

Welcome to the 11th issue of *Influenza - Asian Focus*, the official newsletter of the Asia-Pacific Advisory Committee on Influenza (APACI). Since its establishment in 2002, the APACI has continued to highlight the impact of influenza in the Asia-Pacific region and offer guidance on disease control. *Influenza - Asian Focus* offers wide-ranging and in-depth coverage of important issues relating to influenza, and features articles on new recommendations and recent events relating to influenza and its surveillance, control and prevention.

The need for better information on influenza seasonality and disease burden in Asia is increasingly recognised. In this issue, we review the rationale, design and objectives of a study to determine the burden of influenza disease in APACI member countries. The study is currently in the planning stages. Human influenza research in Thailand was the focus of a recent meeting organised by the Influenza Foundation (Thailand) in conjunction with the Centers for Disease Control (CDC) International Emerging Infections Program and the Thailand Ministry of Public Health. In an interview with CDC Thailand's Mark Simmerman, we detail the outcomes of the meeting and his own research into the cost of influenza in Thailand. Our report on influenza vaccination in the Asia-Pacific region summarises vaccination guidelines and usage in Hong Kong, India, Indonesia, Korea, New Zealand and Thailand, while information on influenza policy and vaccine usage in Taiwan appears elsewhere in the newsletter. Our coverage of the APACI Clinician Workshop includes Jen-Hsiang Chuang's discussion of the country's disease burden and influenza surveillance, Paul Chan's update on avian influenza and the clinico-pathology of human H5N1, and an overview of the influenza disease burden in the tropics from Malik Peiris.

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<b>Dr Lalit Kant</b>	India		
<b>Professor Cissy Kartasasmita</b>	Indonesia		





### Dr Lance Jennings

Lance Jennings is a Senior Clinical Lecturer at the Christchurch School of Medicine and Health Sciences, University of Otago, New Zealand. He is a member of two New Zealand Ministry of Health advisory groups and was instrumental in the establishment of the National Influenza Immunisation Strategy Group. He is Vice-Chairman of the Asian-Pacific Influenza Advisory Board, and has recently held WHO consultancies on influenza and measles.



### Prof Paul Chan

Paul Kay-Sheung Chan is a Professor at the Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China. He is a member of several professional organisations involved in policymaking, grant assessment, education and research related to clinical virology and emerging infections.

# The role of the Asia-Pacific Advisory Committee on Influenza

## Mission statement

**To promote influenza awareness in the Asia-Pacific region, with the intent to improve the prevention and control of influenza.**

The Asia-Pacific Advisory Committee on Influenza (APACI) was established in early 2002 to address epidemiological issues relating to influenza and the impact of the disease in Asia. The APACI members are highly regarded influenza and infectious disease experts from across the Asia-Pacific region. The Committee is a joint initiative of five pharmaceutical companies: GlaxoSmithKline, Novartis Vaccines, Roche, Sanofi Pasteur and Solvay Pharmaceuticals.

The activities of the APACI are aligned with those of the World Health Organization (WHO). The APACI intends to work in cooperation with the WHO to complement its work on influenza surveillance and promote influenza awareness throughout Asia.

## Objectives

- To identify and develop activities that complement the WHO Global Agenda on Influenza Surveillance and Control.
- To assist in the development of country-specific public awareness programmes on influenza.
- To promote influenza awareness among healthcare professionals in the region.
- To provide educational resources to support influenza awareness activities.
- To assist in the process of establishing or reviewing country-specific recommendations for influenza prevention and control.
- To advocate the timely access to, and supply of, influenza vaccines and antiviral medications.

## Activities

Activities include:

- promoting influenza awareness to healthcare professionals in the region:
  - identifying country-specific key opinion leaders (KOLs)
  - publishing a regular newsletter (*Influenza – Asian Focus*)
  - producing peer-reviewed publications
- providing educational resources to support influenza awareness activities:
  - healthcare professional's resource package
  - case management guidelines
  - speaker's kit
  - continuing medical education programme

- assisting the process of establishing or reviewing country-specific recommendations for influenza prevention and control:
  - to establish a list of existing recommendations
  - to evaluate international recommendations in the Asia-Pacific context
  - to facilitate development of consensus statements and information exchange
- assisting the development of country-specific public awareness programmes:
  - identifying country-specific requirements
  - developing a strategy to increase country-specific public awareness
  - media kit
  - media training for KOLs
- identifying and developing activities that complement the WHO Global Agenda on Influenza Surveillance and Control.

## Meeting highlights

The 13th APACI meeting was held in Taipei, Taiwan, on 31 August and 1 September 2007. The APACI trialled a new meeting format, with the objective of making its educational messages accessible to a wider local audience. The first part of day 1 consisted of a CDC Workshop attended by representatives from the Taiwan CDC, while the second part featured a Clinician Workshop attended by more than 50 local physicians. Highlights of both workshops are presented in this issue of the newsletter. The APACI resumed its regular board discussions on day 2 of the meeting, with discussions on the development of a disease burden protocol to better define the burden of influenza in the Asia-Pacific region.

As the APACI continues to evolve as a group, it recognises the importance of targeting influenza education at primary care physicians and other professionals who treat influenza on a regular basis. Thus, the APACI aims to hold a Clinician Workshop in each country that sponsors a board meeting, with local physicians being invited to participate.

# Uncovering the influenza disease burden in the Asia-Pacific region

In March 2007, APACI members agreed to conduct joint studies into the influenza disease burden in their respective countries. The rationale for this decision and the major considerations of study designs are reviewed here.

Influenza is not viewed as a priority health issue in many Asian countries. This may be attributed to several factors, including the absence of the seasonal influenza epidemics observed in temperate countries, a perception that the disease is not severe, and the financial constraints or inadequate healthcare infrastructure in developing countries. However, concerns over the possibility of pandemic influenza and a growing awareness of the burden of seasonal influenza have led to greater interest in influenza control strategies. It is now recognised that influenza is active throughout the year in tropical regions,<sup>1</sup> and an unexpectedly high burden of influenza disease has been documented in Hong Kong, Singapore and Thailand.<sup>2-5</sup> Further research to define the seasonality, disease burden and associated costs of influenza in Asia is needed to guide health policy, in particular, the implementation of a well-designed vaccination and/or antiviral strategy to reduce influenza-associated morbidity and mortality.

