Influenza Asian Focus

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Welcome to the 12th 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 ongoing surveillance of influenza seasonality and disease burden has shed more light on the impact of the influenza virus in Asia, but robust data are needed. In this issue, we give an update on the progress of the APACI's influenza disease burden study, which will be based on a new World Health Organization (WHO) generic protocol. Our coverage of the first APACI Clinician Symposium in Jakarta includes a discussion of the links between seasonal, avian and pandemic influenza, presentations on seasonal and avian influenza in Indonesia, an overview of laboratory techniques for influenza detection and subtyping, and a review of strategies for controlling seasonal influenza, among others. We outline the APACI's position on the appropriate use of antivirals in seasonal influenza and include an update on the Chinese influenza vaccine manufacturers' alliance and news of the formation of the Indonesian Influenza Foundation. Also included in this newsletter are a case study contribution from Australia, our usual updates on seasonal and avian influenza developments and a new members' corner page.

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Advisory Committee Members

Visit APACI's website at www.apaci-flu.org

The role of the Asia-Pacific Advisory Committee on Influenza

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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.

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 Biologicals.

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 programmes
- 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 14th APACI meeting was held in Jakarta, Indonesia, on 8 and 9 March 2008. Following the success of the previous Clinician Workshop in Taiwan, the APACI expanded the meeting format in Jakarta in line with the objective of making its educational messages accessible to a wider audience. More than 75 local physicians attended the inaugural Clinician Symposium, which featured presentations on influenza epidemiology and disease burden in Indonesia and the rest of the Asia-Pacific region. Highlights of the symposium are presented in this issue of the newsletter. The APACI resumed its regular board discussions on day 2 of the meeting, focusing on the APACI influenza disease burden study, communication strategies for increasing influenza awareness, and guidelines for prescribing antiviral medication.

The APACI continues to recognise the importance of targeting influenza education to primary care physicians and other professionals who treat influenza on a regular basis. Future APACI clinician symposia will continue to be held in each country that hosts a board meeting, with local physicians being invited to participate in the ongoing discussion and educational debate.

Uncovering influenza disease burden in the Asia-Pacific: an update

Recognising the need for robust data on the impact of influenza burden in the Western Pacific and South-East Asia, the WHO is committed to assisting countries in the region to document their influenza disease burden and, thereby, generate country-specific data to guide health policy. Experts from eight countries met with WHO representatives in November 2007 for initial discussions on developing generic protocols for influenza disease burden studies. The WHO protocol document was subsequently drafted during a National Influenza Centre meeting in Tokyo, Japan, in April 2008. The APACI will adapt this generic protocol to investigate the influenza burden in a subset of its member countries. Several points of interest in the WHO protocol are discussed below, together with their application to the planned APACI study.

Study population

The WHO suggests studying the influenza burden either in outpatients with influenza-like illness or hospitalised patients with acute lower respiratory tract infection (LRTI); the APACI has chosen this latter endpoint for its study. The study sample should reflect the wider at-risk population. To estimate the number of hospitalised patients likely to meet the acute LRTI case definition during the prospective study, the WHO recommends first performing a retrospective analysis of patients hospitalised with pneumonia during the previous year. Ideally, informed consent and respiratory specimens should then be obtained prospectively from all patients meeting the case definition. If this is not possible due to budget and staffing constraints, a random sampling plan should be designed to enrol every *n*th eligible patient. For example, if resources permit the testing of specimens from 25% of the expected eligible population, every fourth patient meeting the case definition should be enrolled.

Specimen collection and laboratory diagnosis

High-quality specimens are essential for the laboratory diagnosis of influenza. Specimens should be collected as close as possible to the onset of illness and the time from the onset of illness to specimen collection should be recorded. While nasopharyngeal samples are ideal, an acceptable alternative is to combine nasal and throat swabs from the same patient in a single specimen vial, which should be transported without delay to the laboratory. Reverse-transcriptase polymerase chain reaction (RT-PCR) and real time-PCR are the preferred diagnostic methods; rapid antigen tests are suitable for use in outpatient studies but are not recommended in patients hospitalised with acute LRTI.

