8th Australian Influenza Symposium

4-5 October 2012

John Curtin School of Medical Research, ANU, Canberra, Australia

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

With the assistance of the
Therapeutic Goods Administration
and the financial support of the
Australian Government Department of Health and Ageing
Front Cover Image:
The image on the front page was produced by Jason A. Roberts, National Enterovirus Reference Laboratory WHO Poliomyelitis Regional Reference Laboratory VIDRL, North Melbourne, Victoria and is a representation of an Influenza B virus nucleoprotein tetramer as determined by X-ray crystallography. Coordinate data derived from PDB file accession No. 3JTO. Further information can be found in the original paper by Ng, AKL et al, J. Virol. June 2012 86:6758-6767 (DOI:10.1128/JVI.00073-12).
Welcome

The WHO Collaborating Centre for Reference and Research on Influenza and the Therapeutic Goods Administration are delighted to welcome you to the 8th 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
- Jayde Simpson

Therapeutic Goods Administration
- Dr. Gary Grohmann
Table of Contents

Program Day 1 ................................................................. 3
Program Day 2 ................................................................. 4
ABSTRACTS ........................................................................ 5-37
Plenary Session 1 ............................................................. 5
Plenary Session 2 ............................................................. 8
Roundtable Discussion..................................................... 12
Workshop 1 - Clinical & Research .................................... 13
Plenary Session 3 ............................................................. 19
Plenary Session 4 ............................................................. 21
Workshop 2 – Epidemiology ............................................ 27
Plenary Session 5 ............................................................. 35
Participants........................................................................ 39
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Chair</th>
<th>Speaker</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:15am</td>
<td>Opening</td>
<td>Ian Barr and Gary Grohmann</td>
<td>Anne Kelso, WHOCC</td>
<td>Opening and welcome</td>
</tr>
<tr>
<td>9:30am</td>
<td>Plenary</td>
<td>Danuta Skowronski</td>
<td>Immuno-epidemiologic insights</td>
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</tr>
<tr>
<td>10:00am</td>
<td>Plenary</td>
<td>Ralph Tripp</td>
<td>Enhancing the T cell response to influenza: A therapeutic approach</td>
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<tr>
<td>10:30am</td>
<td>Plenary</td>
<td>Edward Holmes</td>
<td>Evolution of influenza virus in diverse mammalian hosts</td>
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<td>Morning Tea</td>
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<tr>
<td>11:30am</td>
<td>Plenary</td>
<td>Philippe Buchy</td>
<td>Research on influenza A/H5N1 virus in Cambodia at the human/animal/environmental interface</td>
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<td>11:55am</td>
<td>Plenary</td>
<td>Mark Tompkins</td>
<td>Rapid antibody response engineering and development of human monoclonal antibody therapeutics for influenza</td>
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<td>12:20pm</td>
<td>Plenary</td>
<td>Sue Huang</td>
<td>Southern hemisphere influenza and vaccine effectiveness research and surveillance (SHIVERS) in New Zealand</td>
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<tr>
<td>12:45pm</td>
<td>Plenary</td>
<td>Peter Daniels</td>
<td>Influenza A viral infections in farm animals. Recent trends with an emphasis on Australian experiences</td>
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<td>Opening Presentation: Michael Selgelid</td>
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<td>3:00pm</td>
<td>Workshops</td>
<td>Steven Rockman</td>
<td>Efficacy of a single dose of intravenous immunoglobulin to prevent pandemic influenza</td>
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<td>3:15pm</td>
<td>Workshops</td>
<td>Philippe Buchy</td>
<td>Cross-neutralization activity of anti-H5N1 specific polyclonal immunoglobulins against heterologous strains of H5N1 virus</td>
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<td>3:30pm</td>
<td>Workshops</td>
<td>Jasmina Luczo</td>
<td>The role of endothelium in the pathogenicity of H5N1 highly pathogenic avian influenza in chickens</td>
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<td>3:45pm</td>
<td>Workshops</td>
<td>Sarah Londrigan</td>
<td>Close encounters with macrophages and dendritic cells: entry of influenza virus via C-type lectin receptors</td>
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<td>4:00pm</td>
<td>Workshops</td>
<td>Kevin Downard</td>
<td>Mass trees: Adding weight to the tree of life to study the evolution of the influenza virus</td>
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<td>4:15pm</td>
<td>Workshops</td>
<td>Jenny McKimm-Breschkin</td>
<td>Screening neuraminidase inhibitor susceptibility of avian influenza isolates from SE Asia 2005-2008 identifies H5N1 I222 mutants with reduced oseltamivir sensitivity</td>
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<td>4:50pm</td>
<td>Plenary</td>
<td>Ian Gust</td>
<td>20 years of the WHOCC Melbourne &amp; 60 years of WHO influenza surveillance</td>
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<td>5:15pm</td>
<td>Plenary</td>
<td>Anne Kelso</td>
<td>People, pigs and politics: the WHO Collaborating Centre and WHO’s global influenza program today</td>
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<td>Plenary</td>
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<td>Dinner at the Banana Leaf Restaurant &amp; Café, 250/240 City Walk, Canberra, Phone: (02) 6248 5522</td>
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### Day 2
**Fri 5 October**

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Chair/Presenter</th>
<th>Topic</th>
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</thead>
</table>
| **8:00 am** | Plenary Session 4 | **Chair: Gary Grohmann, TGA** | Progress toward improved influenza control with quadrivalent influenza vaccines  
Investigations into febrile reactions observed in the pediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine – Part 1 |
| **8:25 am** | | Mark Simmerman | Toward improved influenza control with quadrivalent influenza vaccines  
Investigations into febrile reactions observed in the pediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine – Part 1 |
| **8:50 am** | | Darryl Maher | Toward improved influenza control with quadrivalent influenza vaccines |
| **9:15 am** | | Martin Pease | As above – Part 2  
Aspects of the WHO Global Action Plan and the changing technology landscape for novel influenza vaccines. |
| **9:30 am** | | Gary Grohmann | Aspects of the WHO Global Action Plan and the changing technology landscape for novel influenza vaccines. |
| **9:35 am** | | Craig Rayner | Oseltamivir - Recent clinical pharmacology updates on intravenous formulation and PK/PD |
| **10:00 am** | Morning Tea | | |
| **10:30 am** | Workshop 2 - Epidemiology | **Chairs: Kathryn Glass, ANU and Rhonda Owen, DoHA** | Comparison of time series methods for estimated seasonal and pandemic influenza-attributable mortality in Australia, 2003 to 2009 |
| **10:45 am** | | James McCaw | Defining pandemic impact levels to guide a proportionate and flexible operational response to the next influenza pandemic |
| **11:00 am** | | George Milne | Cost-effectiveness of combining social distancing, antiviral and vaccination interventions for pandemic influenza: A modelling study |
| **11:15 am** | | Heath Kelly | Influenza vaccine effectiveness: time for a new orthodoxy |
| **11:30 am** | | Monique Chilver & Nigel Stocks | Out with the old, in with the new? Are new methods of influenza syndromic surveillance set to take over from classical methods? |
| **11:45 am** | | Ee Laine Tay | Using routinely collected data to establish thresholds for influenza surveillance in Victoria, Australia. |
| **12:00 pm** | | Robin Gilmour | Issues affecting the management of influenza outbreaks in residential care facilities. |
| **12:15 pm** | | Niamh Stephenson | “Choice immunity” versus Herd Immunity: The absence of collective notions of immunity in public understandings of influenza |
| **12:30 pm** | Lunch | | |
| **1:30 pm** | Plenary Session 5 | **Chair: Heath Kelly, VIDRL** | Targeting OAT3 for anti-influenza therapy  
Neuraminidase inhibiting antibody as a correlate of seasonal vaccine-induced cross-protection against H5N1 |
| **1:55 pm** | | Ralph Tripp | Targeting OAT3 for anti-influenza therapy  
Neuraminidase inhibiting antibody as a correlate of seasonal vaccine-induced cross-protection against H5N1 |
| **2:20 pm** | | Lorena Brown | Neuraminidase inhibiting antibody as a correlate of seasonal vaccine-induced cross-protection against H5N1 |
| **2:45 pm** | | Danuta Skowronski | Annual influenza vaccine effectiveness monitoring: lessons learned from Canada and the need for vaccine improvement  
Respiratory illness in a piggery associated with novel influenza A viruses: assessing the risk to human health |
| **3:25 pm** | | Paul Effler | Annual influenza vaccine effectiveness monitoring: lessons learned from Canada and the need for vaccine improvement  
Respiratory illness in a piggery associated with novel influenza A viruses: assessing the risk to human health |
| **3:30 pm** | | Closing remarks | Conference concludes |
ABSTRACTS

