

# MISMS Oceania Regional Influenza Meeting and Workshop

## *Abstracts*

**15–19 March, 2010**

**Melbourne Business School, Melbourne, Australia**





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### *Abstracts*

**Presenter:** Ian Barr, PhD, WHO Collaborating Centre for Reference and Research on Influenza, Australia

**Title:** The Small Picture - Detection and significance of influenza quasi species, reassortants and antiviral resistance in human clinical samples.

**Authors:** Barr IG, Deng YM.

**Abstract:**

In the specialist influenza laboratory we are now capable of performing a wide range of analyses on influenza viruses in clinical samples. Apart from the standard typing and subtyping of human influenza viruses as either influenza A (seasonal H1, pandemic H1N1, H3) or B viruses, we can now apply several genetic and antigenic methods to analyse these viruses further. For example it is now possible to determine the level of virus present in a sample, the sub-lineage of the virus, the gene segment composition, the acquisition or loss of an important residue or the antiviral drug susceptibility of the virus, all within a few hours, using modern tools such as real time-PCR and pyrosequencing. Gene arrays also offer a potential wealth of information on the influenza virus from a single assay and may even detect other co-infecting respiratory viruses in the future. The results from using these assays and their significance from both the patients' welfare/treatment and the public health perspective will be discussed.

**Presenter:** Steven Barry, PhD, National Centre for Epidemiology and Population Health, Australian National University, Australia

**Title:** Modeling strain mutation, cross-immunity, seasonality, and global migration of influenza viruses

**Authors:** Barry S.

**Abstract:**

We have developed mathematical models for influenza which include strain mutation, cross-immunity, seasonality and global migration. The model shows that data from the recent H1N1 pandemic can give a unique insight into how seasonality affects influenza dynamics.

The model also shows the important role that temporary immunity has on dynamics (where once infected with one strain a person is generally immune to all strains for 3-6 months). The model also gives some insight into how influenza strains interact and the role of the tropics in spreading influenza into the temperate regions.

**Presenter:** Jim Bishop, MD, Chief Medical Officer, Department of Health & Ageing, Australia

**Title:** Pandemic influenza (H1N1) 2009 in Australia

**Authors:** Bishop JF, Murnane M, Owen R, Goodspeed S.

**Abstract:**

When the WHO declared a "public health emergency of International concern" on 25 April 2009 following the emergence of pandemic influenza (H1N1) 2009 in Mexico, Australia activated its pandemic plan. By mid-May 2009, Australia had its first case and by September the epidemic had run its course. The epidemic was similar to seasonal influenza but had important differences. It had a higher hospital admission rate in children under 5 years and had a higher rate of ICU admissions (around 700 admissions compared with 55 on average for the last 5 years).

Poor outcomes were seen in younger people, many without risk factors, but also in pregnant women, the obese, indigenous individuals and those with underlying medical conditions. The median age of deaths from influenza was 53 years compared to 83 years in other years. Serology is incomplete but the majority of the population was unprotected following the first wave. A specific monovalent vaccine was available from September 2009 with around 7 million doses (to cover 32% of the population) distributed by mid-February 2010. Further uptake of this vaccine and use of seasonal vaccine containing pandemic influenza (H1N1) 2009 antigen in Australia could substantially reduce the impact of this virus next winter.

**Presenter:** Sandra Carlson, BSc, Hunter New England Population Health, Australia

**Title:** Flutracking: Measuring community influenza-like illness during a pandemic

**Authors:** Carlson S, Dalton C, Durrheim D, Fesja J, Butler M.

**Abstract:**

*Background:* Community-based surveillance of influenza-like illness (ILI) is recommended by the World Health Organisation (WHO) as part of a comprehensive surveillance system during inter-pandemic and pandemic periods. Flutracking is a weekly online survey of ILI completed by community members that integrates participants' ILI symptom information with their influenza vaccination status. Flutracking has been trialled in the 2006-2009 winter influenza seasons, and there are currently among more than 6,000 weekly participants Australia-wide.

*Methods:* A weekly email to participants provides a link to an online survey with questions on the previous week's experience of cough, fever and time absent from normal duties. The survey also allows participants to record their past and current influenza immunisation status, as well as age, postcode of residence and exposure to working with patients. The weekly survey took participants less than 15 seconds to complete. Recruitment occurred through organisations' email systems and media releases. In 2009 participants' symptom rates were analysed over time to assess the incidence and severity of H1N1 Influenza 09 at national and state levels.

*Results:* In 2009 there were more than 1,000 regular participants in each of New South Wales, Victoria, Queensland and Tasmania. The peak week of national influenza activity was in mid July, 2009. There was an increase in fever and cough rates for both vaccinated and unvaccinated participants during this peak period, as expected given that there appeared to be no cross-protection offered by the seasonal influenza vaccine against H1N1 Influenza 09. The peak 2009 fever and cough rates were lower than 2007 and 2008 (with peak national weekly rates of 5.2% in 2009, 5.7% in 2008, and 10.7% in 2007). The peak 2009 national fever and cough rate also occurred earlier in the year than the peak rate for 2007 and 2008.

*Conclusion:* Flutracking 2009 data demonstrated sustainability, with weekly jurisdiction reports available to four states. Flutracking data suggested relatively low population attack rates of influenza-like illness in 2009, which were not affected by the increased health seeking behaviour and increased laboratory testing associated with the emergence of swine influenza.

**Presenter:** Mark Chen, MBBS, MPH, PhD, Tan Tock Seng Hospital, Singapore

**Title:** Correlation between symptoms and serological infection in a sero-incidence cohort of pandemic H1N1 in Singapore – insights and implications

**Authors:** Chen MI, Lee VJM, Lim W, Barr I, Lin RTP, Koh GCH, Yap J, Lin C, Cook AR, Laurie K, Tan LWL, Tan BH, Loh J, Shaw R, Durrant C, Chow V, Kelso A, Chia KS, Leo YS.

**Abstract:**

*Background:* Pandemic H1N1 caused a single epidemic wave in Singapore starting in late June, with epidemic activity peaking in early August 2009 and then subsiding by end of September 2009. We explore the validity of different ways of estimating H1N1-2009 infection rates using data collected from a sero-incidence cohort.

*Methods:* The study collected up to 3 serial serological samples from a cohort of 838 community-dwelling adults. Serological testing with hemagglutination inhibition (HI) was performed using pre-, intra- and post-epidemic samples, to measure rise in titres between successive samples. Symptoms of acute respiratory illness (ARI) and febrile respiratory illness (ARI) were also captured through a standardized two-weekly symptom questionnaire.

*Results:* Subjects with 4-fold or greater increase in titer between any of the three samples had a higher prevalence ARI (73% vs 43%) and FRI (45% vs 9%) symptoms as compared to those without any rise in titre. Incident episodes of ARI correlated poorly with population epidemic activity as estimated from general practice (GP) surveillance data on H1N1-2009. FRI episodes mirrored population epidemic activity, and even FRI episodes in subjects who did not have  $\geq 4$ -fold rise in titre appeared to peak at the same time as the population level epidemic. The sero-incidence data using HI suggests that about 13% of all subjects were infected. Using titres  $\geq 40$  in a single post-epidemic sample gives a reasonably similar result of 12%. Use of ARIs and FRIs may give very different results from estimates based on serology, depending on the adjustment factors used.

*Conclusion:* Due to high background illness rates, clinical syndromes such as ARI and FRI may overestimate infection rates. While HI is not perfectly sensitive, serological methods are possibly the most accurate way of measuring infection rates following an influenza pandemic. Single cross-sectional samples provide results comparable to those from our sero-incidence cohort in the setting of an influenza pandemic.