## Study design

Many factors need to be considered when planning a disease burden study (see box). The ability to generalise the results across different countries is an important issue. While results from wealthier areas such as Hong Kong and Singapore may not be applicable to developing countries, conducting a study requires a substantial investment of time and resources, and countries for which this investment is not feasible may need to rely on data from

### Considerations for the APACI study protocol

- Which countries will participate?
- What patient population should be studied?
- Will the sample provide representative data that can be extrapolated to the whole population?
- What sample size is required?
- How should the influenza disease burden be measured?
- What criteria will be used to identify cases?
- How will influenza infection be confirmed?
- How should outcomes be reported?
- What is the required study duration?
- How will the study be funded?

neighbouring countries. A second major issue is how to estimate the influenza burden with respect to the severity of cases included, the age group studied and whether to include direct costs only.

## Objectives and next steps

During initial discussions, the APACI agreed that the primary objective of the study should be to determine the contribution of laboratory-confirmed influenza to hospitalisations for acute respiratory infection over a 24-month period in patients aged over 65 years. This data will then be used to estimate the influenza disease burden in terms of:

- age-specific total hospitalisation days per year
- hospitalisation costs per year.

Additional objectives include identifying the risk factors for hospitalisation, describing seasonal patterns and, where possible, extrapolating the data to the whole population. Further consideration must be given to the feasibility and funding requirements of the study in member countries and the development of a detailed trial protocol. A 2-month 'trial run' may be used to identify any logistical problems prior to the start of the study.

In November 2007, the WHO Western Pacific Regional Office held a consultation to discuss the development of a protocol for measuring influenza disease burden, in which APACI members Lance Jennings and Paul Chan participated. As the APACI makes progress with its own disease burden studies and works alongside the WHO in this endeavour, the close relationship between the two groups will be important to assist both in achieving their end goal of better understanding the influenza burden in the region.

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**Dr Shelley de la Vega**

Shelley de la Vega is Chairperson of the Committee on Aging and Degenerative Diseases for the National Institutes of Health at the University of the Philippines in Manila. Dr de la Vega is a founding member and the Secretary of the Philippine Foundation for Vaccination. In 2004, she served on a Department of Health expert panel on guidelines for influenza vaccination and was involved with the Asian International Influenza Pandemic Preparedness Planning Workshop in Beijing, China.



**A/Prof Nguyen Thi Hong Hanh**

Nguyen Thi Hong Hanh is Deputy Director of the National Institute of Hygiene and Epidemiology, Hanoi, Vietnam. She serves as the Vice-head of both the Vietnamese Committee for Rabies Control and Prevention and the Vietnamese National Influenza Surveillance Committee.



# Highlights from the APACI Clinician Workshop in Taiwan

The APACI held its first Clinician Workshop on 31 August 2007 in Taipei as part of the 13th APACI meeting. APACI Chair, Lance Jennings, commenced with a summary of the APACI's background, mission statement, objectives and achievements. Jen-Hsiang Chuang, Director of the National Health Command Center, Taiwan CDC, discussed the Taiwan CDC's influenza surveillance systems and the disease burden and mortality associated with influenza in Taiwan. This was followed by an update on avian influenza and severe human clinical manifestations of influenza by Paul Chan, and an overview on the clinical impact and disease burden of influenza by Malik Peiris. David Smith concluded the workshop with a discussion on the various pharmacological and non-pharmacological influenza prevention and control strategies.

## Influenza epidemiology and disease burden in Taiwan

The major influenza surveillance systems in Taiwan include the Sentinel Physician Surveillance System, which monitors influenza-like illness (ILI); the National Influenza Center at Taiwan CDC and collaborating laboratories, which observe viral strains; and the Notifiable Disease Surveillance System, which examines human cases of influenza A(H5N1) and influenza with severe complications. In addition, there are 530 Sentinel Physician Surveillance practices throughout Taiwan, which on average cover 43,000 people

each and report weekly on ILI, enterovirus infections and diarrhoea. Surveillance in Taiwan demonstrates that although influenza occurs throughout the year, peak activity is evident in winter (Figure 1).

Although the annual vaccine compositions recommended by the WHO usually match with approximately 77% of circulating strains worldwide, high mismatch rates between the influenza vaccine and epidemic strains have been observed in Taiwan. With some epidemic strains appearing earlier in Taiwan than in other countries, match rates of 82%, 53% and 47% for influenza A(H1N1), influenza A(H3N2) and influenza B virus, respectively, have been noted in 1987–2003.<sup>1</sup> As a result, the disease burden is high, with pneumonia and influenza accounting for over 200,000 hospitalisations and over 2.2 million outpatient visits in 2002. The greatest morbidity is seen in those aged over 65 years.<sup>2</sup>

Despite increasing vaccination, there has been little decline in influenza-related mortality in the elderly in Taiwan. This is possibly due to immune senescence in the elderly (clinical vaccine efficacy in the elderly is 17–53%), vaccination not adequately targeting the frailest elderly and a higher strain mismatch. With clinical vaccine efficacy approaching 90% in young adults, vaccination of school children has been introduced to Taiwan's Influenza Vaccination Policy for the 2007/2008 season to try to combat influenza transmission in the community.