Plenary Session 1

Immuno-epidemiologic insights

Danuta Skowronski

University of British Columbia

The burden of influenza varies from year-to-year in part due to the dynamic interaction between evolving influenza viruses and population immunity. The immuno-epidemiology of influenza is highly complex but its understanding is central to optimal prevention and control strategies. Annual vaccine approval relies upon biological markers of potency and immunogenicity studies that may not reflect functional antibody response to circulating strains or take into account other important immunologic indicators or interactions. Recent experience with the 2009 pandemic H1N1 epidemic waves, other novel emerging swine-origin viruses, and seasonal drift strains, have shown the importance of the underlying immunologic landscape in influencing protection and risk assessment. These events have also provided opportunity to re-examine hypotheses such as original antigenic sin and the related concept of antibody dependent enhancement, long debated by influenza scientists. These immunologic concepts will be discussed at the individual and population level and interpreted through an epidemiologic lens.
Plenary Session 1

Enhancing the T cell response to influenza: A therapeutic approach

Ralph A. Tripp*, Julie M. Fox*, Leo K. Sage†, Kimberly D. Klonowski‡, Andrew L. Mellor†, and S. Mark Tompkins*

*Department of Infectious Diseases and † Department of Cellular Biology, University of Georgia, Athens, GA 30602, USA; ‡Immunotherapy Center and Department of Medicine, Georgia Health Sciences University, Augusta, GA 30912, USA

Influenza virus is a worldwide health concern, particularly for persons at the extremes of age, i.e. the young and elderly. Influenza infection induces an increase in the level of indoleamine 2, 3-dioxygenase (IDO) activity in the lung parenchyma. IDO is the first and rate limiting step in the kynurenine pathway where tryptophan is reduced to kynurenine and other metabolites. The depletion of tryptophan, and production of associated metabolites, attenuates the immune response to infection. The impact of IDO on the primary immune response to influenza virus infection was determined using the IDO inhibitor 1-methyl-D, L-tryptophan (1MT). C57BL/6 mice treated with 1MT and infected with A/HKx31 influenza virus had increased numbers of activated and functional CD4+ and CD8+ T cells, influenza-specific CD8+ T cells, and activated pulmonary leukocytes in the lung. Inhibition of IDO enhanced IFN production and was linked to a resurgence of CD8+ T cells at day 12 post-infection. These studies show that inhibition of IDO facilitates a more robust T cell response to influenza virus and suggests an approach for enhancing the immune response to influenza vaccination by providing increased T cell memory generation and potential heterosubtypic immunity.
Plenary Session 1

Evolution of influenza virus in diverse mammalian hosts

Edward C. Holmes\textsuperscript{1,2}

\textsuperscript{1}Sydney Emerging Infections and Biosecurity Institute, School of Biological Sciences and Sydney Medical School, The University of Sydney, Sydney, NSW 2006, Australia
\textsuperscript{2}Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA

My aim in this lecture is to briefly overview a number of recent developments stemming from the evolutionary analysis of influenza virus in humans and other animals. First, I will explore the pattern and determinants of the spread of human influenza virus on a global scale, with a particular focus on patterns of virus evolution in southern China. Using a combination of incidence and sequence data I will show that southern China is unlikely to represent an epicenter of global influenza activity. Rather, it appears that novel influenza viruses emerge and evolve in multiple geographic localities. Second, I will examine the extent, nature, and consequences of intra-host genetic diversity in influenza virus. Using a natural outbreak of equine influenza virus as an example I will show that mixed infections may be commonplace in nature with related minor variants transmitted between horses. Hence, transmission bottlenecks may be loose in natural situations. Importantly, frequent mixed infections can influence the size of epidemics and assist viral emergence by facilitating segment reassortment. Similarly, I will show how the ultra-deep sequencing of viral populations from individual hosts can provide key information on the emergence of drug resistance and the fitness of drug resistant compared to wild-type mutants. Specifically, in an examination of serial nasopharyngeal specimens from an immunocompromised child and from two individuals in a household outbreak, the Y275 (NA) mutation associated with oseltamivir resistance was present as a minor variant in infected hosts prior to onset of drug therapy. The drug-resistant variant was also transmitted between hosts alongside drug-sensitive viruses. Third, I will also explore evolutionary aspects of PA-X – a recently discovered fusion protein of influenza A virus encoded in part from a +1 frameshifted ‘X-ORF’ in PA. I will show that the X-ORF of diverse influenza A viruses can be divided into two groups that differ in selection pressure and likely function, reflected in the presence of an internal stop codon and a change in synonymous diversity. Notably, truncated forms of PA-X evolved convergently in swine and dogs, suggesting a strong species-specific effect. Finally, I will end with some general comments on what aspects of the future emergence and evolution of influenza virus are predictable.
Plenary Session 2

Research on influenza A/H5N1 virus in Cambodia at the human/animal/environmental interface

Philippe Buchy

Head of Virology Unit, Institut Pasteur in Cambodia, Phnom Penh

Since 2003, over 600 laboratory-confirmed human cases with avian influenza A/H5N1 virus infection have been reported from 125 countries. Over 350 patients (~60%) died from the disease. The endemic circulation of H5N1 virus in several countries and the risk that the virus might evolve and acquire the ability to easily spread from person to person is a serious public health concern.

The primary risk factor for human infection appears to be direct or indirect exposure to infected birds or contaminated environments. Surprisingly, the role of the environment in the transmission of H5N1 virus remains poorly studied.

Other the last few years, the Virology Unit at Institut Pasteur in Cambodia developed with international partners several projects to study H5N1 virus genomics, evolution, sensitivity to drugs, and also to better understand the role of the environment (soil, water, etc.) in virus natural cycle, persistence, and in human or animal infection.
Plenary Session 2

Rapid antibody response engineering and development of human monoclonal antibody therapeutics for influenza

Stephen M. Tompkins¹, Scott K. Johnson¹, Krista McCutcheon², Shelly J. Samet¹, Jon D. Gabbard¹, Daniel A. Dlugolenski¹, Minha Park¹, Keyi Liu¹, Stote L. Ellsworth², Lawrence M. Kauvar², Ralph A. Tripp¹, and William R. Usinger²

¹Univ. of Georgia, Athens, GA 30602
²Trellis Bioscience, South San Francisco, CA 94080

Seasonal influenza virus infections cause significant morbidity and mortality each year, particularly in the young and elderly populations, and pandemic influenza continues to be a looming threat. While vaccines are generally effective, production time, strain matching, and vaccine failure in at-risk populations continue to be major problems. Licensed anti-viral drugs can reduce disease; however drug resistance is increasing and may render existing antivirals useless. New therapeutic strategies are needed. Therapeutic monoclonal antibodies have been shown to be efficacious in humans against a variety of diseases, including viral respiratory infection. While neutralizing antibodies against the hemagglutinin glycoprotein (HA) of influenza A virus are protective, the multiple circulating subtypes and constant antigenic drift of the immunodominant portion of the HA limit the cross-reactivity of antibody responses. Accordingly, broadly neutralizing cross-reactive monoclonal antibodies are exceedingly rare. We have used CellSpot™ technology to identify and isolate B cells from human peripheral blood that are reactive for multiple subtypes of influenza HA. Positive clones were used to generate fully human monoclonal antibodies. Here we describe the identification and characterization of fully human monoclonal antibodies specific for the HA of influenza A virus, which bind with high affinity and cross-react with multiple subtypes of influenza virus, including H5N1 highly pathogenic avian influenza and pandemic H1N1 viruses, as well as seasonal and swine influenza viruses. We show these antibodies neutralize multiple strains and subtypes of influenza virus and protect against lethal influenza virus challenge in a murine model of infection.
Plenary Session 2

Southern hemisphere influenza and vaccine effectiveness research and surveillance (SHIVERS) in New Zealand

Sue Huang on behalf of the SHIVERS science team for SARI surveillance

Institute of Environmental Science and Research, Wellington, New Zealand

Background:
In October 2011, the Centers for Disease Control and Prevention (CDC) awarded New Zealand’s Institute of Environmental Science and Research (ESR) a five year grant to conduct influenza surveillance and vaccine effectiveness research. This research programme, called SHIVERS (Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance) is a multi-centre and multi-disciplinary collaboration among ESR, Auckland District Health Board (ADHB), Counties Manukau District Health Board (CMDHB), University of Otago, University of Auckland, WHO Collaborating Centre at St Jude Children’s Hospital in Memphis, USA and CDC. The study has nine specific objectives. These are: 1) determine the incidence and prevalence of severe respiratory infections; 2) assess influenza vaccine effectiveness; 3) study the interaction between influenza virus and other pathogens; 4) ascertain the causes of respiratory mortality; 5) determine the incidence and prevalence of non-severe respiratory illness; 6) conduct an influenza seroprevalence study; 7) determine influenza risk factors; 8) study the immune response to influenza; 9) determine the healthcare, societal economic burden and vaccine cost-effectiveness.