**Presenter:** Vuong Duc Cuong, MSc, National Influenza Centre, Vietnam

**Title:** Characteristics of H5N1 viruses in Vietnam, 2003-2008

**Authors:** Cuong VD.

**Abstract:**

In late 2003 and early 2004, concurrently with the seasonal influenza outbreak, an occurrence of influenza A with subtype H5N1 was seen in humans in Vietnam. The epidemic in humans related closely to poultry outbreak. Since the first case of influenza A (H5N1) was detected in Vietnam until March, 4<sup>th</sup> 2008, there had been 4 waves of epidemic with 106 infected cases, of those 52 cases were fatal. The characteristic of H5N1 in Vietnam (2004-2008) showed that: H5N1 viruses circulating in Vietnam have been adapted to human and highly homology to contemporary poultry isolates. These viruses have high affinity to avian cell receptors and are high pathogenic. The different lineages of H5N1 viruses have been introduced in Vietnam multiple times and the viruses have changed from clade 1 (2003-2005) to clade 2.3.4 (2007-2008) which is closely associated with H5N1 viruses circulating in bordering countries (China, Laos, Cambodia).

Reducing susceptibility or resistance of H5N1 viruses to antiviral drugs (oseltamivir) were recognized that are related to mutations on Neuraminidase Inhibitor protein (at I117V, H274Y and N294S positions). However, these viruses appeared to be susceptibility (sensitive) to M2 blocker medications (sensitivity to Amantadine and remantadine), it suggested that the combination therapy should be considered.

[1] Nguyen TD, Nguyen TV, Vijaykrishna D, et al. Multiple sublineages of Influenza A virus (H5N1), Vietnam, 2005–2007. *Emerg Infect Dis* 2008; **14**(4):632-636.

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

[3] Le QM, Kiso M, Someya K, et al. Avian flu: isolation of drug-resistant H5N1 virus. *Nature* 2005; **437**(7062):1108.

[4] de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; **353**(25):2667-72.

**Presenter:** Andrew Davies, MBBS, Alfred Hospital Intensive Care Unit, Australia

**Title:** The impact of influenza A (H1N1) 2009 on intensive care services during the Australian and New Zealand winter

**Authors:** Influenza Investigators, Australian and New Zealand Intensive Care Research Centre (ANZIC).

**Abstract:**

The novel Influenza A/H1N1/2009 pandemic reached Australia and New Zealand (ANZ) in June, 2009. We established an Influenza Registry to collect data on all patients admitted to Intensive Care Units (ICUs) in ANZ with a diagnosis of influenza since June 1st, 2009. All ICUs participated with full case ascertainment for the two countries.

Critical illness due to H1N1/2009 differed from usual patterns of seasonal influenza. Significant numbers of previously well young and middle aged adults required intensive care, of whom 49% had acute respiratory distress syndrome (ARDS) secondary to influenza pneumonitis and 20% had a secondary bacterial pneumonia.

From June 1 to August 31, 2009, 856 critically ill patients with influenza were admitted to ICU, of whom 722 patients had confirmed H1N1/2009 infection. This corresponds to 28.7 (95% CI 26.5-30.8) cases per million inhabitants. Of affected patients, 669 (92.7%) were aged < 65 years and 66 (9.1%) were pregnant women. 28.6% were obese, with a body mass index greater than 35kg/m<sup>2</sup>. Patients with H1N1 2009 occupied 8815 (350 per million inhabitants) ICU bed days. The median (IQR) duration of ICU treatment was 7.0 (2.7-13.4) days; 456 of 722 (64.5%) patients were treated with mechanical ventilation for a median (IQR) of 8 (4-16) days. The maximum daily ICU occupancy was 7.4 beds (95% CI 6.3 – 8.5) per million inhabitants. At the time of data censoring 103 (14.3%, 95% CI 11.7-16.9%) patients had died.

68 patients with proven or suspected influenza-associated ARDS were treated with extracorporeal membrane oxygenation (ECMO) (2.6 cases per million people), of whom 53 (2.0 cases per million) had confirmed H1N1 2009. Their median (IQR) age was 34.6 (SD 26.6-43.1) years, and 50% were male. The median duration of ECMO support was 10 (7-15) days. Forty-eight (71%, 95%CI 60-82%) patients survived to ICU discharge and 14 (21%, 95%CI 11-30%) patients had died.

The ANZIC Influenza Registry will be maintained through winter 2010. We are completing follow up on all patients including those who were discharged still pregnant. We are planning a 1 year followup of selected patients, an economic analysis and a more detailed examination of specific subgroups.

**Presenter:** Andrew Davies, MBBS, Alfred Hospital Intensive Care Unit, Australia

**Title:** Extra-corporeal membrane oxygenation for novel influenza A (H1N1) acute respiratory distress syndrome during the 2009 winter in Australia and New Zealand

**Authors:** The Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigators, ANZIC.

**Abstract:**

*Introduction:* The novel influenza A (H1N1) pandemic affected Australia and New Zealand during the 2009 Southern Hemisphere winter. A large number of patients were admitted to Intensive Care Units (ICUs) and some of these patients developed severe acute respiratory distress syndrome (ARDS) and were treated with extracorporeal membrane oxygenation (ECMO). Our objective was to describe the characteristics of all patients with novel influenza A (H1N1)-associated ARDS treated with ECMO and to report the incidence, peak utilization and patient outcomes.

*Methods:* We performed an observational study of all consecutive patients with novel influenza A (H1N1)-associated ARDS treated with ECMO in ICUs in Australia and New Zealand from 1st June to 31st August 2009. We obtained information on incidence, clinical features, degree of pulmonary dysfunction, technical characteristics of intervention, duration of ECMO, complications and survival.

*Results:* Sixty-eight patients with severe influenza-associated ARDS were treated with ECMO (2.6 cases per million inhabitants), of whom 53 (2.0 cases per million) had confirmed novel influenza A (H1N1). Their median age was 34.4 (inter-quartile range [IQR] 26.6-43.1) years and 50% were male. Prior to ECMO, these patients had developed severe ARDS unresponsive to advanced mechanical ventilatory support with a median PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 56 (IQR 48-63) and positive end-expiratory pressure of 18 (IQR 15-20) cm H<sub>2</sub>O. The median duration of ECMO support was 10 (7-15) days. Fifty-three (78%; 95% confidence interval [CI], 68%-88%) were weaned from ECMO and 51 (75% (95% CI, 65%-85%) survived to hospital discharge.

*Conclusions:* ECMO support was used frequently for severe novel influenza A (H1N1)-associated ARDS during the 2009 Southern Hemisphere winter in Australia and New Zealand. Despite severe illness and protracted support, three-quarters of these patients survived.

**Bibliographic Citation:** An earlier version of this work was published in JAMA in November 2009 (ANZICS ECMO Influenza Investigators. 'Extracorporeal Membrane Oxygenation for 2009 Influenza A (H1N1) Acute Respiratory Distress Syndrome.' JAMA 2009; Nov 4; 302(17):1888-95. Epub 2009 Oct 12). The final patient outcomes have now been determined for this series, and we wish to submit this for presentation at the meeting.

**Presenter:** Luzhao Feng, MD, MSc, Office for Disease Control and Emergency Response (ODCER), Chinese Center for Disease Control and Prevention, China

**Title:** Influenza-associated deaths in Northern, Southern cities and Shanghai of China, 2003-2007

**Authors:** Feng L, Shay D, Chen X, Ye M, Zhou H, Jiang Y, Zheng Y, Jiang L, Zhang Q, Lin H, Wang S, Ying Y, Xu Y, Wang N, Feng Z, Yang W, Yu H.

**Abstract:**

*Background:* Influenza results in substantial morbidity and mortality, and statistical models have been used for estimating influenza-associated deaths in temperate, subtropical or tropical climates. Estimates on mortality burden of influenza with mortality data in China have not been published.

*Methods:* Age-specific negative binomial regression models using mortality data in 3 Northern cities, 4 Southern cities and Shanghai for 2003-2007 and national influenza viral surveillance data of China were used to estimate influenza-associated respiratory and circulatory deaths and mortality rates, by age group, and influenza type and subtype.