Data analysis and key indicators

Simple proportions, such as the proportion of all LRTI patients whose LRTI is caused by influenza virus infection, can be useful measures of the disease burden. Calculating proportions requires accurate recording of the total number of patients meeting the specified criteria during a defined time period. Incidence rates should be reported consistently, for example as *n* influenza cases per 100,000 persons/year. If the size of the at-risk population is unknown, specialised epidemiological advice may be needed. Wherever possible, patient-level data should also be collected and the socioeconomic burden of influenza reported in terms of direct treatment costs, lost work or school days, and expenses incurred by patients and their families.

Key indicators for measuring the influenza disease burden: hospitalised acute LRTI due to laboratory-confirmed influenza virus infection[1]

Essential data

- Number of pneumonia (acute LRTI) cases per month and year
- Proportion of all pneumonia cases caused by influenza
- Distribution by age group (0–2, 3–4, 5–17, 18–49, 50–64 and ≥ 65 years)
- Demographic data (gender, residence and ethnicity of the study population)
- Clinical data (history, symptom presentation, status at discharge).

Desirable data

- Incidence per 100,000 persons per year
- Measurements of severity and outcome
- Requirement for oxygen therapy, intensive care or endotracheal intubation
- Length of hospital stay (mean, median, range)
- Clinical status 21 days post-discharge (alive or dead).

The APACI burden of disease study

The APACI will conduct the 12-month prospective study in a subset of member countries, investigating the proportion of hospitalised patients with acute LRTI who have laboratory-confirmed influenza. Prior to the study, a random subset of hospital discharge diagnoses from the previous year will be retrospectively reviewed to estimate the eligible patient population. It is recognised that some APACI countries will be unable to define the catchment population for each study centre; this should not be a barrier to study entry. Collection of socioeconomic data will be optional. Some countries have already identified study sites and principal investigators, whereas others will require substantial additional resources in order to participate. Board members are currently undertaking feasibility assessments in their respective countries, with the first sites to commence the study before the end of 2008.

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 Symposium in Jakarta

The APACI held its first Clinician Symposium: 'Uncovering the impact of influenza' on 8 March 2008 in Jakarta in conjunction with the 14th APACI meeting, which reinforced its focus on promoting the control of seasonal influenza. APACI Chair, Lance Jennings, commenced with a brief summary of the APACI's background history, mission statement, objectives and achievements. Endang Sedyaningsih Mamahit discussed the epidemiology, disease burden and surveillance of seasonal influenza in Indonesia. This was followed by a discussion of the clinical diagnosis of seasonal influenza by David Smith, an overview of laboratory detection methods by Paul Chan, and a summary of the seasonal influenza burden in Asia-Pacific countries by Malik Peiris. Renowned virologist, Ab Osterhaus, also presented evidence on the links between seasonal, avian and pandemic influenza, while Nyoman Kandun gave an update on the current avian influenza situation in Indonesia. Lance Jennings concluded the workshop with a discussion of pharmacological and non-pharmacological influenza prevention and control strategies.

Influenza epidemiology, disease burden and surveillance in Indonesia

Surveillance data for influenza-like illness (ILI) in Indonesia from 2004 to 2007 demonstrate that the influenza B strain occurs consistently throughout the year, while influenza A shows increased incidence during the rainy season (Figure 1). Both strains were detected across all monitored provinces.

Surveillance has also shown a steady rise in the number of suspected avian influenza cases from 2005 to 2007, partly due to increased awareness of the disease by primary care physicians; only 7.7% of suspected cases were identified as A(H5N1) infection.[1] Seasonal influenza is still seen as a low priority in Indonesia, and the national sentinel surveillance programme is supported by international funds. Public vaccination programmes in Indonesia do not include the influenza vaccine, though recently, more healthcare workers on the avian influenza frontline have been given precautionary vaccinations against seasonal influenza. Future proposals for influenza surveillance in Indonesia include expanding data collection and analysis across age groups, the inclusion of control group surveillance to determine circulation levels of other viral respiratory infections in healthy people, and testing for amantadine and oseltamivir resistance.