## Update: avian influenza and severe human clinical manifestations of influenza

Of the hundreds of strains of avian influenza A virus, only a few are known to have caused human infections.<sup>3</sup> In general, human infection with these viruses has resulted in mild symptoms and very little severe illness, although H7N7 infection caused one death in the Netherlands in 2003<sup>4</sup> and H7N2 infection led to three hospitalisations in the UK in May 2007.<sup>5</sup> The most notable exception to the generally mild nature of avian influenza in humans has been the highly pathogenic H5N1 virus, which is currently of greatest concern for human health. Since 2003, having already crossed the species barrier, the H5N1 virus has caused the greatest number of human cases of severe disease (357) and deaths (224).<sup>6</sup>

Investigations of the most recently confirmed human cases have identified direct contact with infected birds as the most likely source of exposure. When assessing possible cases, suspicion should be aroused by individuals showing ILI – especially those with fever and symptoms in the lower respiratory tract – who have a history of bird contact in an area where confirmed H5N1 avian influenza outbreaks are occurring. Even though exposure to an environment contaminated by the faeces of infected birds is a less common source of human infection, it is still a possibility.

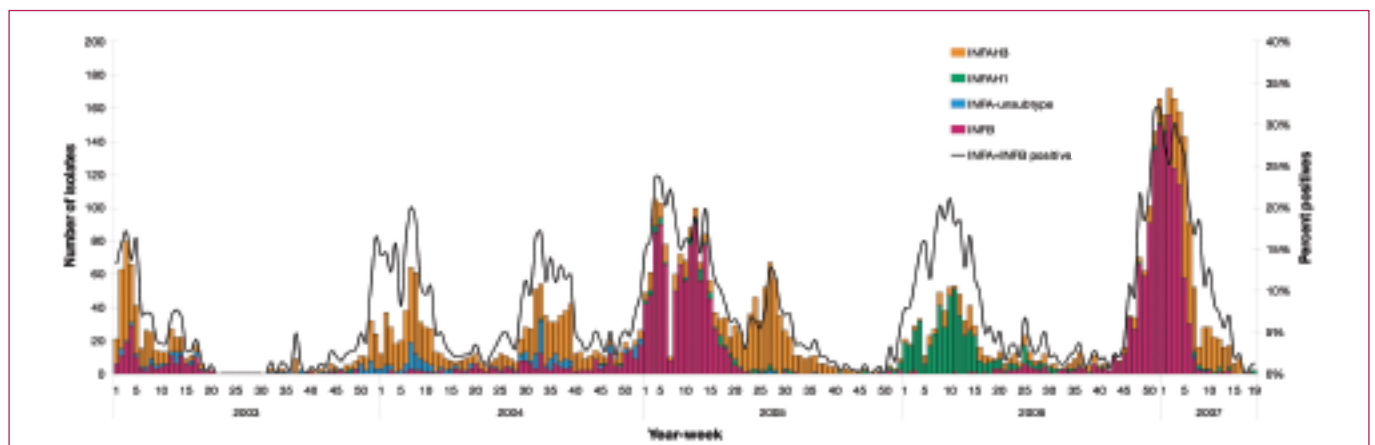


Figure 1. Summary of Taiwan CDC virological isolates from 2003/2004 to 2006/2007.

In patients infected with the H5N1 virus, clinical deterioration is rapid, with respiratory failure in as little as 3–5 days after symptom onset. Observational data on oseltamivir treatment in the early stages of disease suggest its usefulness in reducing A(H5N1) virus infection-associated mortality. As a result, in suspected cases, oseltamivir should be prescribed ideally within 48 hours of symptom onset to maximise its therapeutic benefits. However, administration should also be considered in patients presenting later in the course of illness.

### Clinicopathology of H5N1 in humans

Human H5N1 infection is not simply a severe version of influenza, a result of naïve immunity or a manifestation of avian infection in an unadapted host. It is a severe disease that can ultimately lead to multi-organ failure, unlike severe human influenza, which can result in bacterial pneumonia following an upper respiratory tract infection. The clinicopathological course begins when the H5N1 virus moves from chicken to the human respiratory tract, where the infection may cause hypercytokinaemia and haemophagocytic syndrome, eventually leading to multi-organ failure.

### Influenza: clinical impact and disease burden

Influenza morbidity and mortality is present in the tropics and subtropics, although many believe it is not a clinical problem in these regions, because its impact is less obvious than in temperate locations. Determining the full extent of infection is made even more difficult because few hospital admissions, and even fewer deaths, are attributed to influenza in the region. In addition, the seasonality of virus circulation is less predictable in the tropics, and other circulating respiratory viruses can further confound the estimation of influenza-related illness.

Wong *et al.* used Poisson regression modelling to relate weekly mortality in Hong Kong to laboratory-confirmed influenza virus activity from 1996 to 1999 to derive an estimate of influenza-associated mortality. This showed the excess (all-cause) deaths per 100,000

population per year to be 16 and 136 among individuals of all ages and those aged over 65 years, respectively.<sup>7</sup> Although respiratory diseases accounted for the majority of influenza-related deaths, influenza also contributed to approximately 4–6% of deaths related to ischaemic heart disease.<sup>7</sup> These estimates are very similar to those obtained in temperate regions. Similarly, influenza has been associated with excess hospitalisation due to cardio-respiratory diseases, cerebrovascular disease, ischaemic heart disease and diabetes mellitus in the tropics and subtropics, further warranting influenza vaccination in the region.<sup>8</sup>

### Prevention and control: vaccination and other strategies

Two types of influenza vaccines are available globally for the prevention of influenza and associated complications. Hundreds of million doses of these inactivated split- and subunit vaccines have been used over many years. Both vaccine types have been proven safe and well-tolerated. In adults aged under 60 years, influenza vaccination is up to 70–90% effective. While vaccination is less effective in the elderly than in younger recipients for a number of reasons, it can still reduce hospitalisations and all-cause mortality in the elderly by up to 70%. Although the main burden of medical costs caused by influenza infection comes from older individuals, the vaccination of healthy adults reduces absenteeism due to influenza in the workforce. This enhances productivity, reduces the disruption of business, educational and social activities caused by illness, and reduces the chance of healthy adults spreading infection to those at risk of serious disease. Similarly, vaccinating daycare<sup>9</sup> and school-aged children<sup>10</sup> helps reduce influenza-related morbidity among their household contacts.