Methods:
We propose to establish two prospective and enhanced surveillance systems (hospital-based and community-based) for Auckland’s ADHB and CMDHB population (838,000):
Hospital-based surveillance: enhanced, active, year-round (5 years), longitudinal, population based surveillance for hospitalized severe acute respiratory infection (SARI) cases, ICU admissions and deaths caused by influenza and other respiratory pathogens,
Community-based surveillance: enhanced, active, year-round, longitudinal (4 years), sentinel general practice surveillance for community influenza like illness caused by influenza and other respiratory pathogens in Auckland.
The two surveillance systems will provide data and laboratory specimens to comprehensively investigate influenza epidemiology, aetiology, immunology and vaccine effectiveness for nine specific objectives.

Results:
The hospital-based SARI surveillance was established and has been in operation since 30 April 2012. The community-based surveillance will commence in 2013. This presentation will detail the SARI surveillance focusing on specific aims, study population, sample size justification, SARI case definition, case ascertainment and laboratory testing. The data obtained from the surveillance since 30 April 2012 will be presented in terms of SARI incidence and trends including demographics, co-morbidities, health and environmental factors. It will also focus on aetiological agents such as influenza and other respiratory pathogens including co-infections.

Conclusion:
The results from the SHIVERS will guide improved methods for disease surveillance, assist early detection and prediction, guide targeted vaccination strategies for population and subgroups and better vaccine design, optimize clinical management and laboratory diagnosis, identify risk factors, understand host immune response and identify better immune diagnostic markers.
Plenary Session 2

Influenza A viral infections in farm animals. Recent trends with an emphasis on Australian experiences

Peter Daniels¹, Frank Wong¹, Yi Mo Deng², James Watson¹, Paul Selleck¹ and Ian Barr²

¹CSIRO Australian Animal Health Laboratory, PMB 24, Geelong Vic 3220
²WHO Collaborating Centre for Reference and Research on Influenza, Victorian Infectious Diseases Reference Laboratory (VIDRL), 10 Wreckyn St, North Melbourne, Vic 3051

During 2012 influenza A viral infections have been detected in farm animals in 6 different outbreaks. Large teams of people have been involved in the investigations, from Commonwealth and State Departments of Agriculture and from public health agencies. Analysis of data has been greatly facilitated through comparisons with the data developed by the National Avian Influenza in Wild Birds surveillance program. These national collaborations to develop full understandings of the epidemiological circumstances of occurrences of influenza virus infections in livestock are excellent examples of the “One Health” approach in action.

Low pathogenic avian influenza infections have been detected in commercial poultry enterprises in three states. There has been H5N3 infection of duck farms in Victoria in January, an H4N6 infection of a duck farm in NSW in April, H9N2 infection in turkey farms in NSW in April and an H10N7 infection of a chicken farm in Qld in June. This is an unusual number of detections of such influenza A infections in poultry. Also unusual has been the further detection of influenza A infections in pigs in Australia, which were first reported where the pandemic H1N1 2009 virus was transmitted from people to pigs in that year, with occurrences detected in NSW, Qld and WA. In July 2012 influenza virus infection was detected in a pig enterprise in WA comprising a number of farms managed as an epidemiologically linked enterprise – not the location where pH1N12009 was reported previously. Viruses with H1 and H3 haemagglutinin types and different N2 neuraminidase proteins have been identified in a number of reassortant configurations. In August in Qld in a separate incident a reassortant influenza A virus with gene segments coding for H1 and N2 proteins different from those in the WA outbreak was identified on a pig farm in that state. There have been no human infections associated with these infections.

Internationally the study of influenza viruses in farm animal populations has been intensified, with OFFLU engaged and coordinating activities where possible. An OFFLU activity has been established that brings together expertise in influenza infections in swine from around the world. This group meets annually and communicates to share information and advocate increased surveillance in pig populations. OFFLU continues to collate all available data on avian influenza viruses considered to have pandemic potential, especially H5N1 “bird flu” and also H9 infections in poultry. Such information is specifically prepared for the WHO VCM process so that recommendations for antigens in pandemic preparedness stockpiles can be kept current with respect to strains being transmitted in poultry.
Roundtable Discussion: Ethics of influenza virus manipulations

Opening Presentation by Michael Selgelid, Monash University:

Ethics and dangerous discoveries: Dual use life science research

This paper provides analysis of the concept of “dual use” and examines ethical issues associated with dual use implications of life science research in particular. The dual use phenomenon creates an ethical dilemma for individual scientists, policy makers and others. This paper reviews recent controversial cases of dual-use life science research (with emphasis on H5N1 transmissibility studies), highlights the ethical responsibilities of various actors at different levels of the science governance hierarchy, and evaluates the ethical propriety of governance mechanisms that might be employed at various stages of the dual-use pipeline. While upstream governance mechanisms might involve things like ethics education and codes of conduct for scientists, downstream mechanisms could involve imposition of tighter controls over who has access to dual-use materials and technology. The upstream mechanisms required to protect against dual use dangers partly depend upon those employed downstream, and vice-versa. Rather than ultimately choosing between upstream and downstream governance mechanisms, however, a “web of prevention” is ultimately wanted.
Workshop 1 - Clinical & Research

Efficacy of a single dose of intravenous immunoglobulin to prevent pandemic influenza

Steven Rockman*, Sue Lowther^, Sarina Camuglia*, Kirsten Vandenberg*, Deborah Middleton^ Darryl Maher*

*CSL Limited Parkville Australia
^ Australian Animal Health Laboratories CSIRO Geelong Australia

Objective of the study:
Intravenous immunoglobulin (IVIG) is widely used to treat immune deficiencies, autoimmune disease and chronic inflammatory conditions. Sporadic reports have suggested that IVIG may be useful in the influenza setting. The influenza pandemic of 2009 and global circulation of highly pathogenic H5N1 has sparked interest in alternative therapies for the treatment of serious influenza infection. IVIG has been demonstrated to contain cross-reactive antibodies to pandemic influenza. Further, IVIG has properties of modulating the immune response that may influence the hypercytokinaemia or “cytokine storm” which is a suspected contributing factor to mortality in the pandemic influenza setting.

The aim of this study was to investigate the efficacy of IVIG in two ferret models of pandemic influenza.

Methods:
Two models of pandemic influenza were analysed. The swine origin H1N1 pandemic of 2009 and highly pathogenic H5N1 model in ferrets. IVIG was administered as a single dose at the time of challenge. Ferrets were assessed for weight loss, temperature, activity and viral replication over a 14 day post-challenge period.

Results:
IVIG harvested prior to 2009 prevented significant viral replication (number of isolates and viral titre) of the swine origin H1N1 virus in the lung but not the upper respiratory tract. A single dose of IVIG prevented mortality and significant morbidity following challenge with a lethal dose of H5N1 virus. The level of virus replicating in the deep lung response was related to the dose of IVIG administered. The mechanism of IVIG in this setting will be discussed.

Conclusion:
These studies suggest that human IVIG is effective in preventing serious influenza infection and provides an alternative treatment option requiring clinical trials.
Workshop 1 - Clinical & Research

Cross-neutralization activity of anti-H5N1 specific polyclonal immunoglobulins against heterologous strains of H5N1 virus

Philippe Buchy¹, Cécile H. Herbreteau², Vincent Deubel¹ and Jean-François Saluzzo²

¹Institut Pasteur du Cambodge, 5 Monivong blvd, PO Box 983, Phnom Penh, Cambodia
²Fab’entech, 321 avenue Jean Jaurès, Bâtiment Domilyon, 69007 Lyon, France

Objectives:
Highly pathogenic avian influenza virus (H5N1) remains a major global health concern. Since 2003, the regular emergence of new outbreaks is observed in Southeast Asia and over 600 human cases (with almost 60% of deaths) were recorded. Polyclonal immunoglobulins are known for their ability to present cross-reactivity capacities. The objective of this study is to confirm the neutralization activity of anti-H5N1 specific polyclonal immunoglobulins on heterologous H5N1 viral strains representative of virus evolution since 2004 in Cambodia.

Methods:
We used classical sero-neutralization in vitro assay to investigate the neutralization activity of anti-H5N1 immunoglobulins derived from horse plasma immunized with inactivated H5N1 A/Vietnam/1194/04 strain. 100 TCID50 of 10 different clade 1 H5N1 strains belonging to 6 distinct lineages were incubated with a range of dilution of immunoglobulins and then transferred to MDCK cells for neutralization analysis. Results obtained were confirmed by using a hemagglutination inhibition assay (HIA).

Results:
Incubation of specific anti-H5N1 immunoglobulins developed on A/Vietnam/1194/04 inactivated strain with various H5N1 strains isolated in Cambodia between 2004 and 2011 provided in vitro neutralization with similar titer comprised between 1:2000 to 1:4000 for all tested strains. Results were confirmed by HIA.

