenotype. In most ferrets infected with A/Laos, virus was primarily confined to the respiratory tract and no signs of disease were displayed. However, 2 of the 10 ferrets developed an infection that spread beyond the respiratory tract, accompanied by substantial weight loss. Virus-infected tissue and nasal wash samples from both of these ferrets yielded viruses with the same amino acid substitution from Glu to Lys at position 627 of the viral polymerase subunit PB2. This mutation has been associated with virulence of H5N1 viruses in mice but its role in ferrets has been controversial. During a subsequent second ferret passage of virus reisolated from these two ferrets, a dramatic increase in pathogenicity was observed. Finally we utilized reverse genetics techniques to create A/Laos and A/Viet H5N1 viruses encoding either Glu or Lys at PB2 627 in order to specifically analyse the pathogenic importance of this single amino acid mutation. Our results demonstrate that PB2 627 Lys leads to an enhanced pathogenicity phenotype in ferrets and emphasises the potential importance of H5N1 polymerase adaptations in disease severity in mammals.

This study highlights the remarkable ability of H5N1 viruses to mutate towards increased pathogenicity during a single passage in the mammalian host.

Workshop 1 - Clinical & Research

Viruses selected through classical reassortment have phenotypic characteristics directed by PB1 composition that impact on vaccine yields

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Influenza vaccines are administered annually to induce protection against current circulating strains. The properties of the vaccine seed viruses used to infect eggs are critical in determining whether sufficient HA (and NA) antigen yields can be achieved. To maximise this, the process of classical reassortment is used, which involves co-infection of eggs with the seasonal isolate and an egg-adapted virus strain.

The high yielding PR8 virus (H1N1) is used for the production of H3N2 seed viruses. The H3N2 seed strain is then grown in the presence of antibody to PR8, and virus progeny with the HA and NA of the seasonal isolate but with enhanced growth properties is selected. The optimal genetic composition of vaccine seeds that give the highest antigen yields is poorly characterised. We and others have determined that the seasonal PB1 gene is selected in over 50% of reassortment events analysed, while the incorporation of other seasonal genes is significantly less frequent. Through the use of reverse engineered viruses, we showed that the inclusion of a model seasonal PB1, with its HA and NA, into a PR8 backbone results in an inferior growing virus (2-fold lower HA titre, 8-fold fewer viral particles) compared to a virus containing the seasonal HA and NA and PR8 PB1, even though in a classical reassortment it was more often selected. Growth differences observed did not appear to be due to differences in vRNA or mRNA production, however the inclusion of the seasonal PB1 resulted in higher HA/M1 protein ratios in infected cells. This was consistent with a higher HAU/particle and HA/NP protein ratios in the corresponding egg-grown virus (each 4-fold), which suggested an increase in HA density in the virion. This observation was supported by a retrospective analysis of vaccine seed strains, which showed a higher HA/NP protein ratio when the seasonal PB1 was present.

Although this does not explain why inferior growing viruses are often selected during reassortment, it does indicate that the effect of poor virus production on antigen yield can be somewhat offset by increased HA in the viral particle itself.

Workshop 1 - Clinical & Research

Nanopatch targeted delivery of both influenza vaccine and adjuvant to skin synergistically drives enhanced antibody responses.

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The Nanopatch is an array of thousands of 100 µm long projections dry-coated with vaccines. When applied to the skin, these projections pierce the outer skin layer and precisely deliver the vaccine to thousands of antigen presenting cells in both the epidermis and dermis. We have previously shown that delivering influenza vaccine – without adjuvant – directly to these antigen presenting cells, induced the equivalent immune responses as generated by the conventional needle and syringe intramuscular vaccination – but at a much lower delivered dose (up to 150X dose reductions) with one vaccination. Furthermore, Nanopatches are also: (1) needle-free; (2) pain-free; and, (3) the dry-formulated vaccine does not require refrigeration and could be stored at room temperature without refrigeration up to 12 months with no significant loss of vaccine potency – which is particularly important for developing world applications.

So far, however, we have not rigorously explored the immunological effect of extending the Nanopatch to co-delivering influenza vaccine and adjuvant to the skin. This is the focus of this presentation. In addition to a conventional split-virus antigen (Fluvax®) we selected Quil-A – a well studied adjuvant and a surfactant.

Following Nanopatch vaccination in mice (with a delivered dose of 6.5 ng of vaccine and 1.4 µg of Quil-A), we found the induced antibody response to be equivalent to that generated by conventional intramuscular (IM) injection using the needle and syringe (6000 ng of vaccine injected). The result demonstrates that Nanopatch co-delivery of the antigen and adjuvant achieves an unprecedented ~900 fold reduction, with one vaccination – compared with IM injection of antigen alone. Therefore, the possibility of enhanced immune responses with very low antigen doses is opened up by directly depositing the vaccine to thousands of skin antigen presenting cells. The successful rollout of this approach with a practical Nanopatch device could be of immense utility in vaccines where improved reach is required, such as dose-shortages – like an influenza pandemic.