A recent study showed a strong association between the early, sustained, and layered application of non-pharmaceutical interventions and social mitigation strategies in the reduction of consequences during the 1918–1919 influenza pandemic in the USA.<sup>11</sup> Increased personal hygiene and minimising the opportunities for infection, via school closures and bans on public gathering,

could potentially provide valuable time for pandemic-strain vaccine and additional antiviral production and distribution. As a result, appropriate implementation of non-pharmaceutical interventions could decrease the burden on healthcare services and critical infrastructure, as well as lower and delay mortality peaks. It is therefore imperative that when planning for future influenza pandemics, non-pharmaceutical interventions be considered as companion measures to vaccine development and antiviral production.

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**Prof Li-Min Huang**

Li-Min Huang is a Professor at the National Taiwan University in the Department of Paediatrics and the Graduate Institute of Preventive Medicine in the College of Public Health. He is also Chief of the Division of Paediatric Infectious Diseases at National Taiwan University Hospital. He has served on the editorial boards of the *Journal of AIDS Prevention* and the *Journal of Microbiology, Immunology and Infection*.



**Prof Ilina Isahak**

Ilina Isahak is Assistant Head of the Department of Diagnostic Laboratory Services at the Hospital University Kebangsaan in Kuala Lumpur, Malaysia. She is a member of several regional organisations and has been involved in the registration of new antiviral agents and vaccines in Malaysia.

# Influenza vaccine usage in the Asia-Pacific region

As part of the CDC Workshop, APACI member representatives discussed the current drivers and barriers to influenza vaccine uptake in their countries.

## Hong Kong

Approximately 220,000 doses of the Northern Hemisphere influenza vaccine are distributed annually by the Hong Kong government to elderly persons living in residential care homes and/or those aged over 65 years, long-stay residents of institutions for the disabled, persons with chronic illnesses, healthcare workers, poultry workers, children aged 6–23 months and pregnant women. Additional doses are delivered through the private market. The uptake rate for the elderly residing in care homes is especially high at approximately 93%, while for those in the community, it is only approximately 30%. Similarly, uptake among healthcare professionals in care homes is higher on average than for those working in the community at public hospitals.

Vaccine cost and accessibility, awareness and perception of influenza disease, responsibility to patients, understanding of side-effects and vaccine effectiveness in the elderly appear to be the highest-ranking drivers and barriers to vaccine uptake in Hong Kong. The government can successfully promote vaccination by educating the public about susceptibility to influenza and the benefits of vaccination, publicising locations where vaccinations are available, and having both family and physicians encourage individuals to be vaccinated.

While there are no established guidelines for the use of antiviral drugs in seasonal influenza, healthcare workers tend to use antivirals as treatment for elderly hospitalised patients and consider prophylactic antiviral treatment for outbreaks in institutions.

## India

Despite its vast population (1.13 billion), only 137,000 doses of the Northern Hemisphere vaccine are distributed annually in India. Currently, there are no guidelines for seasonal vaccination in adults or the elderly, but the Indian Academy of Pediatrics recommends vaccination for children and adolescents in high-risk groups. While the precise vaccine uptake for various patient populations remains unknown, 2006 data showed that 67% of doses were distributed to children aged under 6 years, with the balance administered to healthy adults.

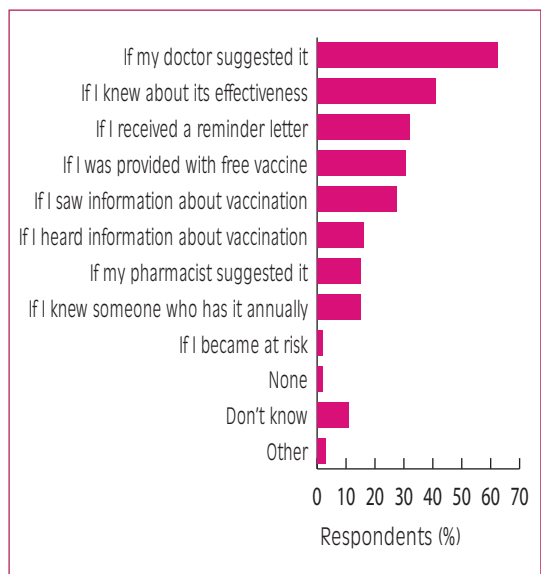
The prevailing attitude towards influenza vaccination among healthcare workers, parents and the general population is one of indifference. Many still see the

disease as a ‘7-day illness’ with no major complications and more severe cases only affecting those with weak or compromised immune systems. The main driver behind vaccine uptake is physician recommendation, while the main barrier is a lack of disease burden data to support the need for vaccination.

Although there are no guidelines for the distribution of antiviral drugs in seasonal influenza, over 12 million strips of adamantanes are distributed annually for use in neurological disorders.

## Indonesia

Public awareness of human influenza is still relatively low in Indonesia, with most of the 300,000 vaccine doses given annually going to those on pilgrimage to Mecca. However, the recent outbreaks of avian influenza in humans have heightened disease awareness to some degree. The main barriers to vaccination remain a lack of information and education, vaccine price and a lack of insurance reimbursement. There are also logistical concerns, with the administration of vaccines being limited to hospitals at this stage. The low priority given to influenza vaccine by healthcare providers is also problematic, with over 60% of unvaccinated high-risk individuals stating they would receive the vaccination if their doctor suggested it (Figure 1). A number of factors need to be addressed before adult immunisation services can be increased, including health professional training, integrated (paediatric and adult) services in primary care, vaccine availability and affordable cost, and guidelines.