Conclusion:
These data underpin the excellent cross-reactivity of these specific polyclonal immunoglobulins on various H5N1 strains isolated in Cambodia and representative of different lineages of clade 1 H5N1 virus circulating strains in Southeast Asia.
The role of endothelium in the pathogenicity of H5N1 highly pathogenic avian influenza in chickens

Jasmina M. Luczo1,2, John Stambas1,2, Wojtek P. Michalski1, Sandra Sapats1, John Bingham1

1CSIRO Animal, Food and Health Sciences (CAFSH), Australian Animal Health Laboratory, Geelong, Australia
2School of Medicine, Deakin University, Geelong, Australia

Background:
Highly pathogenic avian influenza (HPAI) infection is dependent on the cleavage of the virion surface glycoprotein, haemagglutinin, by host cell proteases. The presence of a polybasic cleavage site motif within the haemagglutinin glycoprotein is a prime determinant of pathogenicity in chickens. In contrast, low pathogenic avian influenza viruses lack a polybasic cleavage site motif. Associated with the pathogenicity of HPAI viruses is the targeting of vascular and lymphatic endothelial cells.

Aims:
By selectively targeting key residues within the H5 haemagglutinin cleavage site motif for mutagenesis, we aim to understand the molecular determinants of endothelial tropism of H5 HPAI infection in chickens. Previous research efforts have focused on mutagenesis and virus pathogenicity, whereas we seek to probe the relationship of the H5 HPAI cleavage site motif and endothelial tropism.

Methods:
Utilising both site-directed mutagenesis and reverse genetics techniques, mutations within the H5 HPAI haemagglutinin cleavage site motif were introduced, followed by rescue of the mutated viruses using reverse genetics. A pathogenicity trial in a defined chicken animal model was undertaken. Specific pathogen free (SPF) chickens were infected by the mucosal route; pathogenicity was assessed and endothelial tropism was analysed via immunohistochemistry.

Results/Discussion:
Using A/Viet Nam/1203/2004, conversion of a highly pathogenic cleavage site motif to that representative of a low pathogenic cleavage site motif (RRRKKR → RETR) resulted in a virus that lacked endothelial tropism and eliminated the peracute infection pattern seen with the highly pathogenic sequence. All other mutations introduced into a highly pathogenic haemagglutinin cleavage site motif (H5 immature protein - R343Q, K345T, S336V, del341-342) resulted in a highly pathogenic phenotype that was associated with endothelial tropism. Mutation from arginine to glutamine at residue 343 resulted in a significantly increased survival time over the WT sequence, though modelling of the spatial structure of R343Q haemagglutinin did not suggest structural clues for the increase in survival time. Of note was a virus isolated from one chicken in the R343Q challenge group, Q343L. This additional mutation, Q343L, seemed to exhibit a reduction of endothelial tropism, which correlated with the lack of clinical signs the particular chicken displayed. Modelling of the 343L haemagglutinin cleavage site displayed a structurally altered cleavage site.

Conclusion:
The association of endothelial tropism with a highly pathogenic phenotype was demonstrated with the above mutant viruses. Mutation of residue 343 may help to elucidate the molecular mechanisms of H5N1 HPAI endothelial tropism, and further investigation into this position is to follow.
Workshop 1 - Clinical & Research

Close encounters with macrophages and dendritic cells: entry of influenza virus via C-type lectin receptors

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Airway macrophages (Mϕ) and dendritic cells (DC) are important components of innate host defense and play a critical role in limiting the severity of influenza virus A (IAV) infection. However, the precise mechanisms underlying Mϕ and DC control of IAV infection are complicated and largely undefined. Historically, one way in which Mϕ and DC have been considered to reduce the severity of IAV infection is by their inability to support productive infection. Nevertheless, recent reports show some IAV strains have the capacity replicate productively in Mϕ and DC. In addition, some IAV strains do not infect Mϕ or DC altogether. Therefore, identifying host-encoded and virus-encoded determinants of IAV attachment and entry into Mϕ and DC has important implications in regard to understanding IAV tropism and pathogenesis. In addition, identification of host or virus-encoded restriction factors that determine non-productive versus productive IAV infection in Mϕ and DC is also required. It is well established that cell-surface sialic acid acts as the primary attachment factor for IAV, however the particular receptors or co-receptors that mediate IAV entry into any cell type have not been clearly defined. C-type lectin receptors are specialised receptors on Mϕ and DC that act as attachment and/or entry receptors for many viral pathogens. We have evidence to demonstrate that Mϕ mannose receptor (MMR), Mϕ galactose like lectin (MGL) and DC-SIGN are CLRs involved in IAV infection of Mϕ and DC. We are currently investigating whether these molecules have the capacity to act as direct entry receptors for influenza virus or as attachment factors that concentrate virus at the cell surface to promote infection by other (as yet unknown) receptors. We will present our current working model of CLR-mediated enhancement of IAV infection of Mϕ and DC.
Workshop 1 - Clinical & Research

Mass trees: Adding weight to the tree of life to study the evolution of the influenza virus

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Understanding the evolution of the influenza virus is essential in order to be able to prepare for, treat and control the spread of the virus. This has proven difficult to predict due to random mutations that occur in viral genes through replication errors and the selective pressure applied to the virus following widespread vaccination and anti-viral drug administration. Viral evolution is further shaped by reassortment events involving the transmission of the virus from animal and human hosts.

A new approach employing so-called “mass trees” to chart the evolutionary history of the virus will be presented. It utilizes mass spectral data produced from the proteolytic digestion of viral proteins, rather than partial or complete gene or translated gene sequences.

The concept and validity of the mass tree approach will be demonstrated using both theoretical and experimental mass data. A comparison of mass trees with the conventional sequenced-based phylogenetic trees, using two separate tree comparison algorithms, reveals a high degree of similarity and congruence among the trees. Given that the mass map data can be acquired more rapidly and directly than viral gene sequences, and with high mass accuracy, mass trees offer new opportunities and advantages for future phylogenetic analysis of the virus.

Figure: A mass tree of all (3208) human H1 sequences of type A influenza virus
Workshop 1 - Clinical & Research

Screening neuraminidase inhibitor susceptibility of avian influenza isolates from SE Asia 2005-2008 identifies H5N1 I222 mutants with reduced oseltamivir sensitivity

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There is an increasing awareness globally of One Health, involving transboundary diseases such as avian influenza which can transmit from birds to humans. Since the emergence of the pandemic H1N1/09 virus from swine there is more complacency about the pandemic potential of avian H5N1 strains. However avian H5N1 viruses continue to evolve and spread through Asia and parts of the Middle East. Surveillance is of critical importance to know both the antigenic variation for vaccine preparation, for both birds and in the event of a pandemic for humans, as well as their antiviral susceptibility. In collaboration with the Indonesian Ministry of Agriculture CSIRO has been involved with an FAO-implemented OFFLU project monitoring hemagglutinin genetic and antigenic changes in Indonesian H5N1 isolates. These isolates also provided a rare and valuable source for screening for susceptibility to the neuraminidase inhibitors, oseltamivir and zanamivir, which form part of many countries’ pandemic stockpiles. We previously reported that clade 2 H5N1 isolates from Indonesia have reduced susceptibility to oseltamivir compared to clade 1 isolates. We also identified isolates from Cambodia which had reduced oseltamivir sensitivity. We have extended these studies here screening more than 160 H5N1 isolates in the MUNANA based enzyme inhibition assay from Indonesia, Cambodia and Thailand and found no virus with an IC50 >5 nM for zanamivir. In contrast the median IC50 for oseltamivir for the Indonesian isolates was~25 nM, around 30-fold higher than for the clade 1 viruses. We found that an S246G mutation correlated with reduced oseltamivir sensitivity in some Cambodian isolates. Surprisingly we identified 8 clade 2 isolates from Indonesia which were mild or extreme outliers to oseltamivir with I222T/V/M mutations. These mutations appear to act synergistically with the H252Y mutation seen in clade 2 compared to clade 1 viruses since IC50s for oseltamivir for I222T/V mutants ranged from 43-63 nM and for I222M mutants were >250 nM. Outliers were from different geographic locations in Indonesia. Mutations at I222 led to loss of slow binding of oseltamivir, but had minimal effect on peramivir or zanamivir binding. We also detected another 4 Indonesian isolates with IC50s around 30 nM also demonstrating loss of slow binding, including one with an I117V mutation. As H5N1 still remains a pandemic threat the incidence of mutations conferring reduced oseltamivir sensitivity is a concern and emphasizes the need for greater surveillance to ensure stockpiling of appropriate antivirals.
Plenary Session 3

WHO's Australian Influenza Centre; 1948-2006

Ian Gust

The University of Melbourne
Plenary Session 3

People, pigs and politics: the WHO Collaborating Centre and WHO’s global influenza program today

Anne Kelso

WHO Collaborating Centre for Reference and Research on Influenza, Melbourne
Plenary Session 4