Plenary Session 4

Improving Influenza Control with Quadrivalent Influenza Vaccines

Mark Simmerman

Background:

Seasonal influenza viruses cause significant morbidity and mortality worldwide every year. While influenza A is responsible for the majority of seasonal influenza infections, influenza B represents 20 – 25% of circulating strains on average, is responsible for seasonal epidemics every 2-4 years, and is common in children and young adults. Among elderly persons, type B is the second most common cause of influenza-related morbidity and mortality after A/H3N2. Two distinct B influenza lineages (Victoria and Yamagata) have co-circulated for over a decade, making it very difficult to predict which will predominate the next season. Consequently, the B strain selected for trivalent influenza vaccine (TIV) often fails to match the circulating B strain and there is little or no cross-reactive protection between the influenza B lineages. Therefore, to reduce the morbidity and mortality from influenza B virus infections a clear need exists for a quadrivalent influenza vaccine (QIV) containing both B lineage strains. QIV would provide a substantial benefit to vaccine recipients whenever a large number of circulating influenza B viruses does not match the lineage chosen for trivalent vaccines. This can occur if the prediction of the dominant lineage is incorrect or if both lineages co-circulate to a significant degree. For example, a CDC analysis of the 2007/08 season when the B strains in the vaccine were mismatched, suggested that use of quadrivalent vaccines in the United States would have resulted in approximately 1,090,514 fewer cases, 7,488 fewer hospitalizations, and 321 fewer deaths. As a result of recent large investments made in influenza vaccine production, industry capacity is greatly in excess of forecasted global demand for seasonal influenza vaccines and methods to identify the influenza B strains to include in such vaccines are well established. Most international manufacturers have initiated QIV clinical studies.

Conclusions:

Quadrivalent influenza vaccine formulations represent a logical next step to improve seasonal influenza vaccines. QIV is expected to improve public confidence in influenza vaccine by reducing the frequency of vaccine mismatches. In addition, expanded antigen production capacity from QIV will help to improve pandemic preparedness. Additional epidemiologic and health economic data regarding the burden of influenza B infections are needed to provide an improved understanding of the potential global benefit from QIV for the prevention of seasonal influenza disease. Quadrivalent influenza vaccine represents an improved standard of care for all age groups.

Plenary Session 4

Seasonal vaccine studies on the protection of seasonal vaccines against pandemic

Peter Richmond

Plenary Session 4

Scientific investigations into febrile reactions observed in the paediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine

Eugene Maraskovsky, Megan Barnden, Allison Dyson, Sandra Koernig, Adriana Baz Morelli, Steve Rockman, Peter Schoofs, Derchie Hung, Michael Greenberg, Martin Pearse

Aims During the 2010 Southern Hemisphere (SH) season, an increased incidence of febrile reactions was reported in the paediatric population following vaccination with the trivalent influenza vaccine (TIV). These adverse events appeared to be more prevalent with the CSL Limited TIV, and a series of scientific investigations were initiated to determine the root cause. The primary objectives were: 1) investigate the immunogenicity/reactogenicity of the CSL 2010 TIV as compared to previous season and comparator vaccines; (2) Identify vaccine components that may have contributed to the adverse events; (3) identify surrogate parameters that can be used to prepare future TIVs which are safe and effective in the paediatric population.

Methods CSL Limited has implemented a detailed investigational plan to elucidate the mechanisms underlying these adverse events, including in vitro cytokine/chemokine assays following stimulation of adult and paediatric whole blood, as well as mammalian cell lines and primary cells (Center for Biologics Evaluation and Research; CBER), profiling of molecular signatures using microarrays, biochemical tests for neuraminidase activity and content (Center for Disease Control and Prevention; CDC), and in vivo studies in rabbits, ferrets, new born rats and rhesus non-human primates (NHPs). Various TIVs (approved commercial vaccines as well as re-engineered) and their individual monovalent pool harvest components were examined in these assays and animal models. The full array of cytokines and chemokines screened by Luminex arrays IL-1 α , IL-1 β , IL-1RA, IL-6, IL-8, IL-9, IL-10, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1 α , MIP-1 β , RANTES, GRO, TNF- α , IFN- α , IFN- γ , G-CSF, Eotaxin, PGE2 and Activin-A.