Clinical diagnosis of seasonal influenza

The proper diagnosis and treatment of seasonal influenza is dependent on having knowledge of the clinical manifestations of influenza virus infection, and the availability of reliable and consistent clinical diagnostic criteria. The clinical presentation of influenza infection can vary widely, from asymptomatic illness to disease caused by secondary bacterial infections and the deterioration of pre-existing conditions. Seasonal influenza, which causes high fever, sore throat and myalgia, and has a recovery time ranging from several days to weeks, is frequently confused with the common cold by the general population.

Respiratory and non-respiratory complications, with illnesses such as otitis media, sinusitis, bronchiolitis and primary viral and secondary bacterial pneumonias, account for most of the influenza disease burden. Clinicians, when faced with advanced complications, such as myocarditis or even renal failure, may not recognise the connection with a previous influenza infection. Sprenger *et al.* retrospectively studied hospital records in the Netherlands and found that for every overt influenza death identified, there were two or three more deaths attributable to the effects of influenza.[2]

The clinical diagnosis of influenza during the influenza season varies internationally in terms of sensitivity and specificity. Positive predictive values ranged from 87% in Canada,[3] to between 28 and 60% in an Australian study,[4] to less than 25% using the Indonesian ILI diagnostic criteria.[1] Influenza diagnosis in young children and the elderly brings additional difficulties. Poehling *et al.* found that in US children under 5 years of age with laboratory-confirmed influenza, only 17% of those seen as outpatients and 28% of those hospitalised had been clinically diagnosed with influenza by their primary care physician.[5]

Ultimately, patient testing remains the most accurate measure in determining influenza activity, but using specific diagnostic criteria and information about community activity to determine the likelihood of infection may be more practical.

Laboratory detection methods

Different laboratory techniques exist for the detection of H5 and non-H5 type influenza viruses, with varying levels of clinical sensitivity and specificity. The available techniques can be classified as direct detection, virus culture, molecular amplification and serology.

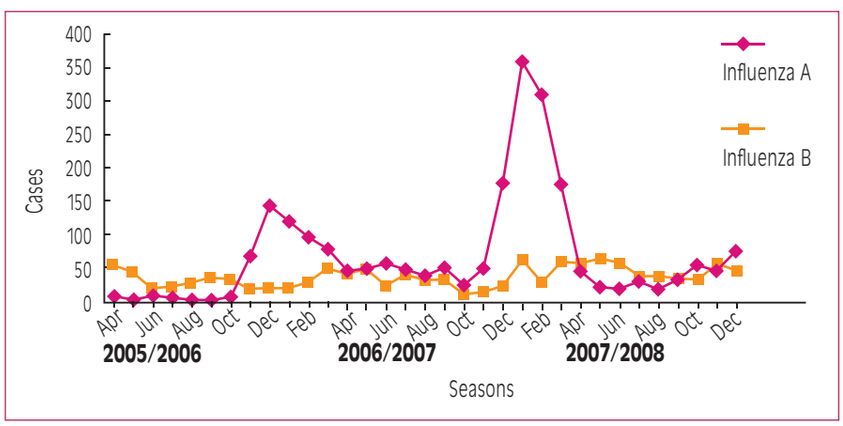

Figure 1. Summary of Indonesian National Institute of Health Research and Development (NIHRD) and US Naval Medical Research Unit 2 (NAMRU-2) surveillance data for seasonal influenza from 2005/2006 to 2007/2008.

Direct detection involves a straightforward examination of the patient specimen using rapid antigen detection kits or immunofluorescence assays to identify the viral protein component. Direct methods can achieve a clinical sensitivity of 90% or higher for common influenza strains, but struggle to detect influenza A(H5N1) with an adequate level of sensitivity.

Virus amplification involves conventional culturing practices. The long turnaround time of 10–14 days is the method's major drawback, whereas rapid cell culture techniques can produce results after 2 days of incubation. Virus amplification offers excellent clinical specificity and sensitivity and is useful for strain characterisation, but requires a Biosafety Level 3 laboratory when handling specimens from patients suspected of avian influenza.