Progress toward improved influenza control with quadrivalent influenza vaccines

Mark Simmerman
Regional Director of Epidemiology, Asia Pacific, Sanofi Pasteur

Influenza B viruses represent on average 20-25% of circulating strains detected by global surveillance. Type B viruses cause epidemics about every 2-4 years, with clinical symptoms and individual level risk of hospitalization and death similar to that of Type A viruses. In addition to children and adolescents, influenza B infection is prominent in older adults causing nursing home outbreaks and excess mortality. Since 1985, two antigenically distinct lineages of influenza B viruses have co-circulated globally. However, licensed trivalent seasonal influenza vaccines (TIV) contain antigens from only a single influenza B virus, providing limited immunity against circulating influenza B strains of the lineage not present in the vaccine. Predictions about which B lineage will predominate in an upcoming influenza season have been correct in only 5 of the past 10 seasons in the US and Europe. Therefore, seasonal influenza vaccines could be improved by inclusion of influenza B strains from both lineages. Quadrivalent influenza vaccine (QIV) is expected to reduce cases, hospitalizations and deaths from influenza, especially in years where B virus strains not included in the TIV predominate, and could improve public confidence in influenza vaccination. Manufacturing capacity for seasonal influenza vaccines greatly exceeds forecasted demand, allowing for the production of additional antigen for QIV without compromising supply. Several large international vaccine manufacturers have QIV clinical development programs in advanced stages. Broadly, data from recent trials indicate that quadrivalent influenza vaccines have similar safety profiles to TIV, and elicit immune responses to all four influenza virus strains that are non-inferior to TIV for the common strains. Additional work is needed to document the public health benefit of QIV including the analysis of disease burden data due to influenza Type B. Public health and economic impact modeling of QIV will be useful to inform policy decisions regarding the transition to QIV. In 2012 for the first time, the WHO recommended a second B strain virus for inclusion in quadrivalent vaccines and WHO SAGE recommended the consideration of QIV vaccines in addition to TIV in national vaccine recommendations. Depending on national regulatory approvals, QIV is expected to become available in the 2013/2014 seasons in Europe and North America and 2015 in certain countries in the Asia Pacific region. The conditions and timing of the transition to QIV will be specified by national health authorities while considering the advice of international agencies.
Plenary Session 4

Investigations into febrile reactions observed in the pediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine – Part 1

Martin Pearse¹, Darryl Maher¹, Dorit Becher¹, Sandra Koernig¹, Allison Dyson¹, Adriana Baz Morelli¹, Megan Barnden¹, Mimi Tang², Peter Schoofs¹, Steve Rockman¹ and Eugene Maraskovsky¹

¹CSL Limited, Parkville, Australia
²Royal Children's Hospital, Parkville, Australia

During the influenza season of 2010, CSL’s 2010 Southern Hemisphere (SH) Trivalent Influenza Vaccine (TIV) was associated with increased reports of fever-related (febrile) convulsions in children compared to previous seasons. The febrile convulsions, which occurred at an estimated rate of 5 - 7 per 1,000 doses³, occurred predominantly in children under the age of 5 years, shortly after administration of Fluvax®. CSL’s TIVs have not been licensed for use in children aged under 5 years since these events. Preliminary conclusions as to the likely cause of the febrile convulsions have been drawn from a comprehensive two year investigation that has been monitored by the Therapeutic Goods Administration (TGA) and the Food & Drug Administration (FDA). The investigation has comprised clinical data analyses, manufacturing reviews and scientific studies. The clinical data analyses showed CSL’s TIV to be associated with a higher rate of fever in children compared to at least one other licensed trivalent influenza vaccine, but that Fluvax® had not been previously linked to a significant risk of febrile convulsion²,³. CSL’s extensive manufacturing investigations, which reviewed all aspects of the manufacturing process from starting materials through to finished product, did not identify any raw material issues, process changes or deviations from the CSL standard method of manufacture that explained the increased febrile reactions in children in 2010. Scientific investigations included in vitro adult and paediatric whole blood and mammalian cell line assays, genomics profiling and studies in rabbits, ferrets, newborn rats and rhesus non-human primates. Investigations have excluded bacterial-derived pyrogens, the method of inactivation and the role of neuraminidase. The extensive laboratory investigations indicated that the CSL 2010 SH TIV was generally, more stimulatory than previous seasons CSL TIVs or comparator 2010 SH TIVs. The investigations have also led to the identification of key heat labile, viral-derived components from the new strains used in the 2010 SH season that potentially mediated the reactions, as well as the manufacturing process steps that may have contributed to their retention in the CSL 2010 SH TIV. CSL’s preliminary conclusion is that its standard method of manufacture retains more virus components than that of other manufacturers, and that the particular characteristics of the 2010 virus components elicited an excessive immune response in some young children, triggering increased fever and fever-related convulsions. Confirmation of the causal component(s) and the development of surrogate assays will assist in the formulation of CSL’s TIVs to minimise the future incidence of febrile reactions in the paediatric population.

References
Plenary Session 4

Investigations into febrile reactions observed in the pediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine – Part 2

Martin Pearse
CSL Limited, Parkville, Australia

See abstract on page 22
Plenary Session 4

Aspects of the WHO Global Action Plan and the changing technology landscape for novel influenza vaccines.

Gary Grohmann

Therapeutic Goods Administration, Canberra

Egg-based inactivated influenza vaccines for humans as well as live and inactivated vaccines made in cell culture with or without adjuvants, have a long history of providing safe and efficacious vaccines. Novel technologies, including the use of expression systems involving the expression of proteins in plants and fungi, viral vectors, DNA vaccines, and universal protein vaccines, are emerging, and most are in clinical trials and some are before USFDA and European regulators. The interest in new technologies has been prompted by a number of factors including; the need to find faster systems of vaccine manufacture, the need for low-cost, rapid-response technologies to serve the world in a pandemic outbreak, the threat of novel influenza viruses such as H5N1, H7N7, H9, novel H1 viruses and variant viruses, the need for simpler technologies for developing countries – especially those threatened by highly pathogenic H5 viruses, and the need for animal/avian vaccines.

There are regulatory and scientific issues and challenges accompanying this move from egg-based/live vaccines to more novel ones including; reviewing the current status of clinical trial requirements, determining appropriate correlates of protection, using methods other than SRID to determine potency, the rational design and regulatory approval of new adjuvants and exploring laboratory correlates/technicalities.

To date, the immune correlates of protection for inactivated vaccines have been based on robust and reliable HI and/or microneutralisation tests which provide a means to predict efficacy and effectiveness and also a way to compare the efficacy of different vaccines. Other layers of immunity also need to be considered especially for live vaccines, whole virus vaccines and universal vaccines involving fusion and matrix proteins, e.g. CMI responses, cytotoxic T cells and antibodies to NP and M protein. However, such correlates of protection are almost certainly not appropriate for live attenuated vaccines (LAIV) and the newer technology vaccines using expression methods, as other pathways of the immune system would be of more importance. Manufacturers and regulators need to think laterally and be willing to accept alternative correlates of protection together with appropriate strategies and studies.
Plenary Session 4

Oseltamivir - Recent Clinical Pharmacology Updates on Intravenous Formulation and PK/PD

Craig Rayner

Roche Products, Pty Ltd, Australia and Adjunct Associate Professor, Monash University

**Part 1: The safety, tolerability, and pharmacokinetics of oseltamivir following multiple intravenous infusions administered to healthy volunteers**

**Background:**
There exists an unmet medical need for an intravenous (IV) neuraminidase inhibitor to treat influenza in patients who cannot tolerate, swallow or absorb orally administered medications. Single IV infusions of oseltamivir were previously shown to be safe and well tolerated at doses up to 400mg over 2 hours (Davies et al ISRV1 2010). The objective of this study was to investigate the safety, tolerability, and pharmacokinetics (PK) of the pro-drug oseltamivir and its active carboxylate metabolite (OC) following multiple IV infusions in healthy subjects.

**Methods:**
This was a double-blind, placebo-controlled, parallel-group study that randomized healthy volunteers in a 2:2:1 ratio to receive IV oseltamivir 100mg over 2 hours (Group 1), 200mg over 2 hours (Group 2), or matching placebo, all twice daily (b.i.d.) for 5 days. Serial PK samples were collected on Days 1 and 5 for determination of single-dose and steady-state PK parameters of oseltamivir and OC. Safety and tolerability were evaluated by physical and laboratory tests, vital signs, ECGs, and adverse events (AE).

**Results:**
A total of 49 healthy volunteers completed the study. Dose proportional increases in mean exposure were observed between 100 and 200mg for oseltamivir and OC (Table). Day 1 PK parameters were consistent with the single dose study. No accumulation of oseltamivir was observed, while OC accumulated approximately 2-fold between Day 1 and Day 5 for both groups. IV oseltamivir was well tolerated and all reported AEs were mild. Infusion site AEs (e.g., mild pain/erythema) were reported more frequently with IV oseltamivir than with placebo.

**Conclusions:**
Following a 2 hour infusion of 100 or 200mg oseltamivir, PK was dose proportional, and trough concentrations (Cmin) of OC were at least as high as those observed following oral administration of 75 or 150mg oseltamivir, respectively (Tamiflu USPI). IV oseltamivir at doses of 100 and 200mg over 2 hours administered b.i.d. for 5 days was generally well tolerated.