Results Studies using myelomonocytic cell lines conducted by CBER confirmed the findings of the rabbit pyrogenicity studies, that the CSL 2010 TIV and corresponding individual strains do not contain bacterial-derived pyrogens. Assays using 21 adult blood donors have been completed and assays using paediatric blood have been initiated. Statistical analysis of the cytokine/chemokine data from the adult whole blood assays indicates that the CSL 2010 TIV is generally, more stimulatory than previous season TIVs. Analysis of the individual viral components implicates a combination effect of the specific viral strains used in the 2010 SH TIV formulation. NHPs (n=4 per vaccine cohort) immunized with adult doses of various CSL TIV formulations or competitor 2010 TIVs indicated no statistically significant change from baseline in body temperature (T=0, 4, 8, 24, 72h) or complete blood cell count parameters (T=72h). Genomics microarray analyses have been performed and data is being analysed. Preliminary results indicate that CSL TIV formulations generally induce more potent gene signatures than the competitor vaccine and that replacement of the H1N1 pandemic A/California/7/09 strain in the 2010 TIV with another H1N1 strain alters the gene signatures. However, the monovalent A/California/7/09 pandemic vaccine, containing 15 μ g HA, induced weaker gene signatures. This possibly implicates a combination effect of the three viral components in the CSL TIV or relates to the total antigen content administered. Serum haemagglutinin inhibition (HAI) and microneutralization (MN) titres (T= 28d) and cytokine profiling (T= 0, 4, 8, 24h, 7, 14, 21d) have been examined. Analysis of neuraminidase (NA) activity indicates that the H1N1 A/California/07/2009 contains substantially higher NA activity than previous H1N1 strains and other H3N2 and B strains.

Discussion/conclusion Although the scientific investigations are still ongoing, the emerging hypothesis is that there are one or more viral-derived components within the CSL 2010 TIV that may contribute to the unusually high proportion of fever and other febrile reactions in children during the 2010 SH season. Identification of the causal components may result in the identification of surrogate parameters that can assist in the formulation of future TIVs to minimise the incidence of febrile reactions in the paediatric population.

Plenary Session 4

Widespread community transmission of oseltamivir-resistant A(H1N1)2009 influenza

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Background

Oseltamivir is widely used for the treatment of influenza, particularly in severely ill or high-risk patients, and was extensively used for prophylaxis when the A(H1N1)2009 influenza strain emerged in 2009. Oseltamivir resistance in A(H1N1)2009 influenza strains has been rare, particularly in untreated community cases, and transmission of oseltamivir-resistant A(H1N1)2009 viruses has only been detected occasionally in closed, near-contact settings. Sustained community transmission has not previously been reported.

Methods

Virological analyses are conducted year-round on influenza specimens from the Asia-Pacific region at the WHO Collaborating Centre for Reference and Research on Influenza in Australia. Detailed information was collected on patients with a confirmed oseltamivir-resistant virus infection.

Results

Twenty nine (16%) of 182 A(H1N1)2009 viruses collected between May and August from the Hunter New England region of New South Wales (NSW), Australia, contained the H275Y neuraminidase substitution responsible for oseltamivir resistance. Only one of the patients had received oseltamivir prior to influenza specimen collection, three were pregnant and none was immunocompromised. Based on sequence analysis, the resistant strains were genetically closely related, suggesting the spread of a single variant. The majority of cases lived within a 50 kilometre radius of Newcastle, NSW, but the resistant variant was also detected in Sydney and elsewhere in the state.

Conclusions

This is the first report of widespread community-transmission of H275Y oseltamivir-resistant A(H1N1)2009 influenza. Cases continue to be detected within the region and state. If these strains spread and circulate widely, then oseltamivir may not be appropriate for the empiric treatment of suspected influenza.

Plenary Session 4

The discovery and development of the next generation influenza neuraminidase inhibitors: long-acting neuraminidase inhibitors for once-only treatment of influenza

Simon Tucker

Vice President Research, Biota, Melbourne

Authors: the Daiichi Sankyo and Biota long-acting neuraminidase inhibitor R&D teams

The first generation neuraminidase inhibitors oseltamivir and zanamivir are currently licensed worldwide for influenza treatment and chemoprophylaxis. In both cases a treatment course comprises twice-daily administration for 5 days. Through functionalisation at the C7 position of zanamivir, Biota (Melbourne, Australia) and Daiichi Sankyo Co., Ltd, (Tokyo, Japan) have discovered a new generation of neuraminidase inhibitors with surprisingly improved pharmacokinetic properties and excellent potency. These long-acting neuraminidase inhibitors exhibit long residence time in the lung and a once-only treatment course. The most advanced of these is called laninamivir, which is delivered in a prodrug form known as laninamivir octanoate. Laninamivir was recently approved in Japan as a single inhalation for treatment of influenza patients and is commercially available as Inavir(r).

The next most advanced is a particularly potent dimeric compound which also offers a long-acting pharmacokinetic profile. This compound, currently at the preclinical stage of development, consists of two zanamivir molecules linked via the C7 position by a flexible alkyl linker. Both long-acting neuraminidase inhibitors are broad spectrum inhibitors of influenza A and B viruses, including subtypes N1-N9, pandemic (2009) H1N1 virus, highly pathogenic avian influenza (HPAI) H5N1 viruses and oseltamivir-resistant viruses in vitro and in vivo.