*Findings:* For 2003-2007, an annual mean of 9.8 (range, 6.0-16.2), 7.1 (range, 4.1-9.8) and 9.0 (range, 4.3-12.8) influenza-associated respiratory and circulatory deaths per 100,000 people were estimated in 3 Northern cities, 4 Southern cities and Shanghai, respectively. The greatest mean numbers of deaths were associated with influenza A(H3N2) viruses, followed influenza B, and influenza A(H1N1) in Northern cities, however, influenza B viruses contributed 65.3% and 56.7% of all deaths respectively and no deaths associated with A(H1N1) viruses were estimated in Southern cities and Shanghai.  $\geq 92\%$  of influenza-associated deaths occurred among persons aged 65 years or older.

*Interpretation:* In China, influenza has a significant impact on deaths both in temperate Northern cities, and warm climate zone in Southern cities and Shanghai. The overall influenza-associated mortality is comparable with that documented in other countries. Our finding that mortality associated with influenza circulation disproportionately affects those aged 65 years or older support the strategy to vaccinate elderly persons for preventing the severe and fatal outcomes.

**Presenter:** Edward C. Holmes, PhD, Center for Infectious Disease Dynamics, The Pennsylvania State University; Fogarty International Center, National Institutes of Health

**Title:** The Evolution of Influenza A Virus

**Author:** Holmes E.

**Abstract:**

This seminar will cover three rarely considered aspects of influenza virus evolution: (i) the ‘unseasonal’ transmission of seasonal influenza viruses, (ii) the extent of mixed infection in influenza virus, and (iii) experimental studies of intra-host viral evolution. The initial wave of pandemic H1N1/09 in the United States during the spring-summer of 2009 also resulted in an increased vigilance and sampling of seasonal influenza viruses (H1N1 and H3N2), even though they are normally characterized by very low incidence outside of the winter months. In part (i) I will provide evidence that both seasonal H1N1 and H3N2 viruses were transmitted within New York State until at least June 2009, and therefore during the normal influenza ‘off-season’. In the case of H3N2 I will also provide evidence for the presence of a large transmission chain of H3N2 viruses centered on the south-east of New York State and which continued until at least June 1st 2009. These results suggest that the unseasonal transmission of influenza A viruses may be more widespread than is usually supposed. In part (ii) I will summarize the growing evidence for mixed infection among both avian and human influenza viruses. With respect to the latter I will describe in detail the case of mixed infection with pandemic H1N1/09 in a T-cell leukemia patient who was persistently infected with influenza. In this case mixed infection is associated with the development of the neuraminidase mutation H274Y that confers oseltamivir resistance. Finally, I will briefly outline the results of experimental infections of influenza virus in horses and dogs, with a particular focus on the nature of intra-host genetic variation and the size of the transmission bottleneck. The key observations from these studies are that; (a) most of the mutations observed were deleterious and therefore only transiently apparent, (b) both antigenic and host-range mutations appear within individual animals, (c) although the consensus sequence remained unchanged in the horse experiments, intra-host genetic variants followed the transmission chain, and (c) multiple viral lineages were transmitted, so that the population bottleneck at transmission was not especially severe.

**Presenter:** Heath Kelly, Victorian Infectious Diseases Reference Laboratory, Australia  
**Title:** Influenza seasonal vaccine provides no protection against pandemic influenza H1N1 2009  
**Authors:** Kelly H, Grant K, Carville K.

**Abstract:**

*Background:* Pandemic influenza H1N1 2009 (pH1N1) vaccine trials from Australia and the US suggest some degree of cross protection against pH1N1 from previous influenza infection and/or vaccination. A case control study from Mexico suggests that seasonal influenza vaccine prevents approximately 73% of infections due to pH1N1 but a series of unpublished studies from Canada suggest that seasonal vaccine may actually increase the risk of serious infection due to pH1N1.

*Aim:* We aimed to estimate the protective effect of seasonal influenza vaccine against pH1N1 in Victoria.

*Method:* We performed a prospective case control study using patients recruited from sentinel general practices in Victoria during the 2009 pandemic. Cases had an influenza-like illness (ILI) and tested positive for influenza by real-time PCR. Controls had an ILI and tested negative. Case and control status was unknown at the time of recruitment. We used logistic regression to estimate the odds ratio (OR) for receipt of vaccine by case and control status. We adjusted for age group and pandemic phase, and included only patients who had been swabbed within 4 days of symptom onset. Vaccine effectiveness (VE) was calculated as 1-OR.

*Results:* The pandemic virus circulated in Victoria for approximately 12 weeks and replaced all other circulating strains. Vaccination status was validated for 98% of all participants. Of 1029 eligible patients, 773 were included in the analysis. VE was confounded by age. Younger patients appeared to be (non-significantly) protected by seasonal vaccine while vaccination appeared (non-significantly) harmful in patients aged 50-64 years. The adjusted VE for patients of all ages was 6% (-42% to 38%).

*Conclusion:* Seasonal influenza vaccine was neither harmful nor protective. Observational studies are not the optimal design for estimating VE.

**Bibliographic Citation:** Interim analysis published online in Eurosurveillance 2009. This analysis was presented at a National Health and Medical Research Council (NHMRC)-sponsored meeting, Canberra, December 2009.

**Presenter:** Chwan-Chuen King, DrPH, National Taiwan University

**Title:** Temporal and spatial variations of 2009 pandemic influenza A (H1N1) viruses in northern versus southern Taiwan

**Authors:** King CC, Kao LC, Chu KY, Chan TC, Tsai CH, Chuang SF, Chang LY, Huang LM, Lee PI.

**Abstract:**

Influenza viruses with short incubation period can spread to many areas within a short time periods. The tempo-spatial analysis becomes very important while the novel influenza viruses can be emerged due to reassortment. A pandemic influenza A (H1N1) virus, a triple reassortant virus carrying most swine-origin segments, has infected many persons since it was detected to enter mass human population in Mexico and the USA in the spring of 2009. Due to the high transmission ability of this novel virus, pandemic influenza A (H1N1) has been spread rapidly across the globe. At the end of year 2009, more than 200 countries reported cases and more than ten thousands of patients died.

In order to understand the impact of pandemic influenza A (H1N1) virus infections in two metropolitans – Taipei City and Kaohsiung City in Taiwan, the clinical specimens from patients with influenza-like illness from August, 2009 to January 2010 were collected from patients lived in both cities and inoculated in MDCK cells. The pandemic influenza A (H1N1) viruses were identified initially by culture or rapid test screening and finally confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) method. The results indicated that there were two waves of epidemics. The patterns and peaks of these two waves were very similar in northern and southern Taiwan. The first and second peaks were in September and November, respectively. Almost one half of the virus strains were isolated from 10-19 year-old young adults and 28% of strains were isolated from 10-year-old children. Interestingly, older persons over 50 years of age (birth cohort born before 1957) who are generally the high risk populations for seasonal influenza in past years had fewer percentage of pandemic H1N1 viruses isolated. The difference in age distribution of virus isolation positive patients in northern vs. southern Taiwan did not show statistical significance. The results of Taiwan's seven 2009 H1N1 isolates with complete sequence data available revealed that three of them were all identical in the sequence alignment. Additionally, several amino acid residues diversity can be identified. The significance of this diversity in the HA1 region needs further investigation by increasing sample size and close monitoring of vaccine recipients (work in progress).

In conclusion, the pandemic H1N1 subtype was the dominant subtype after summer of 2009 in Taiwan. Antigenic drift of 2009 pandemic influenza H1N1 viruses were lower even in two metropolitans of Taiwan before mass vaccination campaign was implemented. We are currently monitoring the antigenic variations of 2009-2010 pandemic influenza viruses after the mass immunization program among school children at different geographical areas of Taiwan.