<table>
<thead>
<tr>
<th>Day 5 (±SD) Mean PK Params</th>
<th>Oseltamivir 100mg IV N=19</th>
<th>200mg IV N=20</th>
<th>Oseltamivir Carboxylate 100mg IV N=19</th>
<th>200mg IV N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>266±73.1</td>
<td>497±69.7</td>
<td>488±84.1</td>
<td>960±178</td>
</tr>
<tr>
<td>AUC0-12 (ng·h/mL)</td>
<td>581±178</td>
<td>1143±178</td>
<td>4147±742</td>
<td>7966±1427</td>
</tr>
<tr>
<td>Cmin (ng/mL)*</td>
<td>0.616±0.791</td>
<td>1.79±0.861</td>
<td>238±61.8</td>
<td>458±110</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.64±0.492</td>
<td>1.81±0.416</td>
<td>3.69±0.917</td>
<td>3.41±0.851</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.40±0.328</td>
<td>1.88±0.457</td>
<td>7.98±1.82</td>
<td>8.17±2.23</td>
</tr>
</tbody>
</table>

*Cmin: trough concentration 12 hours post infusion
Part 2: Pharmacokinetic-Pharmacodynamic (PK-PD) Determinants of Oseltamivir Efficacy Using Data from Two Phase 2 Inoculation Studies.

Background:
Oseltamivir is a pro-drug of oseltamivir carboxylate (OC), a neuraminidase inhibitor (NAI) approved for influenza treatment. Given the limited understanding about PK-PD determinants of oseltamivir efficacy, data from two Phase 2 inoculation studies were evaluated.

Methods:
Healthy volunteers in Studies 1 and 2 were experimentally infected with influenza A/Texas (IC50=0.18nM) or B/Yamagata (IC50=16.76nM), respectively. Study 1: 80 subjects randomly received oral oseltamivir 20, 100, or 200mg twice daily (BID), 200mg once daily or placebo for 5 days. Study 2: 60 subjects randomly received oral oseltamivir 75 or 150mg BID or placebo for 5 days. OC PK was evaluated using individual PK data and a population PK model (ACOP 2011) to derive the following individual exposure measures: AUC0-24h, Cmin, and Cmax. Univariable exposure-response relationships were evaluated using continuous (area under composite symptom score curve (AUSC), area under the viral titer curve (AUVC), and peak viral titer) and time-to-event (alleviation of composite symptom scores and cessation of viral shedding) as dependent variables. Exposure measures were evaluated as continuous, 2- and 3-group categorical independent variables.

Results:
Data on 115 subjects were evaluated. Univariable relationships for efficacy were evident for all exposure measures. Given the high degree of correlation among OC Cmax, Cmin, and AUC (r≥0.81), we focused on results for AUC (eg’s in Table).

Conclusions:
This is the first description of NAI exposure-response relationships for efficacy in humans, showing that both clinical improvement and antiviral activity are related to systemic exposure of OC.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>AUC0-24h threshold (ng·hr/mL) identified</th>
<th>Time to 50% and 75% achieving time-to-event (days) or mean value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to alleviation of composite symptom score</td>
<td>≤7,361</td>
<td>3/4.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7,361 to 13,688</td>
<td>1.5/2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&gt;13,688</td>
<td>0.5/1.5</td>
<td></td>
</tr>
<tr>
<td>Time to cessation of viral shedding</td>
<td>0</td>
<td>4.5/7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;0 to 14,180</td>
<td>2.5/5.5</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>&gt;14,180</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>Composite symptom score AUC</td>
<td>≤1,495</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1,495 to 7,611</td>
<td>7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&gt;7,611</td>
<td>4.6</td>
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</tr>
</tbody>
</table>
Comparison of time series methods for estimated seasonal and pandemic influenza-attributable mortality in Australia, 2003 to 2009

David J Muscatello¹, Anthony T Newall¹, C Raina MacIntyre¹, Dominic E Dwyer²

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Background:
In 1848, William Farr recognised that official mortality statistics underestimate deaths attributable to influenza, and this is still true today. Time series methods are therefore used to provide more comprehensive estimates of influenza-attributable mortality. A common feature of the methods is modelling background, non-influenza, mortality using a cyclic, harmonic regression model based on Serfling’s approach. A limitation of the model is that it forces the seasonal background mortality to have the same shape and magnitude each year.


Methods:
We used a conventional harmonic regression model and a generalized additive model (GAM). The GAM allowed us to replace the cyclic time terms with a smoothed function of time to provide a more flexible fit to background weekly mortality. The dependent variable of the model was a weekly population rate of Australian respiratory deaths, 2003 to 2009. Independent variables were weekly count time series of positive virology results for influenza A(H1N1)pdm09, and seasonal influenza A and B.

Results:
The GAM model improved model fit by 10% in <65 year-olds and 22% in ≥65 year-olds. In <65 year-olds, the highest annual estimate from the spline model of seasonal influenza A-attributable mortality was for 2003, with 135 (95% CI 106-164) respiratory deaths. The pandemic strain estimate for 2009 in this age group was 94 (95% CI 62-126). The harmonic model estimates were similar. In ≥65 year-olds, the highest annual seasonal influenza A mortality estimate was 653 (95% CI 560-745) deaths in 2003. The 2009 pandemic strain estimate was not statistically significant (155, 95% CI -80-389) deaths. The harmonic model produced a similar estimate for 2003 influenza A, in this age group but divergent estimates for other years, and produced a negative estimate for the pandemic strain in 2009. Seasonal influenza B estimates were negligible in all years and both age groups.

Conclusions:
The GAM model produced a better model fit and thus more sound estimates of influenza-attributable mortality than the harmonic model. It was also able to produce a plausible, albeit non-statistically significant, estimate for older persons for the pandemic strain in 2009. The total of both age groups for 2009 was 249 deaths, which was somewhat greater than the reported count of 191 confirmed pandemic deaths in 2009, but about one-third of the estimated mortality from seasonal influenza A in 2003 and one-half of that in 2007.
Workshop 2 – Epidemiology

Defining pandemic impact levels to guide a proportionate and flexible operational response to the next influenza pandemic

James M McCaw, Jodie McVernon

Melbourne School of Population Health, The University of Melbourne, Australia

Background:
Following the emergence of the influenza A(H1N1)pdm in 2009, national governments have been evaluating the strengths and weaknesses of their pandemic plans. In Australia, pre-2009 plans focused primarily on responding to a severe pandemic with a 1918-like signature of high severity and high clinical attack rate. The generally mild nature of the 2009 pandemic posed challenges for targeted case-based intervention strategies designed to limit transmission such as antiviral deployment, reactive quarantine and selective school closures.

As part of its review and strategic response to the 2009 pandemic, the Australian government contracted research to define an appropriate measure of pandemic impact, and investigate under what circumstances different interventions may be effective in modifying the course of an epidemic.

Findings:
Here, we report on the outcomes of that research, presenting a framework for decision support that utilises early available information to predict both the likely impact and controllability of a pandemic.

We demonstrate the utility of the underlying framework using a well-established mathematical model of pandemic influenza transmission and a suite of intervention measures. Over a range of possible future pandemic scenarios exhibiting different innate transmissibility and severity characteristics, we considered the ability of different interventions to mitigate key characteristics of epidemics including the total and clinical attack rate, peak incidence rate and time to peak.

Model outputs under application of these interventions were related to baseline epidemic scenarios to allow assessment of controllability and how it varied with different assumptions for transmissibility and severity.

The sensitivity of model outputs to uncertain epidemic and intervention parameters was explored using Latin Hypercube Sampling to provide guidance to public health authorities on where to focus on capacity improvements, and what pandemic characteristics are most critical to estimate for the purposes of real-time decision support.

Conclusions:
Our framework for assessment of impact – as measured through transmissibility and severity – aligns with recent work from the CDC, ECDC and WHO. Using a model based approach we have then considered the controllability of epidemics, gaining key insights into epidemic drivers and potential mechanisms for disease control. Our results indicate that assessment of epidemic growth rates and case severity during the initial within-country transmission phase of a pandemic provide critical information regarding the likely success of an intervention.
Workshop 2 – Epidemiology

Cost-effectiveness of combining social distancing, antiviral and vaccination interventions for pandemic influenza: A modelling study

George Milne, Nilimesh Halder, Joel Kelso

University of Western Australia

Background:
A critical issue in planning pandemic influenza mitigation strategies is the delay between arrival of the pandemic in a community and the availability of an effective vaccine. The likely scenario, born out in the 2009 pandemic, is that a newly emerged influenza pandemic will have spread to most parts of the world before a vaccine tuned to the pandemic influenza strain is produced. In the case of a highly pathogenic strain, other intervention measures that can be rapidly activated will be required if a large death toll is to be avoided.