These next generation neuraminidase inhibitors promise significant improvements over the first generation agents in such areas as dosing convenience and resistance profile as well as the potential for pandemic preparedness stockpiling efficiencies.

Workshop 2 – Epidemiology

What are the greatest contributors to short-term changes in all-cause mortality?

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Background

In temperate countries, all-cause mortality displays a strong seasonal pattern with peaks in winter and troughs in summer. While the short-term mortality impacts of influenza, extreme temperature and air pollutants have been extensively studied, often in isolation, there has not been an attempt to rank them according to their mortality burden. Risk estimates from regression models give insufficient information to achieve this.

Aims

To compare the cumulative short term effects of influenza, extreme temperatures and air pollutants on all cause mortality in the Sydney population, with adequate control of seasonality.

Methods

For the Sydney Statistical Division between 2002 and 2007, we assembled time series of daily counts of all-cause deaths, laboratory-confirmed influenza infections, average temperatures and air pollutants. A generalized additive model was used to estimate the short-term relationship between each variable and mortality. Lagged and moving average effects were considered. Cumulative deaths associated with each variable were estimated from the model.

Results

The estimated increase in daily all-cause mortality for a 10 count increase in 7-day moving average of influenza was 8.9% (95% CI: 7.1%-10.8%), for each degree above the heat threshold or each degree below the cold threshold was 3.3% (1.4%-5.1%) and 14.3% (5.5%-24.0%) respectively, and for an interquartile increase in ozone or sulphur dioxide (SO₂) was 0.9% (0.01%-1.9%) and 0.8% (0.07%-1.6%) respectively. Amongst all variables studied, ozone was associated with the greatest annual average number of deaths (495, 2.0% of total deaths), followed by influenza (464, 1.8%), SO₂ (191, 0.8%), cold (59, 0.2%) and heat (36, 0.1%).

Conclusions

Among the risk factors examined, ozone and influenza were associated with the greatest mortality burden. Considerations in public health prioritisation and decision-making should encompass both epidemic communicable diseases and environmental risk factors that can have substantial short-term influences on mortality in populations.

Workshop 2 – Epidemiology

Can the SCCS method estimate influenza vaccination effectiveness in the elderly?

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Community-acquired pneumonia (CAP) in the elderly is a common cause of hospitalisation and mortality¹, often as a complication of influenza². However, investigations of influenza vaccine effectiveness (IVE) in the elderly may be subject to confounding and “healthy-vaccinee” bias²⁻⁴, or conversely, bias due to vaccination of persons most at risk of complications⁵. Unbiased estimates of IVE are yet to be determined⁶. The self-controlled case series (SCCS) method implicitly controls for fixed confounders such as genetics, frailty and socio-economic status within individuals, estimating the incidence rate ratio (IRR) as the ratio of the rate of events within defined post-exposure period(s) to event rates when unexposed, taking into account variation in this baseline risk⁷.

We applied the SCCS method to a series of elderly patients admitted with CAP as their principal diagnosis, with no prior admissions for pneumonia, and confirmed vaccination status for influenza and 23-valent polysaccharide pneumococcal (23vPPV) vaccines. The observation period was 1/1/2001 – 31/12/2001, including the influenza season 30/6/2001-30/11/2001. Incidence of death (n = 89) was significantly increased 4 to 6 months after influenza vaccination relative to the baseline period (IRR 4.28 [95% CI 2.02-9.07]) but not during the immediate 4 month period (IRR 1.13 [0.48-2.65]). Relative incidence of CAP admission (n = 323) was significantly increased to 4 months post-influenza vaccination (IRR 2.12 [1.49-3.00]) and 4 to 6 months (IRR 2.27 [1.55-3.32]). No protective effect of prior vaccination with 23vPPV was detected.

In contrast to previous studies which have shown a protective effect of influenza vaccination^{1,8}, although paradoxically, greater effects have been observed pre-season^{3,6}, our results suggest a lack of protection against CAP admission and death by influenza vaccination. Unfortunately we cannot exclude the possibility that residual bias has undermined the validity of the SCCS method in our study, due to the potential for confounding by the non-randomised nature of vaccination decisions, influenza seasonality and vaccination timing, small case numbers, and non-specific outcomes. The option of record linkage between hospital admission and vaccination databases may enhance the applicability of the SCCS method, enable estimation of IVE, and inform policy on influenza vaccination in the elderly.

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Workshop 2 – Epidemiology

Windows on influenza – laboratory-confirmed influenza infections seen through administrative databases

D Muscatello, J Amin, CR MacIntyre, S Thackway, W Rawlinson & R Gilmour

Background

Laboratory confirmed influenza infection is a notifiable disease in Australia. Understanding the natural history of disease leading to notified influenza would improve our interpretation of this surveillance information.