**Presenter:** Stephen Lambert, MBBS, Queensland Paediatric Infectious Diseases Laboratory, Australia

**Title:** The proportion of influenza tests that are positive: an important influenza metric unbiased by testing volume

**Authors:** Lambert SB, Faux CE, Grant KA, Williams S, Bletchly C, Catton MG, Smith DW, Kelly HA.

**Abstract:**

*Background:* Seasonal surveillance, based on counts of influenza-like illness or laboratory confirmed infections, is currently used for monitoring the impact, timing, and spread of influenza in Australia. Based on national surveillance data of laboratory-confirmed influenza, Queensland has had the largest seasons in recent years. Given there are no epidemiological reasons why Queensland should disproportionately suffer the effects of influenza season compared to other states and territories, it is likely such findings are related to information bias.

*Methods:* We compared monthly values (2004-2008) of influenza A and B laboratory tests performed, number positive, and the proportion of tests positive for major laboratories in three Australian states: Queensland – Queensland Health laboratory network (QH), Victoria – Victorian Infectious Diseases Reference Laboratory (VIDRL), and Western Australia – PathWest Laboratory Medicine, QEII Medical Centre.

*Results:* There were year-on-year increases in influenza tests performed in each laboratory, with growth between 2004 and 2008 being QH: 216%; VIDRL: 85%; and PathWest: 196%. The rise in the number of tests performed and absolute count of positives at all three laboratories was matched by a rise in influenza notifications in each state. Comparing the month-by-month figures shows a remarkable correlation between the timing and peak value of the proportion of all tests positive for influenza across the states. This finding is independent of the variation in number of tests performed. Further, during the severe influenza season of 2007, all laboratories had increased numbers of tests performed, positive, and the proportion positive.

*Discussion:* We believe the proportion of laboratory tests that are positive for influenza is an important, readily calculated metric for monitoring the seasonal influenza epidemic that should be used in addition to currently collected data. As with all passive surveillance mechanisms, this metric will not perfectly represent influenza epidemiology in the community and is unlikely to be free from bias itself. However this value will be less biased by the recent growth in laboratory testing. We believe consideration should be given to a trial period of requesting notification of laboratory negative influenza tests to allow for calculation of the proportion of laboratory tests positive for influenza.

**Bibliographic Citation:**

1. 5th Australian Influenza Symposium, 24-25 September 2009, Melbourne, Australia  
[http://www.influenzacentre.org/reports/ais\\_5\\_program.pdf](http://www.influenzacentre.org/reports/ais_5_program.pdf)

2. Manuscript just accepted for publication in the Medical Journal of Australia. "Influenza surveillance in Australia: we need to do more than count"

**Presenter:** Chang-Chun David Lee, National Taiwan University, Taiwan

**Title:** Different epidemiological features on pandemic and epidemic influenza mortality

**Authors:** Chan TC, Lee CC, King CC.

**Abstract:**

Although the 2009 pandemic H1N1 influenza virus has been associated with low fatality rates, increased incidence of fatal pediatric and young adult cases (as of December 2009) worldwide illustrates the dynamic nature of the pandemic. As an emerging disease, the 2009 H1N1 virus has the potential to further evolve into a much more virulent and serious human threat. The epidemiological feature of age distribution provided an important clue for influenza surveillance. In comparing seasonal influenza mortality and pandemic 2009 influenza mortality in Taiwan, the age distributions were significantly different ( $p < 0.05$ ). Mortality ratios for children aged 0-9 years old and adults aged 50-64 years old were also abnormally high in comparison to adults  $\geq 65$  years during the 1957, 1968, and 2009 pandemics. In the contrast, seasonal influenza has historically posed a minimal threat to adolescents and young adults, with the majority of deaths occurring within the elderly age group. That is to say, there must be several etiological agents and factors cause such mortality differences. Like, *Streptococcus pneumoniae*, which can be discovered in patients who manifested severe H1N1 clinical signs, for example, pneumonia, however, why the mortality rate of people who  $\geq 65$  yrs is lower than that of people who are 50-64 yrs is still unknown. And quite interesting, although the mortality of age distribution is very similar to the past H1N1 Spanish flu, there are still some different virological characteristics among them. The antiviral cytokine and chemokine expression are higher in patients who got 1918 Spanish flu than people who got the 2009 pandemic flu.

In conclusion, all epidemiological outcomes showed that there must be a balance between host immunity, virus characteristics, and the environment to this abnormal different age distribution on pandemic and epidemic influenza mortality. However, there are still many factors that differed than the past pandemic should be distinguished.

**Presenter:** Shui Shan Lee, MD, The Chinese University of Hong Kong, Hong Kong, Hong Kong

**Title:** Spatial heterogeneity in the initial spread of human swine influenza H1N1 in Hong Kong

**Authors:** Lee SS.

**Abstract:**

The emergence of human influenza H1N1 (swine flu) has led to the accumulation of a considerable amount of surveillance data at country level. These data, often with spatial and temporal attributes, can be useful in characterizing swine flu epidemiology. In Hong Kong, home to a 7 million population, over 3000 laboratory confirmed cases were recorded in the initial three months. Of these, 3460 could be geocoded which contributed to a georeferenced dataset with basic demographics, residence locations and dates of confirmation. About half of the cases were between the age of 3 and 20, who were likely to be attending schools at different level in the territory (referred as “students”). Covering an area of 1000 km<sup>2</sup>, Administratively, Hong Kong is divided into 3 major regions, 18 districts, and 400 District Council Constituency Areas (DCCA). Overall, districts on Hong Kong Island (one of the 3 regions) gave the highest per 100,000 population reporting rates, the level of which did not however correlate with population density. Whereas almost all DCCA have reported at least one case in the first three months, only 19 (4.75%) have reported over 20 cases. We further explored the spatial diffusion of cases using an inverse distance weighting (IDW) model for interpolation, superimposed on clusters ( $p < 0.05$ ) identified by SaTScan™ in the different geographic regions. Diffusion maps were created, which displayed multiple foci spreading largely over Hong Kong Island and Kowloon Peninsula, most of which were associated with the student status of the data points. The study has allowed us to characterize the diffusion pattern of swine flu using regularly collected surveillance data. Diffusion is an important though often neglected aspect of epidemiology, the description of which may potentially enhance the fine-tuning of our preparedness in an epidemic.

**Presenter:** Vernon Lee, MBBS, MPH, MBA, Ministry of Defence, Singapore

**Title:** Influenza excess mortality from 1950-2000 in tropical Singapore

**Authors:** Lee VJ, Yap J, Ong JBS, Chan KP, Lin RTP, Chan SP, Goh KT, Leo YS, Chen MIC.

**Abstract:**

*Introduction:* Tropical regions have been shown to exhibit different influenza seasonal patterns compared to their temperate counterparts. However, there is little information about the burden of annual tropical influenza epidemics across time, and the relationship between tropical influenza epidemics compared with other regions.

*Methods:* Data on monthly national mortality and population was obtained from 1947 to 2003 in Singapore. To determine excess mortality for each month, we used a moving average analysis for each month from 1950 to 2000. From 1972, influenza viral surveillance data was available. Before 1972, information was obtained from serial annual government reports, peer-reviewed journal articles and press articles.

*Results:* The influenza pandemics of 1957 and 1968 resulted in substantial mortality. In addition, there were 20 other time points with significant excess mortality. Of the 12 periods with significant excess mortality post-1972, only one point (1988) did not correspond to a recorded influenza activity. For the 8 periods with significant excess mortality periods before 1972 excluding the pandemic years, 2 years (1951 and 1953) had newspaper reports of increased pneumonia deaths. Excess mortality could be observed in almost all periods with recorded influenza outbreaks but did not always exceed the 95% confidence limits of the baseline mortality rate.

*Conclusion:* Influenza epidemics were the likely cause of most excess mortality periods in post-war tropical Singapore, although not every epidemic resulted in high mortality. It is therefore important to have good influenza surveillance systems in place to detect influenza activity.

This paper has been published in PLOSOne:

<http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0008096>

**Presenter:** Vernon Lee, MBBS, MPH, MBA, Ministry of Defence, Singapore

**Title:** Combination strategies are effective in mitigating pandemic influenza: Evidence from a prospective observational cohort study

**Authors:** Lee VJ, Yap J, Cook AR, Chen MI, Tay JK, Kelso A, Barr I, Tan BH, Loh JP, Lin R, Cui L, Kelly PM, Leo YS, Chia KS, Kang WL, Tambyah PA, Seet B.