The most recent development in virus detection is molecular amplification, where the viral gene fragment itself is amplified using conventional or real-time PCR. While fast and applicable to all types of respiratory specimens, the chance of false-positives with molecular amplification fluctuates depending on workload and the laboratory environment, which may be of concern during a pandemic situation.

Serology is more useful for exclusion of infection and for surveillance or prevalence studies. However, one should be aware that some serological methods lack sensitivity and specificity for H5N1.

Influenza: a global perspective

Despite increasing documentation of influenza-associated morbidity and mortality in the tropics and subtropics, many continue to believe that influenza is not a serious concern in these areas compared with temperate locations. The full extent of infection is not realised because few hospital admissions, and even fewer deaths, are attributed to influenza in the region. Different case definitions and other circulating respiratory viruses further confound the estimation of ILI (Figure 2).

Several studies demonstrate that tropical countries have comparable influenza-related morbidity and mortality rates to the USA. A Hong Kong study estimated that the incidence of influenza-associated mortality from 1996 to 1999 revealed excess (all-cause) deaths per 100,000 population per year to be 136 among

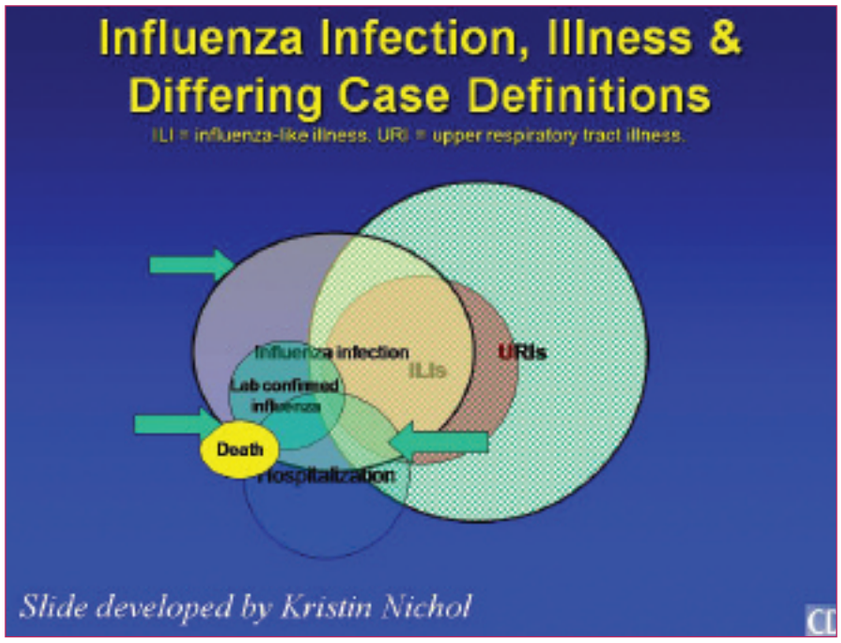

Figure 2. Slide illustrating the overlaps in influenza infection, laboratory-confirmed infection, influenza-like illness, upper respiratory tract illness, hospitalisations and deaths.

individuals aged 65 years and over, and 16 among individuals of all ages.[6] This is comparable to the US influenza associated mortality rate of 100 all-cause deaths per 100,000 population annually among the 65 years and over age group.[7] Data from Thailand[8] and Singapore[9] also show comparable rates of influenza-associated excess morbidity and mortality.

While the broad seasonality of the influenza virus in tropical countries makes the impact of the infection less obvious to clinicians, the belief that influenza is less serious in the tropics is mistaken, and increased uptake of influenza vaccination is crucial to reduce the mortality and morbidity associated with the disease.

Seasonal versus pandemic influenza: how are they linked?