Methods

For the period 2005 to 2007 in NSW, we used probabilistic record linkage to match laboratory confirmed influenza notifications with Emergency Department (ED) presentations, hospital admissions and death registrations.

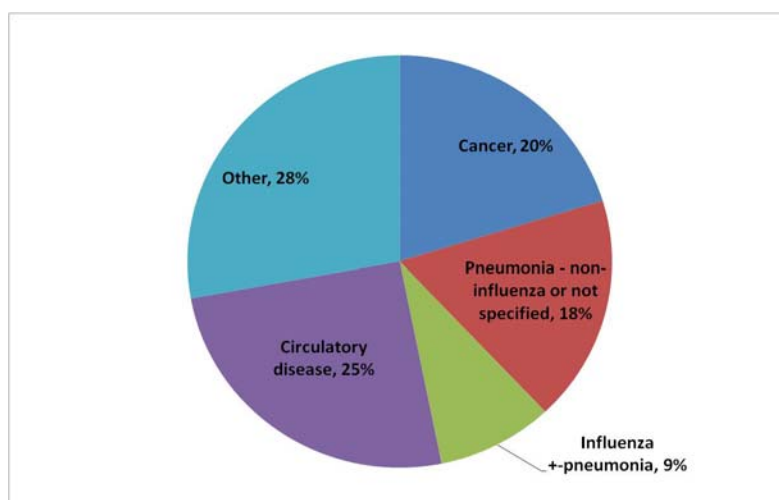
Results

During 2005 to 2007, there were 3121 influenza notifications, of which one third were in children. Of the 3121 notifications, 1914 (61%) matched an ED presentation, 1734 (56%) matched a hospital admission, and 79 (2.5%) matched a death. Ten (13%) of the 79 deaths were not recently hospitalised. Influenza was recorded as a primary diagnosis in only 6% of the 1914 matching ED presentations, and 20% of the 1734 admissions. It was recorded as the underlying cause of death in only 9% of the 79 death registrations.

Conclusion

Notified influenza is weighted towards people, particularly children, encountering the hospital system. Influenza is uncommonly recorded as a main diagnosis or cause of death. Notified influenza represents the tip of the iceberg, but may be useful for monitoring trends in more severe infections.

Figure: Underlying cause of death among 79 deaths with an associated influenza notification, NSW, 2005-2007



Note: Preliminary analysis only

Workshop 2 – Epidemiology

Impact of influenza on intensive care unit (ICU) admissions in NSW 2007-10

AL Schaffer, D Muscatello, R Gilmour, S Tobin

Background

In NSW, the 2009 epidemic of pandemic (H1N1) 2009 virus was reported to have led to unprecedented demand for intensive care services (ICU).

Methods

We used time series from the NSW Admitted Patient Data Collection (APDC) to investigate the impact of seasonal and pandemic influenza on the number of ICU admissions, in the general population and in high risk populations.

Results

In 2009, the weekly number of ICU admissions with influenza peaked at 51, compared to a high of 9 in all other years. Patients receiving extracorporeal membrane oxygenation (ECMO) and pregnant women both with any respiratory illness and with influenza were also at their highest. Overall though, the number of ICU admissions with any respiratory illness was greater in 2007 than in 2009 (Figure 1). In Aboriginal persons, similar counts were admitted to ICU with respiratory illness in both these years (Figure 2).

Discussion

The 2009 epidemic led to increased use of ECMO and intensive care (ICU) admissions in pregnant women compared with recent seasonal influenza epidemics. Overall and in Aboriginal persons, the number of respiratory ICU admissions in 2009 was similar to 2007, a severe influenza season. This could reflect under-recognition of the impact of influenza on ICU admissions in the past, or reduced susceptibility in older persons. The different pattern in pregnant women and ECMO usage could signify unique characteristics of the pandemic virus.

Figure 1: Weekly counts of ICU admissions with respiratory illness, NSW, 2007-2010