**Figure 1.** Factors that would influence unvaccinated high-risk individuals in Indonesia to accept vaccination.

## Korea

Of the 50 million individuals residing in Korea, priority groups for seasonal influenza vaccination include those aged 65 years and over, individuals with chronic disease, residents in long-term care facilities, children aged 6–23 months, healthcare workers, pregnant women, those aged 50–64 years, avian influenza responders and poultry and swine farm workers. As a result, approximately one-third of the population is vaccinated annually, including 80% of those aged 65 years and over and up to 80% of children aged under 6 years. Knowledge and attitudes are similar in the general population, with both vaccinees and non-vaccinees agreeing that the vaccine is safe and can prevent influenza, while those in high-risk groups agree that the complications of influenza might be serious. The major barriers for vaccine refusal in both the general population and high-risk groups are a general perception of 'good health' and a lack of time, while drivers include female gender, increasing age and co-morbid conditions.

Because the Health Insurance Reimbursement Agency guidelines recommend antiviral usage only after the Korean CDC announces an influenza outbreak, antiviral distribution and uptake depends on the frequency of outbreaks. In such an outbreak, antiviral treatment for influenza-like illness is recommended within 48 hours of onset for the elderly and other high-risk groups with co-morbid conditions. Antiviral prophylaxis would also be recommended for the aforementioned groups.

## New Zealand

Approximately 745,000 Southern Hemisphere vaccine doses are distributed annually among the 4.2 million inhabitants of New Zealand. Vaccine uptake rates vary from 33% in healthy adults to 64% in those aged 65 years and over, with a recommendation by their healthcare professional being the biggest influence in people's decisions to get vaccinated. Among the barriers to vaccination, self-esteem was the most significant, with many individuals believing that immunisation is an admission of vulnerability and weakness, and a threat to masculinity.

In terms of antiviral uptake during seasonal influenza control, approximately 700 doses of neuraminidase inhibitors but no adamantanes are prescribed annually. Awareness of appropriate antiviral usage is low among healthcare providers, with only limited awareness among pharmacists and an increasing awareness in second-degree healthcare sectors. To promote more rapid access, New Zealand has instituted pharmacist prescribing of antiviral medications during the influenza season. Awareness in the general population is usually based on information received from avian influenza and pandemic-preparedness promotional campaigns.

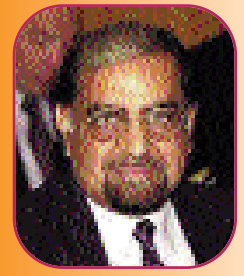
## Thailand

In Thailand, a combination of Northern and Southern Hemisphere vaccines is used, unlike most other regions. In 2006, over 757,000 doses (9% Northern; 91% Southern) were distributed among Thailand's population of 65 million, in accordance with its own influenza vaccine guidelines. The estimated split of the total market according to age is 12%, 73% and 15% for those aged up to 18 years, 19–55 years and over 55 years, respectively. Prior to the avian influenza outbreak in 2004, neither healthcare providers nor the general population showed much interest in influenza vaccination. However, since 2004, interest has increased, leading to requests to the Minister of Public Health for vaccination. Despite this increased interest, lack of awareness still remains the number one barrier to vaccine uptake, followed by shortages in vaccine supply and high cost.

While there are no established guidelines for antiviral use in seasonal influenza control and treatment in Thailand, the use of antivirals is not recommended for the prevention of seasonal influenza but is recommended for close contacts in avian influenza cases. Oseltamivir is the only oral antiviral available, and over 200,000 packets were issued in 2006.

## The Philippines

In the Philippines, drivers for influenza vaccine uptake include the Philippine Constitution and several guideline and recommendation documents endorsed by credible organisations, including the Philippine Society for Microbiology and Infectious Diseases, the Philippine Foundation for Vaccination and the Philippine College of Chest Physicians. In addition, physicians are changing in how they perceive and present influenza vaccination, i.e. not just as a single activity, but as something in the broader context of healthier lifestyles and disease prevention. However, the number one barrier in terms of vaccine uptake is financial – almost 62% of elderly patients surveyed reported money as an obstacle to immediate consultation. Furthermore, approximately 95% of the elderly are without health insurance and 85% do not receive a pension. Education and awareness are other important determinants of vaccine uptake, as only 3.4% of the elderly have ever received an influenza vaccination. Rates of tetanus (14%) and hepatitis B (6.9%) vaccination exceed those seen for influenza, indicating a greater awareness and perceived importance of these conditions. Political barriers include the ongoing debate over the right to vaccination for non-physician groups and to vaccination centres, as well as marketing issues. In terms of antiviral therapy, currently there are no available data regarding antiviral usage and dissemination across the Philippines.



### Dr Lalit Kant

Lalit Kant is Senior Deputy Director-General of the Indian Council of Medical Research, New Delhi, India, and heads the Division of Epidemiology and Communicable Diseases. Dr Kant has facilitated the set-up of a multi-site, epidemiological and virological influenza surveillance network in India.



### Prof Cissy Kartasasmita

Cissy Kartasasmita is President Director of the Dr Hasan Sadikin General Hospital in Bandung, Indonesia. She participated in the Indonesian Ministry of Health's Health Technology Assessment on Influenza in Adults and Children in 2003 and is a member of the Immunization Working Group of the Indonesian Society of Pediatricians.



# Interview with Mark Simmerman



**Dr Mark Simmerman, Thailand CDC, speaks to *Influenza – Asian Focus* about a recent meeting in Thailand held by the International Emerging Infections Program (IEIP), a Thailand Ministry of Public Health (MOPH) and US CDC Collaboration.**

## **What was the purpose for the Thailand Human Influenza Research Meeting and who attended?**

On 11–12 October 2007, 60 Thai researchers who had previously conducted research on human influenza or were interested in doing so gathered at the Davis Hotel in Bangkok. The meeting was designed to review published research on human influenza in Thailand, communicate about ongoing and planned research projects, and identify research gaps that would form the basis of a national research agenda on human influenza. The participants represented a variety of government programmes, universities and private hospitals, as well as representatives from the US CDC IEIP office in Thailand.

## **What were the highlights of the meeting?**

Several speakers presented data from human influenza research conducted in Thailand. Findings from these studies conclusively demonstrated that influenza is a common cause of illness in Thailand. Elderly persons and young children, especially those with chronic underlying diseases, were noted to be at increased risk for serious complications, including hospitalisation and death.