Throughout history, humans have been affected by three different types of influenza: seasonal, avian (H7N7, H5N1), and, in rare cases, pandemic strains. In contrast to the intense media focus on the high mortality rate of human A(H5N1) infection, the severity of seasonal influenza is commonly ignored – yet the difference between the three forms of human influenza is essentially limited to severity and outcome. Every major influenza pandemic (1918, 1957 and 1968) has originated from an avian influenza virus, but it was not until 1997 that researchers realised the virus was replicating between different bird species before eventually moving to other species and humans. The WHO has currently recorded 385 confirmed human cases of H5N1.[10] Increased globalisation and trade has boosted the speed with which viruses are able to cross international borders, but in the event of a pandemic, it may take over 6 months to produce the first vaccine dose. Given current production capacities and the difficulty of stockpiling vaccines without advance knowledge of the strain, alternative manufacturing strategies may need to be considered. The development of new adjuvants, such as MF59 and AS03, may increase vaccine availability as investigational H5N1 vaccines incorporating these adjuvants have been shown to be effective at doses as low as 3.8 µg, compared to 90 µg for non-adjuvanted vaccine.[11] Pre-emptive manufacture and the storage of vaccine components, such as the H5 antigen, could also reduce the delay between the pandemic alert and vaccine availability. In addition, antivirals can play an important role in containing a pandemic prior to the widespread availability of an effective vaccine.

Vigilance and preparation for seasonal influenza is the key to effective preparation against pandemic influenza, which is long overdue. The same strategies of surveillance, social distancing, vaccination and antiviral therapy, if not implemented regularly against seasonal influenza, will be difficult to implement in a pandemic situation.

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 is currently the chief editor of the *Journal of the Formosan Medical Association* and has served on the editorial board of 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.

Control of influenza: an Indonesian perspective

The general perception of influenza in Indonesia is that influenza is a mild and self-limiting disease. The emergence of avian influenza in poultry was first reported in 2003, and over the years has led to Indonesia's unenviable position as a major site of A(H5N1) influenza-related mortality. At the time of the symposium in March 2008, the highest numbers of laboratory-confirmed avian influenza cases were found in West Java (33), Jakarta (32), and Banten (25). A national strategic plan[12] was launched in 2005 to improve control of avian influenza and minimise the risk of a pandemic strain emerging.

A 3-year control model is being developed in Tangerang province as a 'field exercise' in battling avian influenza and allowing localised application of Indonesia's national strategic plan to gauge the performance of its recommendations in practice. Further research is needed in areas such as the H5N1 subtype, rapid and cost-effective diagnostic tools, the role of mammals in viral transmission, and the significance of migratory birds and contaminated environments.

Addendum: As of 19 June 2008, there had been a total of 135 Indonesian A(H5N1) Influenza cases, 110 of which were fatal. Visit www.who.or.id/avian/index.php for the most recent situation updates for avian influenza.

Strategies for seasonal influenza control

Intervention strategies for seasonal influenza consist of two main approaches: pharmacological interventions, such as vaccines and antiviral medications, and non-pharmacological interventions such as respiratory hygiene.

Two influenza vaccine formulations are available for the Northern and Southern Hemisphere influenza seasons, respectively, and are revised annually. These vaccines have been proven safe and effective in the prevention of influenza and associated complications. Influenza vaccination efficacy rates range from 60–90% in children to 70–90% in healthy adults aged less than 60 years.[13] While older people and chronically ill individuals show a reduced response to influenza vaccination, it can still reduce hospitalisations and all-cause mortality in the elderly by up to 70%.[14] Seasonal vaccination of children reduces the incidence of influenza and related illnesses,[15] and also decreases influenza-related morbidity among their household contacts.[16]

Antiviral treatment remains an important adjunct to influenza control, though resistance can occur. Neuraminidase inhibitors, such as zanamivir and oseltamivir, offer up to 90% efficacy in preventing illness.[17] The timely use of antivirals is critical; when taken within 12 hours of influenza symptom onset, antivirals can shorten illness duration by 3 days compared to treatment taken at 48 hours of symptom onset.[18]

Increased personal hygiene and social distancing measures, such as school closures and public gathering bans, could prove crucial in the event of a pandemic. Appropriate implementation of non-pharmaceutical interventions, such as hand-washing and face masks, are also useful companion measures to vaccination and antiviral therapy in mitigating the effects of all types of influenza.