**Abstract:**

*Introduction:* Non-pharmacological interventions have been used in many settings in an attempt to reduce influenza transmission, but there are few studies that conclusively show their effectiveness. We performed a sero-epidemiological study to determine population attack rates and to validate the effectiveness of public health interventions in reducing influenza spread during the A (H1N1-2009) pandemic.

*Methods:* We performed a prospective observational cohort study using paired serum samples and clinical symptom review among three groups of personnel in the Singapore Armed Forces from 22 June to 9 October 2009. “Normal” units were subjected to prevailing pandemic response policies; “Essential” units had additional public health interventions including enhanced surveillance and isolation, segregation of sub-units; while healthcare workers had enhanced surveillance and isolation, and use of personal protective equipment. Samples were tested by haemagglutination inhibition and seroconversion defined as  $\geq 4$ -fold rise in antibody titers.

*Results:* 1,015 individuals across 14 units completed the study with an overall seroconversion rate of 29%. The seroconversion rates among Essential units (17%) and healthcare workers (11%), were both significantly lower compared to Normal units (44%) ( $p < 0.0001$ ). There was no significant difference in seroconversion rate comparing Essential units to healthcare workers ( $p = 0.22$ ). Symptomatic illness attributable to influenza infection were also lower in “Essential” units (5%) and healthcare workers (2%) compared to “Regular” units (12%) ( $p = 0.06$ ). Adjusted for confounders, the type of unit was the only significant variable influencing overall seroconversion ( $p < 0.05$ ). From the multivariate analysis, within each unit, age ( $p = 0.00035$ ) and baseline antibody titre ( $p = 0.012$ ) were inversely related to the risk of seroconversion.

*Conclusions:* During a pandemic, public health measures to limit influenza transmission, such as enhanced surveillance and isolation, and segregation, are effective in reducing the high infection rates in closed-environments.

**Presenter:** Yee Sin Leo, MBBS, FRCP, Tan Tock Seng Hospital, Singapore

**Title:** Wide variation in H1N1-2009 seroconversion rates in Singapore: a comparative seroepidemiological study in four distinct cohorts

**Authors:** Chen MI, Lee VJM, Lim W, Barr I, Lin RTP, Koh GCH, Yap J, Lin C, Cook AR, Laurie K, Tan LWL, Tan BH, Loh J, Shaw R, Durrant C, Chow V, Kelso A, Chia KS, Leo YS.

**Abstract:**

*Background:* Singapore experienced a single H1N1 epidemic wave with national epidemic activity starting in the last week of June 2009, peaking in the first week of August, and largely subsiding within a month. We compared the risk and factors associated with H1N1 seroconversion in different cohorts.

*Methods:* A study with serial serological samples from four cohorts: general population (n=838), military personnel (n=1213), staff from an acute hospital (n=558) and staff as well as residents from long-term care facilities (n=300). Hemagglutination inhibition results of pre-, intra- and post-epidemic samples as well as data from standardized symptom questionnaire were available. A 4-fold or greater increase in titer between any of the three serological samples was defined as evidence of H1N1 seroconversion.

*Results:* Baseline seroprotection (titer of  $\geq 40$ ) is lowest in the community cohort (3%) and highest in the military (9%) with both the hospital and long-term care cohorts having 7%. In the military cohort, 29% seroconverted compared with only 13% in the community and 7% among hospital cohorts. Only 3 subjects seroconverted in the long-term care cohort. Within the community and military cohorts, evidence of likely contact with seroconverted subjects is associated with an increased likelihood of infection. Older age and higher baseline titer correlate with reduced seroconversion. Among hospital staff, only higher baseline titer is associated with decreased risk.

*Conclusion:* Following the first influenza A (H1N1-2009) epidemic wave in Singapore, a substantial proportion of the Singapore adult population remains susceptible to the infection, with only 13% of the community cohort having had serological evidence of infection. The differences in seroconversion rates are likely due to differences in baseline level of protection, age distribution and potential of exposure. These results highlight the need to contextualize intervention strategies as well as focusing on protecting vulnerable populations.

**Presenter:** John Mathews, MD, University of Melbourne Vaccine and Immunisation Research Group (VIRGo), Australia

**Title:** Prior immunity helps to explain wave-like behaviour of pandemic influenza in 1918-9

**Authors:** Mathews JD, McBryde ES, McVernon J, Pallaghy PK, McCaw JM.

**Abstract:**

The ecology of influenza may be more complex than is usually assumed. For example, despite multiple waves in the influenza pandemic of 1918-19, many people in urban locations were apparently unaffected. Were they unexposed, or protected by pre-existing cross-immunity in the first wave, by acquired immunity in later waves, or were their infections asymptomatic?

We modeled all these possibilities and used MCMC methods to estimate parameters to best explain patterns of repeat attacks in 24,706 individuals potentially exposed to summer, autumn and winter waves in 12 English populations during the 1918-9 pandemic (1) We introduced hyperparameters to allow for parameter variation between populations. Before the summer wave, we estimated that only 52% of persons (95% credibility estimates 41-66%) were susceptible, with the remainder protected by prior immunity. Most people were exposed, as virus transmissibility was high with  $R_0$  credibility estimates of 3.10-6.74. Because of prior immunity, estimates of effective  $R$  at the start of the summer wave were lower at 1.57-3.96. Only 25-66% of exposed and susceptible persons reported symptoms. After each wave, those exposed to the pandemic virus were protected, but 33-65% of such persons became susceptible again before the next wave through waning immunity or antigenic drift. Estimated rates of prior immunity were less in younger populations (19-59%) than in adult populations (38-66%), and tended to lapse more frequently in the young (49-92%) than in adults (34-76%).

These findings support earlier work (2) and suggest that in urban populations, the spread of pandemic influenza is often limited by prior immunity rather than by low values of  $R_0$ , supporting earlier work. Higher attack rates for pandemic influenza in isolated populations also appear to reflect high values of  $R_0$ , but with lesser levels of prior immunity, presumably because of less recent exposure to seasonal influenza. We suggest that the spread of the 2009 H1N1v pandemic may also be limited by immunity from prior exposure to, or vaccination against, seasonal influenza. Such heterosubtypic protection may be short-lived, and not well correlated with levels of HI antibody. It is too soon to say whether any recurrent pandemic waves in 2009-10 will have higher mortality rates, as seen in the second and third waves in 1918-19.

(1) Mathews et al (under review – BMC Infectious Diseases)

(2) <http://www.plosone.org/article/info:doi%2F10.1371%2Fjo>

**Presenter:** John Mathews, MD, University of Melbourne Vaccine and Immunisation Research Group (VIRGo), Australia

**Title:** The ecology of human influenza helps to explain pandemic mortality, seasonal mortality and long-term trends in mortality

**Authors:** Mathews JD, McVernon J, McBryde ES, McCaw JM, Pearce D.

**Abstract:**

Influenza has affected human populations through most of recorded history, but only recently have we begun to understand the complex interplay between the environment, the virus, and host immunity.

Historical pandemics, characterised by waves of higher mortality, spread only as fast as human transport of the time. The last great pandemic, in 1918-19, caused by a novel H1N1 virus, killed some 50 million world-wide, with higher death rates in poor and isolated populations. In contrast, in some urban populations, attack-rates and death rates were much lower, arguably because of higher rates of protective immunity resulting from prior exposure to seasonal influenza (1).

With improving transport through the 20th century, the world has become even more highly connected, and most populations have become more regularly exposed to endemic or seasonal influenza, often with a high frequency of asymptomatic transmission. The increasing ubiquity of residual cross-protective immunity from previously circulating strains and serotypes can help explain why the mortality impact of influenza has trended downwards over time for more than a century, but with mortality spikes following each antigenic shift. As is well known, after each pandemic, the responsible virus tends to circulate in subsequent years as seasonal influenza, with decreasing mortality from year to year.