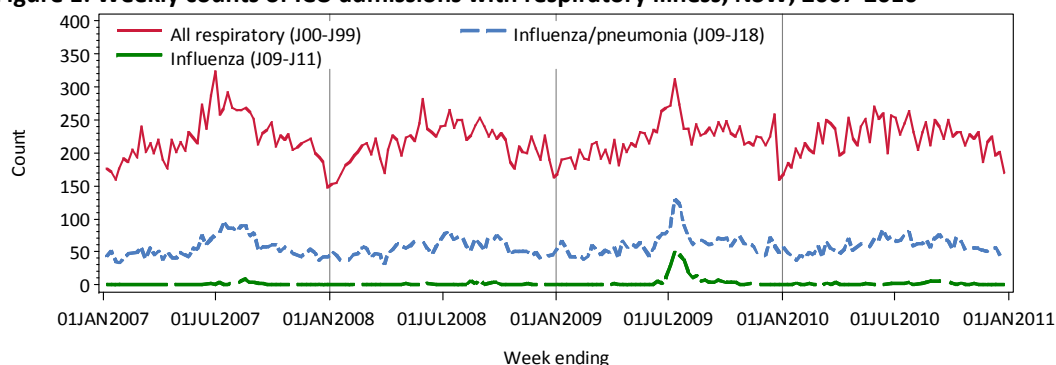
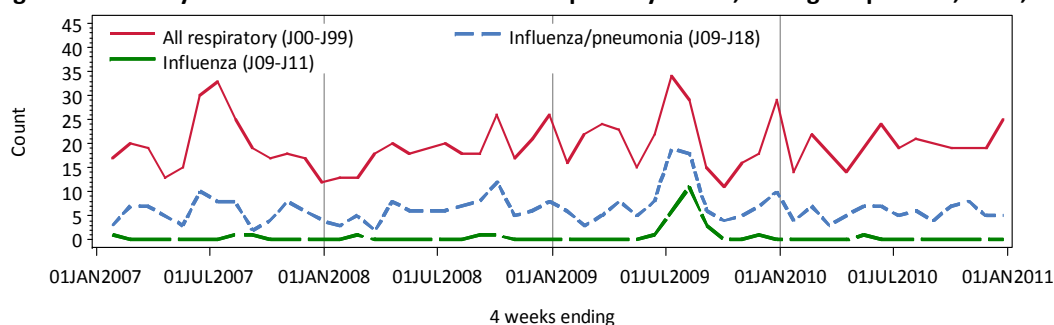


Figure 2: Monthly counts of ICU admissions with respiratory illness, Aboriginal persons, NSW, 2007-2010



Workshop 2 – Epidemiology

Flutracking.net: A syndromic perspective on influenza

Craig B. Dalton, Sandra Carlson, Michelle Butler, John Fejsa, Elissa Elvidge, David N. Durrheim

Flutracking is an online weekly surveillance system of influenza-like illness (ILI) that began in 2006 with 400 participants and has grown to over 10,000 weekly participants each week in winter of 2011. This paper reviews selected features of this syndromic surveillance system and its contribution as one of a suite of national influenza surveillance systems.

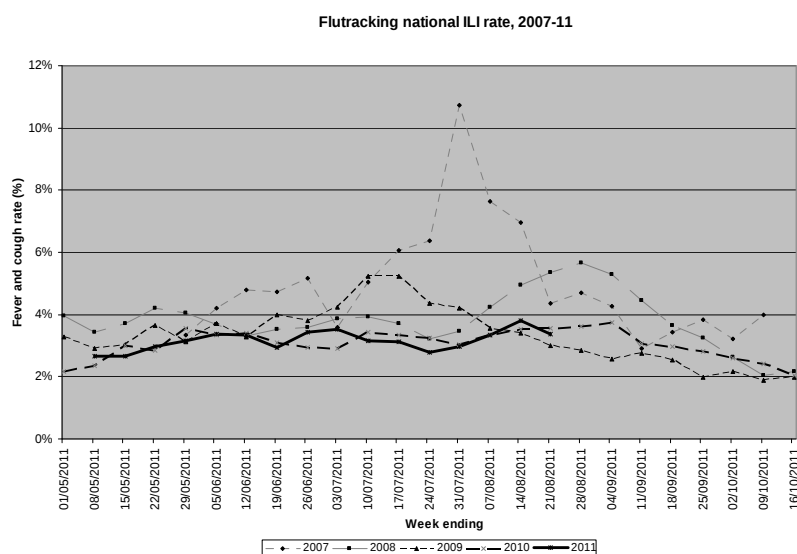
ILI surveillance unbiased by health seeking behaviour or testing practices – Health seeking behaviour and testing practices distorted emergency department ILI and laboratory influenza test surveillance during the 2009 pandemic, Flutracking was not impacted by these biases and was able to demonstrate that the 2009 pandemic had only moderate impact at a community level and was consistent with other syndromic surveillance systems.

National coverage – While the rates of participation are not uniform across the country, Flutracking uses a standardised method of data collection that escapes potential jurisdictional biases.

Influenza vaccine monitoring – Flutracking compares cough and fever rates between vaccinated unvaccinated participants allowing a calculation of field vaccine effectiveness (FVE). This provides an indication of FVE – becoming negative during the pandemic – and also allows rapid identification of changes in vaccine uptake. The decrease in uptake of influenza vaccine in children under 10 years of age was rapidly identified in early 2011 following the adverse reactions identified in 2010.

Socio-economic analyses - Socio-economic factors appear to have been important in the early transmission of A(H1N1) 2009 influenza viruses. Flutracking identified an earlier and higher peak in ILI among participants of lower SEIFA postcodes in NSW in 2009.