Methods:
A simulation modelling study was conducted to examine the effectiveness and cost-effectiveness of plausible combinations of social distancing, antiviral and vaccination interventions, assuming a 6-month delay between arrival of an influenza pandemic and availability of a vaccine. Three different pandemic scenarios were examined; mild, moderate and extreme, based on estimates of transmissibility and pathogenicity of the 2009, 1957 and 1918 influenza pandemics, respectively. A range of different durations of social distancing were examined, and the sensitivity of the results to variation in the vaccination delay was determined.

Results:
Vaccination-only strategies were not cost-effective for any of the pandemic scenarios, saving very few lives yet incurring substantial vaccination costs. Vaccination coupled with long duration social distancing, antiviral treatment and antiviral prophylaxis was cost-effective for moderate pandemics and highly cost-effective for extreme pandemics, where it saved lives while simultaneously reducing the total pandemic cost. Combined social distancing and antiviral interventions without vaccination were significantly less effective, since without vaccination a resurgence in the pandemic occurred as soon as social distancing interventions were relaxed. When social distancing interventions were continued until at least the start of the vaccination campaign, attack rates and total costs were significantly lower, and for these scenarios increased rates of vaccination further improved effectiveness and cost-effectiveness.

Conclusions:
The work reported here has quantified both the effectiveness and cost-effectiveness consequences of the time-critical interplay of pandemic dynamics and intervention timing. For mild pandemics, mass vaccination is not cost-effective because it comes too late. For moderate and extreme pandemics, the combination of vaccination and rapidly activated interventions of sufficient duration is effective and cost-effective for saving lives.
Workshop 2 – Epidemiology

Influenza vaccine effectiveness: time for a new orthodoxy

Heath Kelly¹, Ed Belongia, Danuta Skowronski²

¹Victorian Infectious Diseases Reference Laboratory
²University of British Columbia

The 9th edition of the Australian Immunisation Handbook states that: “In healthy individuals <65 years of age, influenza vaccines are 70-90% effective when the antigenic match between vaccine and circulating strains is good.” This claim should be examined in the context of recent data. It has been shown that PCR is the laboratory test of choice for assessing vaccine effectiveness (VE) conferred by trivalent inactivated vaccines (TIV) against influenza. In 5 years surveillance data from Victoria, using PCR laboratory proven influenza as the outcome in adults aged 20-64 years, VE was estimated as 62% (43-75). In a recent meta-analysis of inactivated vaccines, the median effectiveness from eligible observational studies in Europe, Canada and the United States using PCR confirmed influenza as the outcome was 44% in adults aged 18-64 years. In some years there was no evidence of effective protection. From trial results using the PCR endpoint, vaccine efficacy was estimated as 59% (51-67) in the same meta-analysis. A very large trial conducted in healthy adults aged 18-64 years in Australia and New Zealand in 2008-9 estimated TIV efficacy as 60% (44-72). The five year study in Victoria failed to reveal a consistent relationship between higher VE estimates and an improved match between circulating and vaccine strains of influenza. This discordance was also suggested in the recent meta-analysis.

Studies including more than 50,000 subjects and using appropriate laboratory testing suggest that TIV are likely to prevent about 60% of confirmed influenza infections in patients whose illnesses are managed in the community. Protection for hospitalised patients appears no higher. These data should be reflected in orthodox statements about the effectiveness of inactivated influenza vaccines.
Workshop 2 – Epidemiology

Out with the old, in with the new? Are new methods of influenza syndromic surveillance set to take over from classical methods? An analysis of GoogleFlu trends vs. other methods of surveillance in Australia

Monique Chilver, Professor Nigel Stocks

The University of Adelaide, Adelaide, South Australia; The Department of Health and Ageing, the Commonwealth of Australia, Canberra, Australia; The Institute of Medical and Veterinary Science, Adelaide, Australia

Background:
ASPREN is the national GP disease surveillance network – monitoring the levels of influenza and other communicable diseases circulating in the community.

Materials and methods:
Weekly incidence of ILI data reported by ASPREN GPs from 2007-2012 was compared with data from three separate surveillance systems: ASPREN GP sentinel surveillance; the national laboratory notifications of influenza reported to the National Notifiable Diseases Surveillance System (NNDSS); and GoogleFlu Trends.

Results:
Comparison between increases in ILI rates recorded by ASPREN GPs, and GoogleFlu trends showed similar trends of influenza activity, however this was not always consistent. Initial increases in ILI and peak rates reported by ASPREN occurred before increases and peaks in laboratory notifications by NNDSS.

Conclusions:
New age influenza surveillance methods cannot replace classical methods but can be used in conjunction with them.
Using routinely collected data to establish thresholds for influenza surveillance in Victoria, Australia

Ee Laine Tay
Victoria Infectious Diseases Reference Laboratory

Background:
Many authorities use thresholds to gauge the start and severity of influenza seasons. However, current thresholds are often arbitrary. Using historical surveillance data in Victoria, we adapted a novel method for deriving thresholds from a World Health Organization (WHO) manual.

Methods:
For 2002-2011, we analysed several routinely collected data streams in Victoria, including influenza-like-illness (ILI) from sentinel general practices and a locum medical service; laboratory reports from sentinel surveillance and the state reference laboratory (LAB data); and hospital admissions for influenza. We created two composite variables from the product of weekly ILI and LAB data. We assigned three threshold levels: baseline, determined by inspection; and average and above average, determined by calculations of means or medians and confidence intervals (CI) or percentiles respectively for data aligned on the median week of peak activity. From these thresholds, we inferred the start, end, duration and intensity of each season for each dataset, using hospital data as the validation dataset. We analysed data using Stata 12.1 and assessed correlation between data using the correlation coefficient.

Results:
The median week of peak influenza activity was week 34 for all datasets, except hospital data (week 35). Means and medians were comparable except for the locum dataset. The 90% upper CIs were similar to the 95th percentiles in all datasets. Compared to hospital data, the inferred seasonal duration for the three surveillance dataset differed by 2-9 weeks in the years before 2009 and 1-11 weeks from 2009 onwards. The use of the composite variables resulted in reduced differences in inferred seasonal duration. In describing the intensity of each season, the datasets were in complete agreement in 3/7 seasons. Longer seasonal duration and higher out-of-season activity were observed in hospital admission after 2009. Datasets were found to be well correlated, with mean correlation coefficient of >0.75 for a range of combinations.

Conclusions:
Thresholds for influenza surveillance based on sentinel ILI practice can be easily derived from historical data using this relatively simple approach. Using a composite surveillance variable is helpful for describing influenza season characteristics.
Workshop 2 – Epidemiology

Issues affecting the management of influenza outbreaks in residential care facilities

Robin Gilmour

NSW Ministry of Health

Recently, reports of respiratory outbreaks in residential care facilities (RCFs) have been uncommon in NSW. RCFs have not been required to notify outbreaks of influenza or other respiratory illness. Anecdotally, respiratory outbreaks tend to be reported from facilities with strong links to their local public health units (PHUs). Outbreaks are sometimes also identified when PHUs trace laboratory notified cases back to residents of a facility, or when clusters of illness among residents are reported to PHUs by clinicians from local hospitals.

In 2012 (up to 3 September), NSW PHUs identified 38 influenza outbreaks in RCFs from 12 of the 15 NSW Local Health Districts. These outbreaks affected at least 510 residents with 57 hospitalisations. There were 28 deaths in residents linked to the outbreaks, all of whom were noted to have other significant co-morbidities. The number of RCF outbreaks reported to date in 2012 exceeds the previous highest annual total of 21 outbreaks reported in 2007.

Of the 38 RCF outbreaks reported in 2012, PHU staff reported that 34 (90%) had complete or near complete influenza vaccination rates for residents, but that 30 (79%) has staff vaccination rates of less than 50%. Outbreak control measures were often delayed, with only 11 (29%) facilities having initiated appropriate infection control measures within 7 days of the first case (range 0-30 days). Clinical testing was also delayed, with only 12 (32%) facilities having organised appropriate testing prior to PHU staff intervention. Additional outbreak management concerns raised by PHU staff included delays in reporting confirmed laboratory results back to the PHU, an apparent reluctance of some attending GPs to prescribe influenza antivirals, and difficulties faced by some facilities in accessing influenza antivirals when prescribed.

NSW Health routinely writes to RCFs to encourage voluntary reporting of respiratory outbreaks but it is not known how many respiratory outbreaks go unreported. In light of the experiences in the 2012 influenza season, NSW Health will review its existing respiratory outbreak management resources for both RCFs and PHUs to enable better RCF preparedness for respiratory outbreaks, and for more timely detection, reporting and management of outbreaks.
Workshop 2 – Epidemiology

“Choice immunity” versus Herd Immunity: The absence of collective notions of immunity in public understandings of influenza

Dr Niamh Stephenson¹, Dr Mark Davis²

¹University of NSW
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This paper reports on findings from international, ARC-funded research on public understandings of pandemic influenza. The research was designed to elucidate the public’s underlying social practices pertaining to and understandings of influenza through qualitative inquiry. Here we focus on the relative absence of notions of herd immunity in public accounts. We draw on sociological concepts to a) offer an analysis of this absence as partly an outcome of the recent dominance of individualistic approaches to health which in turn reflect more general socio-political dynamics and b) consider implications for public health efforts to promote herd immunity, e.g. via vaccination.