Nevertheless, influenza is associated with seasonal and pandemic increases in cardiovascular and all-cause mortality, particularly in isolated, indigenous and elderly populations, where there is reason to suppose that protective immunity is either not developed or impaired. Building on much earlier work (2), we have suggested that the circulation of influenza virus, whether pandemic or seasonal, triggers auto-reactive T-cells and inflammation, contributing to vascular damage and to cardiovascular and all-cause mortality in all populations.

The paper summarises historical, epidemiological, and immunological evidence supporting this extended ecological hypothesis, paying particular attention to the experience of Indigenous Australians, and other historically sequestered populations.

The most critical question is whether influenza vaccination has a real effect in reducing cardiovascular and all-cause mortality, particularly in elderly, indigenous and other vulnerable populations, or whether the apparent effect is due to less frequent vaccination of the frail elderly.

(1) <http://mathmodelling.sph.unimelb.edu.au/publications/Mathews-InfluenzaandOtherRespiratoryViruses-2009.pdf>

(2) Mathews JD, Whittingham S, Mackay IR. Hypothesis: Autoimmune mechanisms in human vascular disease. *Lancet* 1974; 2: 1423-26.

**Presenter:** James McCaw, PhD, University of Melbourne, Australia

**Title:** Alternative immune hypotheses for explaining the three mortality waves of the UK 1918-19 influenza pandemic

**Authors:** McCaw JM, Bolton KJ, McVernon J, Mathews JD.

**Abstract:**

The 1918-19 influenza pandemic was characterised by multiple waves of infection, with evidence in the United Kingdom that some individuals were infected on multiple occasions over the three waves.

We have previously presented (1,2) preliminary results from our modeling analyses, incorporating pre-pandemic and wave-to-wave waning protection, that attempt to explain the triple waves in the United Kingdom.

While these models can successfully fit the recorded death data, some of the fits predict extra waves occurring shortly after the pandemic in the latter part of 1919. No such waves were observed. Here, we report on progress to resolve these ambiguities. Alternative model configurations of pre-pandemic partial and temporary protection are presented and the impacts on model behaviour shown.

Our analysis highlights the complexities of the dynamic processes acting during the 1918-19 pandemic, and the pressing requirement to better understand the interaction between the immune system response to influenza, seasonal and pandemic influenza strains, age-cohort effects and environmental influences on the transmission of influenza.

(1) McCaw JM, Pallaghy PK, McVernon J, Mathews JD, Explaining the three mortality waves of the UK 1918-19 influenza pandemic, Epidemics 2 Conference, Athens, Greece (24 December 2009), available at [http://www.epidemics.elsevier.com/virtual\\_programme.asp?ref=5751](http://www.epidemics.elsevier.com/virtual_programme.asp?ref=5751)

(2) Mathews JD, McCaw CT, McVernon J, McBryde E, McCaw JM, A biological model for influenza transmission. Pandemic planning implications of asymptomatic infection and immunity, PLoS ONE 2(11): e1220, doi:10.1371/journal.pone.0001220 (2007)

**Presenter:** Jodie McVernon, MBBS, PhD, Murdoch Children's Research Institute & University of Melbourne, Australia

**Title:** Immunity to influenza A H1N1 (2009) in Australian blood donors, October-December 2009

**Authors:** McVernon J, Nolan T, Owen R, Irving D, Capper H, Hyland C, Faddy H, Laurie K, Carolan L, Barr I, Kelso A.

**Abstract:**

Assessment of the relative severity of disease due to influenza A (H1N1) 2009 in Australian states and territories has been hampered by the absence of comparable denominator data on population exposure. We compared reactivity to the novel virus strain using haemagglutination inhibition assays performed on plasma specimens taken from healthy adult blood donors (>16 years) before (April/May 2009; n=496) and after (October/November 2009; n=779) the H1N1 influenza outbreak which occurred during the Southern Hemisphere winter. Pre-season samples were taken from centres in North Queensland; post-outbreak specimens were from donors at seven centres, dispersed through five states. Using a threshold antibody titre of 1:40 as a proxy marker of recent infection, we observed an increase in the seropositive proportion from 12% to 25%, not dissimilar to recent reports of immunity in this age group from the UK. No significant differences were observed between states, although the ability to detect small increments was limited by the sample size. Based on these figures and national reporting data, we estimated that approximately 0.17% of all H1N1 exposed individuals required hospitalisation, and 0.01% died. The low seroprevalence reported here suggests that some degree of prior immunity to the virus, perhaps mediated by broadly reactive T cell responses to conserved antigens, limited transmission among the adult population to constrain the outbreak.

**Presenter:** Geoff Mercer, National Centre for Epidemiology and Population Health, Australian National University, Australia

**Title:** Community transmission of pandemic (H1N1) 2009 influenza was already established in Victoria, but not in Western Australia, around the time the virus was first identified in North America

**Authors:** Kelly H, Mercer G, Fielding J, Dowse G, Glass K, Carcione D, Grant K, Effler P, Lester R.

**Abstract:**

*Background:* In mid-June 2009 the State of Victoria in Australia appeared to have the highest notification rate of pandemic (H1N1) 2009 influenza in the world. We hypothesise that this was because community transmission of pandemic influenza was already well established in Victoria at the time testing for the novel virus commenced. In contrast, this was not true for the pandemic in other parts of Australia, including Western Australia (WA).

*Methods:* We used data from detailed case follow-up of patients with confirmed infection in Victoria and WA to demonstrate the difference in the pandemic curve in two Australian states on opposite sides of the continent. We modelled the pandemic in both states, using a susceptible-infected-removed model with Bayesian inference accounting for imported cases.

*Results:* Epidemic transmission occurred earlier in Victoria and later in WA. Only 5% of the first 100 Victorian cases were not locally acquired and three of these were brothers in one family. By contrast, 53% of the first 102 cases in WA were associated with importation from Victoria. Using plausible model input data, estimation of the effective reproductive number for the Victorian epidemic required us to invoke an earlier date for commencement of transmission to explain the observed data. This was not required in modelling the epidemic in WA.

*Conclusion:* Strong circumstantial evidence, supported by modelling, suggests community transmission of pandemic influenza was well established in Victoria, but not in WA, at the time testing for the novel virus commenced in Australia. The virus is likely to have entered Victoria and already become established by around the time it was first identified in the US and Mexico.

**Presenter:** Rob Moss, PhD, Melbourne School of Population Health, Australia

**Title:** Considering the influence of health services capacity when developing antiviral deployment strategy

**Authors:** Moss R, McCaw J, McVernon J.

**Abstract:**

Many countries, including Australia, have amassed large stockpiles of antiviral drugs for reducing the impact of pandemic influenza strains such as the Influenza A H1N1 2009 strain. Despite the experience of previous pandemics and a range of modeling studies, it remains unclear how to optimally use these antiviral stockpiles within the constraints of existing healthcare infrastructure.

We extend an existing SEIR model to account for multiple presentation locations (hospitals, GPs and flu clinics), the diagnosis and treatment strategies available at each location, and the finite diagnostic and antiviral distribution capacities inherent in the healthcare system (limitations that were observed in the Australian response to the Influenza A H1N1 2009 epidemic). We identify the optimal diagnosis and intervention strategies for limiting the impact of a future influenza pandemic, and evaluate how current healthcare constraints affect the effectiveness of these strategies.

**Presenter:** David Muscatello, MPH, New South Wales Department of Health, Australia  
**Title:** All cause mortality during the first winter wave of pandemic (H1N1) 2009 virus, New South Wales, Australia  
**Authors:** Muscatello DJ, Cretikos MA, MacIntyre CR.

**Abstract:**

*Introduction:* Influenza epidemics can be associated with increases in all-cause deaths, usually in older people.

*Aim:* To estimate excess all-cause mortality, by age, associated with pandemic (H1N1) 2009 virus in the population of New South Wales, Australia (population 7,000,000) and compare this with excess mortality in recent years, by age.