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Country report: the Philippines

The year 2007 was remarkable for accomplishments in policy-oriented workshops and symposia aiming to increase awareness of seasonal influenza and the economic benefits of influenza vaccination. Influenza vaccination rates increased to 93% among infants in 2007 and the Philippine Health Insurance Corporation is currently studying the possibility of subsidising influenza vaccination for members aged 65 years and older.

Influenza vaccination in older adults was the focus of two presentations given by APACI member Dr Shelley de la Vega. In October 2007, she presented a paper entitled 'Improving vaccine coverage amongst older persons' to the Asia Pacific Geriatric Network during the 8th Asia/Oceania Regional Congress of Gerontology and Geriatrics, held in Beijing. From the ensuing discussion, it was apparent that many geriatricians in the region had not had the opportunity to offer their patients influenza vaccination. Pandemic preparedness for older persons, especially those in nursing homes, was also discussed. Dr de la Vega also presented on the importance of influenza vaccination in reducing cardiovascular morbidity, hospitalisation and death during a plenary symposium on preventive geriatrics at the joint annual convention of the Philippine Society of Hypertension and the Philippine Lipid Society.

Other notable developments included the first 'Curing poverty through vaccination' seminar, which was hosted by the Philippines National Institutes of Health under the leadership of Professor Lulu Bravo. The speakers from government agencies and non-governmental organisations highlighted the benefits of vaccination, emphasising to participants that these extend beyond personal health to social and economic gains. In November 2007, influenza vaccination was discussed with an audience of predominantly school physicians and administrators at the 8th Philippine National Immunization Conference.

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.

Formation of the Indonesian Influenza Foundation

In late 2006, Professors Samsuridjal Djauzi and Cissy Kartasasmita agreed on the need to establish a network of physicians with an interest in minimising the burden of influenza in Indonesia. Around 20 specialists in the fields of internal medicine, paediatrics, geriatrics, clinical microbiology, and epidemiology were invited to an initial meeting held in early 2007 at the University of Indonesia's Department of Allergy and Immunology. The meeting led to the formation of a common interest group, initially known as the Indonesia Influenza Study Group. The group held a second meeting in Jakarta on 16 January 2008, which featured a presentation on influenza pandemic preparedness by the Director of Communicable Diseases, Nyoman Kandun. About 30 doctors attended the meeting.

The launch of the Indonesian Influenza Foundation (IIF) was intended to follow the recent APACI symposium in Jakarta, but was postponed due to technical difficulties. The formal launch of the IIF took place on 31 May 2008 at the JW Marriott Hotel in Jakarta at the close of a clinician symposium on seasonal influenza. The event featured local experts as well as invited speakers, including renowned influenza virologist Professor John Oxford from London, UK.

The expert panel at the launch of the Indonesian Influenza Foundation.

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.

Members' corner

Many APACI members are actively involved in research. On this page, we highlight the recent contributions of APACI members to publications from Hong Kong and Singapore, and to an ongoing Australian study investigating the benefits of influenza vaccination in young children.

Influenza A(H3N2) in Hong Kong

Paul Chan, Hong Kong

Professor Chan and colleagues studied influenza seasonality[1] and the emergence of adamantane resistance[2] in Hong Kong using sequence data from 281 influenza A(H3N2) isolates taken from children admitted to the Prince of Wales Hospital between 1997 and 2006.

Seasonality

Influenza seasonality remains poorly understood, particularly in subtropical and tropical regions. This study compared 10 years of haemagglutinin and neuraminidase sequences from Hong Kong with those of vaccine strains and 315 additional sequences from around the world.[1]

The results indicated that A(H3N2) seasonality may be largely due to global migration, with similar viruses appearing in different countries at different times. However, the analysis also suggested that viruses may sometimes persist in a given location, circulating at sub-clinical levels between influenza seasons and re-emerging during the next season with relatively little genetic change.[1]

Adamantane resistance

Resistance was studied in A(H3N2) isolates from adamantane-naïve children. Prescription data showed that amantadine* use more than doubled between 2000 and 2002, while the frequency of known adamantane resistance mutations in the M2 gene increased from 20% in 2003 to 83% in 2005–2006. The S31N mutation was identified in 58 sequences and a previously unrecognised mutation, I51V, became increasingly common from 2000 onwards. The long-term exposure of circulating influenza viruses to patients receiving chronic amantadine for neurological conditions is considered a potential contributing factor to the development of drug resistance in Hong Kong.[2]

* Rimantadine is not available in Hong Kong.