Study:
The research entailed interviews and focus groups with 105 adult participants in Sydney, Melbourne and Glasgow, men and women, people potentially vulnerable to influenza and healthy others, living in inner city, suburban and outer suburbs/regional centres. Transcripts were coded using NVivo and analysed using inductive, constant comparison to derive themes. This paper considers the implications of 2 significant findings to date.

Findings:
Firstly, a common theme emerging from our data was what we have termed “Choice Immunity”. That is, many people conveyed a reasonable idea of what might be done to help prevent the transmission of influenza; alongside a sense that ultimately preventing exposure might be difficult, if not impossible. In the face of this dilemma, respondents described bolstering their immunity. This involved monitoring the body for stress and flagging vitality, improving diet, seeking out immune-boosting products, and a positive mental outlook. The practices people described were informed by medical knowledge as well as media and, in particular, advertising. Importantly, building immunity was spoken of as a realm of individual volition and choice, and this individualistic approach appeared to inform decision-making regarding vaccination. With the exception of some older (70s plus) participants, there was virtually no discussion of the potential importance of collective or herd immunity. Secondly, “vulnerable groups” and “healthy others” experiences of pandemic influenza are predictably different. Significantly, vulnerable groups often experienced invisibility and isolation that they partially explained as stemming from “healthy others’” failure to act in ways that might prevent transmission to them.

Analysis:
The problem of public understanding and investment in collective, herd immunity is not new, there is wide discussion of promoting its importance broadly in public health (e.g. childhood vaccination campaigns) and specifically in relation to pandemic influenza (e.g. Nature editorial, 2009). A common explanation for the public’s lack of engagement is that most generations living today have little direct experience of severe pandemics. Firstly, our sociological analysis suggests an additional factor: over the past two decades, the public have been increasingly addressed as individually responsible for their health and health outcomes. This mode of address aligns with, and arguably informs, the public’s notions of “choice immunity” and the absence of collective notions of immunity identified in our data. This suggests that, secondly, efforts to address the public’s relative lack of sense of herd immunity need to extend beyond vaccination campaigns. Public health messages are most effective when they engage with the public’s existing understandings and practices. In this case, there is room for public health messages to first trigger and support broad discussions (not confined to vaccines) about what collective, herd immunity entails and how people are - together - involved in producing and maintaining it.

Conclusion:
Our research poses a question for public health efforts that aim to promote herd immunity: what can be done to cultivate broad public understandings of immunity as a shared, collective system, such that future public health campaigns, including but perhaps not confined to attempts to promote vaccination can better engage with public understandings of immunity?
Plenary Session 5

Targeting OAT3 for anti-influenza therapy

Olivia Perwitasari, Xiuxan Yan, Paula Brooks, S Mark Tompkins, Ralph Tripp

University of Georgia, Athena, USA

Influenza A virus infection is a major global health concern causing significant mortality, morbidity, and economic losses. Antiviral chemotherapeutics that target influenza A virus components are available for treatment of influenza A virus infections; however, rapid emergence of numerous drug resistant strains has been reported due to its high rate of mutations and reassortments which drive selection for escape mutants. Consequently, there is an immense need to identify novel anti-influenza A drug targets and for the subsequent development of corresponding chemotherapeutic agents. In this study, we utilized an siRNA screen of host drug target genes to identify novel targets for anti-influenza A therapy. We identified a host organic anion transporter, OAT3, that is important to support influenza A virus infection. We demonstrated that probenecid, a chemical inhibitor of organic anion transporters, was effective in limiting influenza A virus infection in vitro and in vivo. Probenecid is currently available for clinical treatment of gout and other hyperuricemic disorders and has been extensively studied for its pharmacokinetics and safety. Thus, probenecid is an excellent candidate for repositioning as a novel anti-influenza A chemotherapeutic, significantly reducing both cost and time for its development from bench to bedside use.
Neuraminidase-inhibiting antibody is a correlate of cross-protection against lethal H5N1 influenza in ferrets immunised with seasonal influenza vaccine

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Some degree of cross-reactivity between seasonal influenza vaccines and H5N1 virus has been reported and we examined whether this could be exploited for vaccination in the face of an H5N1 pandemic prior to specific vaccine becoming available. Ferrets were vaccinated with two intramuscular inoculations of trivalent inactivated split influenza vaccine or sub-component vaccines, with and without adjuvant, and later challenged with a lethal dose of A/Vietnam/1203/2004 (H5N1) influenza virus. The seasonal vaccine afforded partial protection against lethal H5N1 challenge, confirming the results of others using similar models. In addition, we determined that use of either AlPO₄ or ISCOMATRIX® adjuvant with the vaccine resulted in complete protection against disease and death though not infection. The protection was due exclusively to the H1N1 vaccine component, and although the hemagglutinin contributed to protection, the dominant protective response was targeted towards the neuraminidase (NA) and correlated with sialic acid cleavage-inhibiting antibody titres. Purified heterologous NA formulated with ISCOMATRIX® adjuvant was completely protective. The data suggests NA is an inducer of potent cross-protective immunity, a protein whose levels are not normally monitored in vaccines and whose capacity to induce immunity in recipients is not normally assessed. Seasonal vaccines stocks combined with adjuvant may therefore be a rapidly utilised means of lessening the initial impact of an H5N1 pandemic.
Plenary Session 5

Annual influenza vaccine effectiveness monitoring: lessons learned from Canada and the need for vaccine improvement

Danuta Skowronski

University of British Columbia

Influenza is the only vaccine preventable disease for which an annual booster dose is required. Influenza immunization constitutes the most resource intensive public health program every year - delivered to a greater segment of the Canadian population (~30%) than any other single vaccine and within a short 4-6 week time frame each year. Every year in Canada, about ten million doses of influenza vaccine are distributed by the publicly funded program at a cost exceeding CDN$100million per annum or CDN$1 billion per decade. Program benefit and the return on that investment depend crucially upon vaccine effectiveness (VE). VE, however, changes annually owing to challenges in vaccine strain selection determined 9-12 months prior to the epidemic peak and to variation in vaccine match with circulating but evolving strains. Earlier VE estimates ranging 70-90% were based on administrative datasets, clinical or serologic surrogates rather than virologic outcomes, and likely over-estimated vaccine protection. Their further extrapolation across multiple seasons despite inter-season heterogeneity carries profound implications for the interpretation of cost-effectiveness and herd immunity. Annual VE monitoring is therefore necessary. Randomized controlled trials are methodologically superior but precluded for practical and ethical reasons. In Canada, the sentinel surveillance system has been used since 2004 as an efficient, reliable and sustainable public health approach to monitor influenza VE annually against laboratory-confirmed, medically-attended influenza illness. The short-term (intra-season), intermediate (inter-season) and long-term (social and scientific) benefits of the Canadian approach to annual VE monitoring will be reviewed. Evidence for system validity and lessons learned will be discussed. Finally, the implications of annual VE estimates that seldom exceed 60% will be discussed in the context of advocacy for much-needed improvement in influenza vaccine options as a public health priority.
Plenary Session 5

Respiratory illness in a piggery associated with novel influenza A viruses: assessing the risk to human health


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In July and August 2012, a self-limiting outbreak of respiratory disease occurred in a large piggery outside Perth. There were significant levels of illness and death among the pigs, which were initially attributed to bacterial infections. However, PCR testing of respiratory and post-mortem samples from a number of pigs also identified influenza A. Several of the piggery workers reported mild respiratory illness. Additional PCR testing and culture of pigs and acutely ill workers was undertaken.

Pig samples yielded isolates of at least two previously unrecognised influenza viruses: an H1N2 triple reassortant virus and an H3N2 variant virus. These are distinct from H1N2 and H3N2v viruses currently circulating overseas that have been shown to infect humans. In addition sequencing of PCR products from the pigs suggested the presence of other viruses carrying segments from human pandemic H1N1 2009 virus and another H3N2 variant.

At the time of identification of the outbreak influenza vaccination and oseltamivir prophylaxis were offered to all workers in order to mitigate any potential risk of infections of humans and/or re-assortment of viruses. Sampling of five symptomatic workers yielded the 2012 human seasonal H3N2 virus in one, and rhinovirus in the others. A serosurvey of the staff at the piggery is ongoing but thus far there is no definitive evidence of human infection with the pig viruses.

A similar outbreak with a distinct H1N2 virus has recently been reported at a piggery in Queensland. These findings suggest that influenza A may be circulating in pig populations. Additional serological surveys on affected pig properties and a proposed national survey may provide further information as to the type and prevalence of influenza A viruses in pigs in Australia. While the available data do not support that the current pig outbreaks pose an imminent threat to human health, this information is important for assessing the potential risk of novel influenza viruses emerging in Australia.
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