*Methods:* We applied a Serfling approach to weekly population rates of death registrations, by age, for the period 2003-2009 in New South Wales. A seasonal baseline indicating expected death rates by age was estimated using robust regression. Seasonal excess death rates were estimated by summing the difference between observed and baseline rates for each week of the usual annual influenza period (May to September). In 2009, when the predominant circulating strain was pandemic (H1N1) virus, the estimated excess death rate was -6.0 (95% confidence interval: -11.4,-0.6) per 100,000, indicating lower than expected mortality. The largest decline was in persons aged 80 years and over (-126.7, 95% CI -132.1,-121.3 per 100,000).

*Discussion and conclusion:* Other surveillance systems reported large increases in influenza activity in our population during the 2009 winter, particularly in younger people. These mortality findings are therefore consistent with a pandemic influenza strain that causes mild illness in most people infected, along with relative protection from infection in older people.

**Presenter:** Tim Nguyen, World Health Organization

**Title:** Developing the WHO Public Health Research Agenda for Influenza

**Authors:** Tim Nguyen,\*/\*\* Mary Chamberland\*, John Siu Tam\*, ,Nahako Shindo\*

**Abstract:**

**Background**

Appropriate public health measures to decrease the risk and impact of influenza can save large numbers of lives, reduce health costs and economic loss and mitigate potential societal disruption. However, insufficient knowledge in many areas has hampered efforts to more effectively plan for and address pandemic influenza as well as zoonotic and seasonal influenza epidemics. A robust and multidisciplinary scientific knowledge base, therefore, is an essential foundation for modern public health practices and policy development related to influenza control. Despite these needs an overarching public health research agenda for influenza has not been developed to fill knowledge gaps and identify areas for research that are needed urgently. Moreover, international coordination has been lacking to prioritize and facilitate the funding and implementation of such an agenda.

**Development of the WHO Public Health Research Agenda for Influenza**

In order to address the aforementioned needs WHO has developed a Public Health Research Agenda for Influenza. The research agenda builds upon the 2002 WHO Global Agenda on Influenza and the 2006-2007 WHO Strategic Action Plan for Pandemic Influenza which included the coordination of scientific research and development as one of its five pillars.

WHO sought input from technical and public health experts about critical knowledge gaps in pandemic, zoonotic and seasonal influenza. In addition, previous influenza-related WHO technical consultations and publications that highlighted specific knowledge gaps as well as influenza research priorities articulated by other human and animal public health agencies and organizations around the world were reviewed. An ‘influenza research topics database’ of more than 700 research questions/topics was developed based on these sources which was subsequently consolidated into approximately 250 questions/topics to minimize overlap and duplication. These questions were used in turn to help construct the draft research agenda that was organized around five major public health research streams as follows:

- Stream 1. Reducing the risk of emergence of pandemic influenza
- Stream 2. Limiting spread of pandemic, zoonotic and seasonal influenza
- Stream 3. Minimizing impact of pandemic, zoonotic and seasonal influenza
- Stream 4. Optimizing treatment of patients
- Stream 5. Promoting development & application of modern public health tools in influenza control

Within each research stream, specific areas of focus were identified and supported by a brief rationale and a list of proposed research topics of interest.

A global consultation was convened in November 2009 and brought together over 90 public health decision makers, academic and clinical researchers, donors and other key stakeholders from 35 countries. Participants provided critical feedback about the agenda, identified specific research topics and their importance in meeting public health needs while maintaining a focus on

relatively less well addressed areas, such as operational research and research with applications in under-resourced countries. WHO will publish a revised agenda in early 2010 as well as consult with regional offices and countries to identify research priorities specific for each region and countries. Periodic gap analysis will be performed to identify both research findings that have helped fill information gaps identified in the research agenda and new gaps/research topics.

### **Conclusion**

The research agenda aims to facilitate discussion, coordination and interaction among researchers, donors/funding agencies and public health professionals worldwide.

The WHO Public Health Research Agenda for Influenza would be expected to provide benefits over a medium-to-long term period of approximately 10 years.

**Presenter:** Dora Pearce, PhD, University of Melbourne Vaccine and Immunisation Research Group (VIRGo), Australia

**Title:** Understanding recurrent pandemic waves – a re-analysis of mortality rates from 333 administrative areas in England & Wales in 1918-19

**Authors:** Pearce DC, Pallaghy PK, McCaw JM, McVernon J, Mathews JD.

**Abstract:** Understanding the wavelike behaviour of pandemic influenza in 1918-9 could guide response plans in future pandemics. Following earlier work (1,2), we sought to further explain the spread and severity of the 1918-19 influenza pandemic, particularly its wave-like behaviour, heterogeneous diffusion, and mortality differences between waves.

We built on work of Smallman-Raynor et al. and Chowell et al. and analysed weekly mortality in summer, autumn, and winter pandemic waves in 1918-19 for 333 geographical areas in England and Wales. We sought to maximise spatial resolution, seeking risk factors for influenza onset, spread, and cumulative mortality. Onset patterns for successive waves were increasingly complex: wave 1 spread from few seed locations, while the northward spread of wave 2 was moderated by rurality; wave 3 diffused from widespread foci.

Influenza mortality for each wave averaged 0.26 per 1000 in wave 1, 2.8 in wave 2, and 1.00 in wave 3. Area-specific influenza mortality in each wave increased with area all-cause mortality in pre-pandemic years, and with increasing latitude, linking mortality to social deprivation in the industrialised north and possibly to climatic effects, arguably mediated in part by sunlight and vitamin D.

For areas where mortality was relatively high in one wave, there was a trend for mortality to be relatively low in the succeeding wave, despite the differences in average mortality from wave to wave, and the complex patterns of spread, supporting the idea of immunity from one wave helping to reduce mortality in the next (1,2,3). The substantially lower overall mortality rate in wave 1 is unexplained, but it could reflect out-of-season onset with stronger prior immunity, as suggested by earlier and ongoing work (1,2,3). The very high mortality in wave 2 could be due to greater virulence or to more bacterial complications.

Further modeling is in train using data from historical (3) and 2009 pandemic outbreaks to estimate rates of pre-existing and acquired immunity, viral transmission and virulence, so as to inform understanding to support future intervention strategies. Explaining the link between poor social conditions, influenza, and all-cause mortality is also a high priority.

1. <http://www.plosone.org/article/info:doi%2F10.1371%2Fjo>
2. <http://mathmodelling.sph.unimelb.edu.au/publications/Mathews-InfluenzaandOtherRespiratoryViruses-2009.pdf>
3. Mathews et al. (under review – BMC Infectious Diseases)

**Presenter:** Andrew Rambaut, PhD, University of Edinburgh, UK and Fogarty International Center, USA

**Title:** The spatial and temporal evolutionary dynamics of human influenza virus.

**Authors:** Rambaut A et al.

**Abstract:**

Recent advances in the statistical analysis of viral gene sequences have facilitated the reconstruction of evolutionary and epidemiological dynamics of influenza over time and space. The recent swine-origin H1N1 outbreak was accompanied by an unprecedented global initiative to rapidly isolate, sequence and disseminate influenza samples on a nearly real-time basis. From these it was possible to estimate the origin, timing and initial spread of the pandemic within only weeks of its initial characterization. Nearly a year on and we are able to test how accurate these initial estimates were. Here we find that, although the precision of our estimates has increased considerably, the early inferences remain substantially unchanged by the accumulation of isolates from later in the outbreak. These findings suggest that molecular epidemiological methods have the ability to provide accurate information about the emergence of newly isolated human pathogens. However, the degree to which these analyses will be successful depends on the nature of the virus and the details of the sampling and we discuss the effect of these conditions.