Influenza burden of illness calculations – In 2011, Flutracking collected information on health seeking behaviour by, and testing of, participants to begin to calculate the burden of illness pyramid for influenza.



Workshop 2 – Epidemiology

What was the reproduction number of pandemic H1N1 influenza, and how did it vary by age?

Kathryn Glass¹, Heath Kelly^{1,2}, Geoff Mercer¹

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Many estimates were made of the reproduction number for pandemic H1N1 influenza over the course of the 2009 pandemic. A comparison of these estimates suggests that children may have been disproportionately responsible for disease spread. We present new methods to calculate age-specific reproduction numbers from seroprevalence data, and apply these to pandemic H1N1 data.

Median estimates of the population reproduction number calculated from seroprevalence data ranged from 1.14 to 1.36, with only slight differences between countries. An age-specific analysis of the data indicates that the reproduction number for children was around 1.6, while the reproduction number for adults over 25 was less than one.

These age-specific patterns in transmission may help to explain the variability in estimates of the reproduction number made using outbreak data. In particular, they explain the high estimates of the reproduction number arising from outbreaks involving a large proportion of children.

Workshop 2 – Epidemiology

Pandemic Severity Determines Cost-Effectiveness of Interventions: Results from a Modelling and Economic Analysis

George J. Milne, Nilimesh Halder, Joel K. Kelso

Background

The severity of an influenza pandemic directly influences the total cost of the pandemic, since hospitalisation and mortality rates are higher with a more pathogenic virus. Both high transmission characteristics and high mortality rates will contribute to significant healthcare costs and productivity losses due to death. While models have been extensively used to determine the effectiveness which interventions have on reducing the illness attack rate, there is little evidence as to the effect which severity has on the cost-effectiveness of interventions.

Methods and Findings

We utilised an individual-based simulation model and an economic analysis methodology to determine the overall cost of a range of interventions which aim to reduce the illness attack rate. Using data from the 2009/2010 pandemic, and a pandemic severity scale which relates hospitalisation and ICU rates to case fatality ratios, we determined which interventions are most cost-effective for a particular severity category. We examined a comprehensive range of interventions involving social distancing and antiviral drug measures, singly and in combination, to quantify their effectiveness and cost-effectiveness under three transmission settings and a range of severity levels. For low severity pandemics, as interventions increase in effectiveness (by combining interventions together and having them applied longer), costs also increase. In contrast, for high severity pandemics, increasing intervention effectiveness decreases intervention costs. For example, for a pandemic with $R = 1.8$ a strategy of antiviral treatment, household prophylaxis and continuous school closure is projected to reduce the attack rate from 32.4% to 9.2%. For a pandemic with a case fatality ratio (CFR) of 0.005% (consistent with the H1N1 2009 pandemic) the incremental cost of this intervention compared to no intervention is \$292 per person; for a CFR of 0.1% the cost is \$33 per person; and for a CFR of 0.25% the intervention results in a cost *saving* of \$329 per person. This difference in cost due to severity arises since with low severity pandemics the overall costs are dominated by productivity losses due to illness and social distancing interventions, whereas with higher severity pandemics total costs are dominated by healthcare costs and costs arising from productivity losses due to death.

Conclusions

These findings indicate that strict social distancing policies which may be considered unacceptable for mild or moderate influenza pandemics due to their disruptive effects on society and the economy are, for pandemics in the higher severity categories, both necessary for preserving life and less costly than not enacting them when considering the total cost of a pandemic.

Workshop 2 – Epidemiology

Hospital Capacity and Management Preparedness for Pandemic Influenza in Victoria

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Background

Few reviews of Australian hospital performance during the 2009 H1N1 pandemic have been undertaken or published. Hospitals face particular challenges during an Influenza pandemic for which they need to plan. One of the lessons highlighted by the 2009 H1N1 influenza pandemic was the need for health services, especially those with critical care facilities such as Intensive Care Units and Emergency Departments to plan and prepare for the strain a future pandemic may pose.

Aim

To investigate the Influenza pandemic preparedness of acute hospitals in Victoria, Australia, focusing on planning and management efforts.

Methods

Questionnaires were sent to every hospital in Victoria with an Emergency Department, targeting those individuals responsible for planning and coordinating an emergency management response. Follow-up phone interviews were also conducted on the experience of hospital managers during the 2009 H1N1 pandemic.