## **The meeting discussed the burden, risk factors and seasonality of human influenza in Thailand. Were the results similar to those in other Asian countries or were there unexpected findings?**

With the exceptions of Hong Kong, Singapore, Japan and Thailand, the disease burden of human influenza remains largely undescribed in most of East and South-East Asia. With the recently increased international focus on influenza and substantial new funding targeted for influenza surveillance, research and control efforts, we have a window of opportunity to begin well-

designed, multi-year disease burden studies in the region to answer these important questions.

Research from Thailand has demonstrated that the risk factors for severe complications of influenza infection commonly recognised in the USA and Europe also apply there. High-risk groups include the elderly, the very young, and people with chronic cardiac and pulmonary disease, among others.

The seasonality of influenza in Thailand has now been well documented, with surveillance and research studies conducted over several consecutive years. Thailand typically sees a marked increase in influenza activity from May to September or October. A second, usually smaller, increase in activity often occurs between January and March. It appears that every 2–3 years, this ‘winter’ increase is characterised by epidemics of influenza type B virus.

## **You have authored several papers on the influenza burden in Thailand. In what ways have the findings of your, and other, studies influenced health policy in Thailand?**

I believe that our influenza disease burden data have contributed positively to an increased understanding of the importance of influenza in Thailand and South-East Asia. The IEIP has been able to demonstrate clearly that influenza is very common in Thailand, causes many hundreds of thousands of people to seek medical care and tens of thousands of hospitalisations each year. In addition, these illnesses come at a substantial cost to society and the healthcare system. Our disease burden data became available at a time when, thanks in part to recent outbreaks of SARS and avian influenza, the Thailand MOPH was keen to consider implementing broader human influenza control programmes. This fortunate synchronicity has meant that the Thailand

data have been used extensively in planning and decision-making by the Thailand MOPH.

## **Did the panel discussions at the meeting identify specific research needs or policy considerations?**

There was agreement that this meeting was an important starting point in developing a more systematic, long-term influenza research agenda for Thailand. Until now, various researchers in Thailand have worked largely independently, with little discussion of national research priorities and how best to achieve them. Several research priority areas were identified during the meeting, including the need to better describe influenza-associated mortality in Thailand and to quantify serious, non-respiratory complications of influenza, such as encephalitis and febrile seizures.

## **Are there issues of influenza burden and control that are specific to Thailand?**

While each country is unique, there are many common issues involved when estimating disease burden and improving influenza control. The capacity to implement influenza control programmes is related to the country’s state of economic and social development and the competing public health issues that it faces. Thailand’s recent rapid economic development has put it in a position to confront the public health disease burden from human influenza.

## **Are there lessons for other Asia-Pacific countries in the results emerging from Thailand?**

While it is common for countries to want to see local data before they decide to allocate resources for new disease control programmes, this is sometimes unnecessary. Data from influenza surveillance in Thailand and several other South-East Asian countries suggest that human influenza circulates widely every year throughout the region, resulting in substantial morbidity and mortality. In other words, just as influenza is an important cause of disease in Thailand, it is very likely to be so in neighbouring countries as well. Countries can directly benefit from high-quality influenza disease burden research conducted in other nearby countries.



# Highlights from recent meetings

## **6th International Conference on Bio-informatics (InCoB 2007); Hong Kong, China, 27–31 August 2007**

### **Identification of human-to-human transmissibility factors in PB2 proteins of influenza A by large-scale mutual information analysis**

*Presented by Olivo Miotto, the Institute of Systems Science and Yong Loo Lin School of Medicine, National University of Singapore.*

Miotto and colleagues studied sequence data for the influenza A PB2 protein to identify mutations responsible for viral adaptation to human-to-human transmission, and then applied the results to assess the potential of various influenza strains for human-to-human transmission. All 3132 available PB2 sequences were analysed and avian (excluding H5N1), human H1N1 and human HxN2 subsets were compared. Characteristic human and avian PB2 variants were identified using mutual information analysis, a powerful technique that uses information entropy (a measure of uncertainty) to measure the relationship between two variables. A total of 17 characteristic sites were identified, five of which were from strains first isolated in 1918. The majority of characteristic sites were located in binding domains. Mapping the characteristic PB2 sites to a range of viral isolates revealed that the 1918 isolate had a mostly avian signature, whereas there was no introduction of avian PB2 in the 1957 and 1968 pandemic strains. Overall, human strains were highly stable over time. In contrast, swine influenza strains contained many avian and human mutations. An analysis of avian H5N1 strains from 1997 to 2006 showed that mutations associated with human-to-human transmission occurred more frequently than in other avian strains; however, these rarely persisted, sug-

gesting that H5N1 will not readily adapt to human-to-human transmission.

## **5th World Congress of the World Society for Pediatric Infectious Diseases (WSPID); Bangkok, Thailand, 15–18 November 2007**

*APACI Committee members Paul Chan and Lance Jennings were among the presenters at two satellite symposia held in association with the WSPID meeting.*

### **Advances in the prevention of paediatric influenza**

Paul Chan, who chaired this MedImmune-sponsored symposium, reviewed influenza vaccination guidelines and uptake in the Asia-Pacific region. Vaccination for children aged 6–23 months is now recommended in Korea, Hong Kong and Taiwan. The Taiwanese government has progressively expanded influenza vaccination coverage, adding infants as a target group in 2004 and children aged 7–8 years in 2007. At 249 per 1000 population, Korea has the highest influenza vaccination rate in the region and has achieved 70–80% coverage among children aged below 6 years. Dr Chan also highlighted a rapid increase in influenza vaccination in Thailand. Other topics featured at the symposium included the influenza burden in Asian children, the Japanese experience of vaccinating school children and the use of live attenuated influenza vaccine in children.