**Presenter:** G. Dennis Shanks, MD, Australian Army Malaria Institute, Australia

**Title:** Highly variable mortality on isolated Pacific islands during the 1918-20 influenza pandemic

**Authors:** Shanks GD, Hussell T, Brundage JF.

**Abstract:**

During the influenza pandemic of 1918-9, young adult mortality increased world-wide; however, there was wide disparity in mortality across Pacific islands. Estimated mortality rates (per 100 population) on selected islands were Hawaii 0.5, New Zealand 0.7, Taiwan 0.7, Philippines 1.0, Guam 4.5, Fiji 5.0, Tonga 6.4, Saipan 12, Nauru 16 and Western Samoa 22. Among island residents in general, mortality was relatively low among those whose first lifetime exposures to influenza were in 1918 and/or those exposed to multiple, heterologous respiratory pathogens prior to the pandemic (i.e., less isolated). Across the islands, histories of prior epidemics of influenza-like illness were associated with lower mortality (but not decreased illness) during the 1918-9 pandemic. Of note, on several islands, there were markedly different mortality rates among residents of adjacent communities. For example, on Guam, a single US sailor but 4.5% of the Chamorro population died; on Saipan, 0.4% of the Caroline Islanders but 12% of the Chamorro people (originally from Guam) died; and on Nauru, 1% of the Chinese, 18% of Nauruans, and 39% of Caroline and Gilbert Islanders died. In 1918, a quarantine of American Samoa limited pandemic influenza to Western Samoa; when pandemic influenza reached American Samoa in 1926, there was wide-spread morbidity but very low mortality. There were extreme contrasts in mortality when naval vessels (with seemingly similar crews and living conditions) were affected by influenza. For example, among cruisers protecting the coast of Australia during the 1918 pandemic period, the HMAS Encounter had no deaths while the IJN Yahagi lost 11% of its crew. During the pandemic in general, lethal clinical expressions of influenza resulted from excessive cytokine reactions which enabled secondary bacterial pneumonias. Among island residents, such reactions were most common among young adults who likely had one prior lifetime exposure to influenza and limited exposures to other respiratory infectious agents. Islands bypassed by the 1918-20 pandemic often experienced high mortality rates when confronted with influenza later in the twentieth century. These and other findings suggest that the interconnectedness of populations and the globalization of respiratory viruses make widespread high mortality during future influenza pandemics unlikely.

**Presenter:** Pham Quang Thai, Mphil, MD, National Institute of Hygiene and Epidemiology, Vietnam

**Title:** Household transmission of novel influenza H1N1, Vietnam, 2009-2010

**Authors:** Thai PQ.

**Abstract:**

*Introduction/background:* Swine-origin influenza A/H1N1 affected Vietnam from May 2009. The purpose of this study was to estimate the household reproductive number  $R_0$ , the age-specific attack rate, the spectrum of severity, the duration of infectiousness, and the serial interval of pandemic H1N1.

*Methods:* A prospective household-based cohort design was used. The cohort comprised of a well characterized, household based study population where household structure and contact patterns, pre-existing antibody and cell-mediated immune profile were known. Community and individual consent was obtained.

Cases of ILI were detected through active surveillance or by self-reporting to the commune health center. On detection of an ILI cases, throat/nasal swabs were taken from the case and all family members and tested within 48 hours for influenza (A/H1N1 seasonal, A/H1N1 swine, A/H3N2, & B) by RT-PCR. If any of the swabs were positive for pandemic H1N1 all household members were swabbed daily and completed a daily symptom and intervention (masks, oseltamivir, hand hygiene) for 15 days or until all household members tested negative. Duration of infectiousness was estimated from one day before onset to negative result date.

*Results:* 267 households (909 individuals) were under active surveillance for a period of 18 weeks. An index case of laboratory confirmed pandemic H1N1 was detected in eight percent of households (22/267) and one third of households (6/22) with an index case had secondary cases. The mean duration of infectiousness was estimated at 6 (95% CI: 4.4 - 8.7). Household  $R_0$  estimated at 0.27 (95% CI: 0.21-0.5). Serial interval is 4 (95%CI: 2.7 - 5.6) days. 80% of household members where a case of pandemic H1N1 was detected used mask and practiced hand-washing regularly. All H1N1 positive cases were treated with oseltamivir 75mg x2/ day.

*Discussion/Conclusion:* Because of intervention like hand-washing, oseltamivir treatment, IEC and mass media campaigns, it is difficult to know if the measured household  $R_0$  is a good representation of the true household  $R_0$  that would occur naturally in the absence of interventions. Since, this is preliminary result only, it is needed to wait for the end-term serological testing to have final picture of pandemic influenza H1N1.

*Preliminary results only.*

**Participant:** Chit-Ming Wong, PhD, University of Hong Kong, Hong Kong

**Title:** Disease burden of influenza in three tropic and sub-tropic cities in Asia

**Authors:** Wong CM, Yang L, Chan KP, Ma S, He JF, Chen PY, Chan KH, and Peiris JSM.

**Abstract:**

The impact of influenza on mortality in sub-tropical and tropical countries is poorly quantified. The obstacle is mainly from assessing the disease burden among irregular seasonality of influenza activities in the warm climates. In this study we applied statistical modeling methods to three metropolitan cities in East and Southeast Asia: Guangzhou, Hong Kong, and Singapore, all of which have standardized influenza surveillance networks for years 2004-2006. We applied the method of Generalized Additive Modeling (GAM) to evaluate the effect of influenza circulation in the community on all-cause mortality and on mortality with an underlying cause of cardio-respiratory diseases. The strength of GAM lies on its capability in adjusting for the seasonality of health outcomes in the investigation for their association with influenza activity, particularly in the subtropics and tropics. Our findings indicated that influenza was associated with 12.4 (95% confidence interval (CI): 1.2, 23.0), 13.9 (95% CI: 6.4, 20.9) and 8.7 (95% CI: 3.0, 13.9) deaths for all causes per 100,000 population in Guangzhou, Hong Kong, and Singapore, respectively. For the cardio-respiratory mortality, influenza was associated with 11.2 (95% CI: 2.4, 19.6), 9.1 (95% CI: 4.3, 13.6) and 5.5 (95% CI: 1.6, 9.4) deaths per 100,000 population in the three cities. These results showed that the disease burdens in the two subtropical cities Guangzhou and Hong Kong were similar and slightly higher than those in the tropical city, Singapore. In the future, a cross region study involving temperate, subtropical, and tropical climates could provide more information about the health effects of influenza in Asia.

**Presenter:** JieHui Kevin Yin, MPH, MBBS, National Centre for Immunisation Research and Surveillance, University of Sydney, Australia

**Title:** Assessing cross-protection from 2009 pandemic H1N1 influenza through absenteeism of school teachers including comparison with 2007 experience

**Authors:** Yin JK.

*Background and aims:* The 2009 pandemic influenza A (H1N1) virus has been necessarily novel, at least in those pre-retirement. To assess the cross protection to 2009 pandemic H1N1 influenza, a study was conducted in secondary school teachers. End point was staff absenteeism.

*Methods:* We performed a retrospective cohort study in a Queensland school. Data were obtained on a total of 122 junior and senior staff in 2007 and 67 senior in 2009. Seventy-two staff in 2007 and 38 in 2009 received seasonal trivalent inactivated influenza vaccine before the influenza seasons. The school closed for three-week mid-year holiday which allowed an assessment of absenteeism before and after the holiday. Cross protection was determined by comparing absenteeism (all causes) in staff who were vaccinated with those not.

*Results:* No significant difference in absenteeism (all causes) was detected between vaccinated and non-vaccinated groups in 2009 when the novel influenza A (H1N1) was circulating, whereas those given seasonal influenza vaccine in 2007 had lower absenteeism in 2007 than those non-vaccinated (1.5% compared with 2.2%,  $p=0.05$ ) during the peak month for absenteeism when background rates of influenza were peaking (Absenteeism in other months was identical). School closure (mid-year holiday) did not obviously reduce absentee rates in 2007 or 2009.

*Conclusions:* We found no evidence that vaccination with 2009 seasonal inactivated influenza vaccine induced cross protection to pandemic H1N1 influenza among senior teaching staff as measured by absenteeism.