Results

All services reported having either a general external emergency plan or specific pandemic plan in place with 86% of plans having been reviewed in the last two years. Infection control (78.7%) and OHS (50%) were most commonly represented on planning committees, though supply (7%) and pharmacy (7%) were under-represented. Fewer than a third of plans (28.6%) had been tested in a functional exercise or drill. Contingencies for non-clinical staff, the workforce group most likely to demonstrate absenteeism in a pandemic, had not been accounted for in a high proportion of all health service plans (28.6%) and particularly in metropolitan hospital service plans (42.9%). All Rural/Regional respondents and two thirds of health services overall (66.7%) reported that patient needs could not be met with pandemic level staff absenteeism. Despite the 2009 H1N1 pandemic heightening exposure of the need for vaccination, which contributes not only to absenteeism but to the spread of Influenza and poorer patient outcomes in the health setting, almost half (48.8%) of the Victorian healthcare workforce remained unvaccinated in 2009. Managers reported that with the Victorian health system already running at capacity, issues of workforce, infrastructure and supply would be those that health services would struggle with most. Rapidly changing and often inconsistent communications produced at the State and National levels during the 2009 pandemic created further confusion for health practitioners and managers.

Conclusions

Health services in Victoria displayed a high level of awareness and activity in planning for the next Influenza pandemic, although a lack of formal testing of emergency and pandemic plans through formal exercises and drills may undermine their effectiveness. Workforce, infrastructure and supply capacity in a pandemic remain issues requiring further investment. The concept of mandatory vaccination should be tested amongst the Australian healthcare workforce to determine its acceptability and capacity for adoption.

Roundtable discussion

Childhood vaccination: where do we stand now?

Panelists:

- **Lorena Brown**
- **Peter Richmond**
- **Jodie McVernon**
- **Robert Booy**
- **Ben Cowling**

Should we have a universal vaccination policy for children?

Should there be a selective vaccination policy (eg risk groups)?

Should we have a quadrivalent vaccine for kids?

Should we use live attenuated vaccines for kids?

Plenary Session 5

Non-pharmaceutical interventions to reduce influenza transmission: lessons from the two most sparsely populated countries on Earth.

Jodie McVernon

Pandemic preparedness plans are uniform in recommending implementation of ‘non pharmaceutical measures’ as part of a suite of approaches to control transmission of an imported infection. The absence of data from which to estimate the effectiveness of many such interventions prior to the 2009 pandemic prompted extensive use of modeling for policy decision support to inform their optimal implementation.

In the evaluation of the response to the 2009 pandemic, much attention has been paid to the limited ability of these ‘containment’ measures to control spread, with a few key exceptions. Public health response capability was overwhelmed in most countries that pursued intensive case-finding and quarantine strategies. The social and economic disruption associated with school and workplace closure was a disincentive to application of the kinds of generalized, prolonged measures predicted to be effective.

Elements of the pandemic response involving school closure in two very different settings – Melbourne and Mongolia - will be compared. We will review lessons learned regarding the feasibility and likely effectiveness of alternative approaches, given contextual opportunities and limitations. The critical importance to success of epidemic characteristics, timely and decentralized interventions will be discussed.

Plenary Session 5

Influenza transmission in households

Benjamin J. Cowling

School of Public Health, The University of Hong Kong, Hong Kong

A substantial fraction of influenza transmission occurs in households, and households can provide a good natural setting to examine the epidemiology of influenza.

Controlling transmission in households could help to mitigate seasonal epidemics and influenza pandemics. In the 2009 pandemic many household transmission studies were implemented to understand better the characteristics of the transmission of the novel virus. It is surprising that there appeared to be substantial heterogeneity in the degree of influenza transmission in households in different countries and settings, with 12 studies reporting point estimates of the laboratory confirmed secondary attack rate ranging from 4% to 38%.

I will discuss some experiences and results from household transmission studies in Hong Kong, and review the findings and implications of household transmission studies conducted worldwide during the 2009 pandemic.

Plenary Session 5

Influenza Research In The Sydney Institute For Emerging Infections And Biosecurity

Tania C. Sorrell

The SEIB is a new, multidisciplinary, virtual institute of the University of Sydney, based primarily on three of its major campuses. Its primary goal is to reduce the global impact of emerging infectious diseases in our region by partnering in research, education, training and capacity building, and by improving communication and advocacy.

Influenza constitutes an emerging infectious disease, not because it is "new" but because it undergoes significant recrudescences and emerges or re-emerges in different locations. SEIB research into influenza is primarily translational and involves the medical, veterinary biological and social sciences. Influenza par excellence offers the opportunity for networked research, which builds on basic research and translates through to health services research. Within SEIB the faculties of medicine, veterinary science, science, nursing and midwifery, pharmacy, law, arts and social sciences (including political science), engineering and information technology are all contributing to individual research projects or multidisciplinary programs. These will be outlined in this presentation

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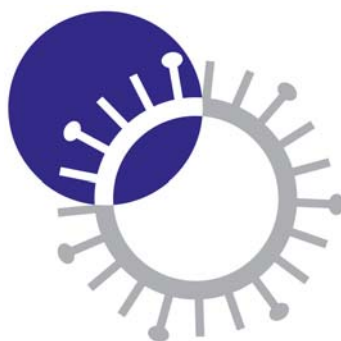
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