### **Antivirals for seasonal and pandemic influenza in children**

Influenza vaccination remains underused and effective treatments are thus needed for infected children. A Roche-sponsored symposium chaired by Catherine Weil-Olivier (France) discussed the burden of influenza in children and the role of antiviral therapy. Children have the highest

infection rates during seasonal influenza outbreaks (approximately 30%, reaching an estimated 50% in children attending daycare centres), resulting in considerable morbidity and associated societal costs. Accurate and early diagnosis is important but can be difficult in children. APACI Chair Lance Jennings presented recent German results showing that rapid diagnostic testing supported 62.6% of positive clinical diagnoses and 82.2% of negative clinical diagnoses in children aged 1–12 years; a hesitant clinical diagnosis was commonly associated with a negative rapid test result (69.2%). The rapid testing results also influenced prescribing patterns. Children with influenza confirmed by rapid testing were substantially more likely to receive an antiviral agent and less likely to receive antibiotics than those with a clinical diagnosis only.

Keith Reisinger (USA) reviewed the efficacy of oseltamivir in children, both for treating symptomatic influenza and when given as post-exposure prophylaxis to prevent the infection of paediatric household contacts. A recent analysis demonstrated that starting oseltamivir within 24 hours of symptom onset reduced the severity of influenza symptoms by 52.4% and the incidence of otitis media by 55.5%, compared with placebo. In the final presentation, Earl Rubin (Canada), explored the potential for antivirals to protect children in the event of an influenza pandemic. Infection with H5N1 avian influenza disproportionately affects children and young adolescents. Daily oseltamivir prevented death in H5N1-infected mice and ferrets; the protection was dependent on the dose and timing of treatment initiation. In humans, initiating oseltamivir within 5 days of symptom onset is associated with improved survival (53%, versus 25% with no intervention based on available data).



### Prof Woo-Joo Kim

Woo-Joo Kim is a Professor in the Division of Infectious Diseases in the Department of Internal Medicine at Guro Hospital, the College of Medicine at Korea University in Seoul, Korea.



### Prof Malik Peiris

Malik Peiris is Chair Professor of Microbiology at The University of Hong Kong and Chief of Virology at the Queen Mary Hospital, Hong Kong SAR, China. His recent research interests have focused on the ecology, evolution, clinical aspects and pathogenesis of avian and human influenza. He was elected a Fellow of the Royal Society of London in 2006.

## Influenza vaccine use in Taiwan

Chang-Hsun Chen, Director of the Fourth Division of the Taiwan CDC, reviewed influenza vaccination in Taiwan – the epidemiological background, policy formulation, implementation, new strategies and challenges – as part of the CDC Workshop at the 13th APACI meeting in Taipei.

Taiwan's Influenza Vaccination Policy was initiated in 1998, with the recommendation that elderly people (aged 65 years and over) hospitalised with chronic cardio-pulmonary disease, and residents and healthcare workers in long-term care facilities be vaccinated against influenza. Studies have confirmed the need for vaccination, with almost 2.5 million pneumonia and influenza patients being reported in 2002, resulting in an incidence rate approaching 11%.<sup>1</sup> While infants and children under 6 years of age had the highest medical-care rate, actual medical costs were highest in elderly patients with pneumonia and influenza for both out- and in-patient care.<sup>1</sup> Mortality was also high in this age group, with more than 80% of the deaths attributed to influenza occurring in those aged over 65 years.<sup>2</sup>

Over the years, the vaccination policy has been expanded to include all elderly people, healthcare and public health workers, poultry and swine workers, children 6–23 months of age and patients with rare diseases. However, despite a 29% reduction in all-cause deaths and a 20% reduction in hospitalisation as a direct result of influenza vaccination,<sup>3</sup> coverage rates for the elderly still only hover around 50–60%.

The 2007/2008 season is seeing major changes to the vaccination policy, with vaccination for all health-

care workers in the hospitals, private clinics and community pharmacies, and the vaccination of all target groups being commenced on the same day ahead of previous target dates in order to pre-empt the influenza season. Children aged 7–8 years are also being included for the first time, based on studies revealing that the vaccination of school children can lead to a reduction in influenza-related mortality in adults.<sup>4</sup>

While the government continually enhances influenza vaccination policy, new approaches are still required to expand the use of seasonal influenza vaccine and reach target populations by 2010. Taiwan also faces the dilemma of acquiring sufficient supplies during a pandemic without having the resources to produce its own vaccine.

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## Antiviral agents for influenza – Australian ISG recommendations

The recent Australian Influenza Specialist Group (ISG) discussion paper on influenza treatment during inter-pandemic periods recommends that antiviral drugs be used responsibly and where they have the greatest benefit, to minimise the risk of escalating drug resistance.

Antivirals should be prescribed as treatment to 'at-risk' groups, carers and those in close contact with at-risk individuals, children, healthcare workers and the general public. For prophylaxis, antivirals are recommended for high-risk individuals, their carers and those in close contact with both at-risk individuals in institutional settings during outbreaks and the general public.

Treatment with neuraminidase inhibitors (NIs) should

only be considered where there is a reasonable likelihood that the patient has been exposed to the influenza virus as part of their local activity or recent travel to an area with currently active influenza. Patients who are highly likely to have influenza will potentially benefit from NIs, and usage should be recommended. For those with potential influenza infection, the treatment decision should be based on whether they have been vaccinated and/or are at risk for more severe disease. All patients recommended for treatment must be able to commence treatment within 48 hours of onset.

For further information, please refer to the WHO Collaborating Centre for Reference & Research on Influenza website at: [www.influenzacentre.org/](http://www.influenzacentre.org/).

## Flu review

**Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med* 2007; 357: 1373–81.**

Influenza vaccination significantly reduces the risk of death and hospitalisation for pneumonia or influenza in community-dwelling elderly persons. These were the findings of a study that analysed the effectiveness of influenza vaccination in 20 cohorts of US health maintenance organisation (HMO) members aged 65 years and over. Data were retrospectively evaluated for a total of 713,872 person-seasons over 10 consecutive influenza seasons. Influenza vaccination was associated with a mean risk reduction of 27% for hospitalisation due to pneumonia and influenza (odds ratio IOR 0.73; 95% CI 0.68–0.77) and 48% for the risk of death (OR 0.52, 95% CI 0.50–0.55), with benefits observed across age and risk subgroups. Sensitivity analyses modelling the effect of a hypothetical unmeasured confounder (i.e. an unrecognised factor leading to over-

estimation of vaccine effectiveness) showed that vaccination remained associated with statistically significant benefits.

**Nelson MI, Simonsen L, Viboud C, Miller MA, Holmes EC. Phylogenetic analysis reveals the global migration of seasonal influenza A viruses. *PLoS Pathog* 2007; 3: 1220–8.**

Global migration of influenza A viruses is a significant contributor to seasonal influenza epidemics, say US researchers. They performed phylogenetic analysis on 487 complete influenza A/H3N2 genomes collected in Australia and New Zealand between 1999 and 2005, and a representative sub-sample of 413 previously analysed genome sequences from New York. The sequence analysis revealed extensive intermixing of isolates from the Northern and Southern Hemispheres, demonstrating that regular, bi-directional viral migration occurs across hemispheres between influenza seasons. The authors highlight the need for expanded global surveillance, particularly in tropical regions where the influenza virus circulates throughout the year.



**Dr Yuelong Shu**

Yuelong Shu is Director of the China National Influenza Center, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention in Beijing, China.

## Avian influenza: recent developments

### Pandemic vaccine challenge

The US Center for Infectious Disease Research & Policy (CIDRAP) has produced a 7-part series of short but informative articles outlining the many barriers to producing an effective and widely available pandemic influenza vaccine. Topics covered include the history of neglect in influenza research, vaccine production capacity, the immunological challenges of H5N1, the potential (and problems) of adjuvants, the role of pre-pandemic vaccination, novel vaccine technologies and the need for a vaccine 'Manhattan Project'.

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### DAS181 protects against influenza A(H5N1)

DAS181, a novel viral receptor inactivator, was protective against avian influenza H5N1 virus in mice.<sup>1</sup> When initiated 1 day prior to infection with A/Vietnam/1203/2004(H5N1) virus, treatment with DAS181 (1 mg/kg/day) prevented infection in 70% of mice and protected against fatal disease in 100% of mice. DAS181 also enhanced survival when given 72

hours after H5N1 virus challenge. *In vitro* and *in vivo* activity against a range of influenza A and B strains has previously been reported.<sup>2</sup>

DAS181 is a recombinant sialidase fusion protein designed to prevent influenza infection by cleaving sialic acid receptors (the entry site for human and avian influenza viruses) in the airway epithelium when inhaled. Enrolment in a phase I clinical study commenced in October 2007.<sup>3</sup> This randomised, double-blind, placebo-controlled, dose-escalating study will investigate the safety, tolerability and pharmacokinetics of a single dose of DAS181 (0.5 mg, 1.0 mg, 2.25 mg, and 4.5 mg delivered via a dry powder inhaler) in 60 healthy volunteers. DAS181 is being developed by NexBio, Inc. (San Diego, USA).

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**Clinical A/Prof David Smith**

David Smith is Clinical Director of the Division of Microbiology and Infectious Diseases at the Western Australian Centre for Pathology and Medical Research. He is also Clinical Associate Professor in the Department of Microbiology at the University of Western Australia, and Director of the Arbovirus Research and Surveillance Group.





### Prof Prasert Thongcharoen

Prasert Thongcharoen is a Professor Emeritus of Virology at Mahidol University, at the Faculty of Medicine, Siriraj Hospital. He currently serves as President of the Thai Clinical Chemistry Association and is a member of numerous other professional organisations, including the Asia-Pacific Society of Medical Virology.



### Prof Jen-Ren Wang

Jen-Ren Wang is Professor in the Department of Medical Technology, College of Medicine, National Cheng Kung University Medical Center (NCKUMC), Taiwan. She is also Principal Investigator for the Department of Health's Taiwan Center for Disease Control Virology Contract Laboratory and the National Health Research Institutes Tainan Virology Laboratory for Diagnosis and Research, NCKUMC.

## Upcoming meetings

### International

#### 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)

Barcelona, Spain  
[www.akm.ch/eccmid2008](http://www.akm.ch/eccmid2008)

19–22 April 2008

#### World Vaccine Congress 2008

Arlington, Virginia, USA  
[www.terrapinn.com/2008/wvc\\_DC](http://www.terrapinn.com/2008/wvc_DC)

21–24 April 2008

#### 26th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID)

Graz, Austria  
[www.kenes.com/ESPID](http://www.kenes.com/ESPID)

13–16 May 2008

#### American Thoracic Society (ATS) 2008 International Conference

Toronto, Canada  
[www.thoracic.org](http://www.thoracic.org)

16–21 May 2008

#### 3rd European Influenza Conference

Vilamoura, Portugal  
[www.eswi.org/Events.cfm](http://www.eswi.org/Events.cfm)

14–17 September 2008

### Regional

#### The Thoracic Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting

Melbourne, Australia  
[www.thoracic.org.au](http://www.thoracic.org.au)

30 March–2 April 2008

#### Australasian Society for Infectious Diseases (ASID) Annual Scientific Conference

Sunshine Coast, Australia  
[www.asid.net.au](http://www.asid.net.au)

2–5 April 2008

#### 13th International Congress on Infectious Disease (ICID)

Kuala Lumpur, Malaysia  
[www.isid.org/13th\\_icid/index.shtml](http://www.isid.org/13th_icid/index.shtml)

19–22 June 2008

### Next APACI meeting

The next APACI meeting will be held in Jakarta, Indonesia, on 8–9 March 2008.

### In the next issue ...

- Reports from the APACI Clinician Workshop in Jakarta
- A protocol for influenza disease burden studies
- Influenza awareness activities in Indonesia.

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