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Paediatric influenza vaccination study

David Smith, Australia

Recent Australian data have shown that children less than 5 years old have the highest influenza hospitalisation rates, but annual vaccination is not universally recommended for children.[1] To obtain further data on the impact of influenza vaccination in young children, the Department of Health in Western Australia is funding a case-control study of universal influenza vaccination for children aged 6 months to 5 years during the 2008 influenza season.[2]

The Children's Western Australian Influenza Vaccine Effectiveness (WAIVE) Study is expected to enrol 1000 children. Two doses of trivalent inactivated influenza vaccine* are being offered free of charge to all children in the target age group in Perth. All children presenting with influenza-like illness (ILI) to participating GPs and emergency departments will have respiratory specimens tested for influenza by PCR. Children with proven influenza will be matched by age and sex to controls without influenza and the outcomes will be analysed by vaccination status (none, one dose or two doses). The main endpoint is the relative risk of confirmed influenza, resulting in presentation to a GP or emergency department, or hospital admission. Follow-up interviews will also assess:

- cases of ILI in other family members
- healthcare visits and costs for all family members
- time off work or school/daycare for parents, affected children and their siblings.

* CSL Limited and Sanofi Pasteur Pty Limited are supplying the influenza vaccine free of charge.

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Vaccination of healthcare workers

Paul Tambyah, Singapore

As only one previous study has reported on the efficacy of influenza vaccination among healthcare workers in the tropics, Dr Tambyah and co-workers studied this question in 541 Singaporean healthcare workers who completed bimonthly questionnaires recording ILI episodes during 2004–2005. Investigators were unaware of the participants' vaccination status, and data were stratified to determine the influence of a known mismatch between the 2003/2004 Northern Hemisphere vaccine and circulating viruses.

Compared to unvaccinated healthcare workers, those who received matched vaccine had a substantially lower rate of ILI (relative risk [RR] 0.49; 95% CI 0.37–0.66; $p < 0.001$), whereas there was no benefit from mismatched vaccine (RR 1.22; 1.01–1.47). Administrative records showed that matched vaccine recipients also took significantly less medical leave for each doctor's visit (mean 0.134 days, versus 0.392 days for mismatched vaccine).

Reference

Kheok SW, Chong CY, McCarthy G, Lim WY, Goh KT, Razak L, Tee NW, Tambyah PA. The efficacy of influenza vaccination in healthcare workers in a tropical setting: a prospective investigator blinded observational study. *Ann Acad Med Singapore* 2008; 37: 465–9.

Antiviral guidelines – seasonal influenza

To ensure that antiviral drugs are used responsibly to confer the most benefit, an APACI discussion, led by APACI member, David Smith, has formulated and agreed upon guidelines for their use in seasonal influenza. The following recommendations aim to enable GPs to decide whether to prescribe, consider prescription based on patient preference, or rule out antiviral therapy (see Figure 1).

Three questions should be asked to determine whether to treat with neuraminidase inhibitors should be given:

1. **Has the person been exposed to influenza?**
   Contact with proven influenza activity, either locally or while travelling, indicates a need for further investigation.
2. **Does the person seem to have influenza?**
   A positive point-of-care (POC) test during the influenza season is a strong indication of influenza infection, with new test kits yielding positive and negative predictive values of over 90%.[1] A strong clinical suspicion is also indicative of likely influenza if POC testing is unavailable.
3. **Will the person gain significant benefit from treatment?**
   If the illness is highly symptomatic, and there is either a risk of complications or a high likelihood of transmission to high-risk contacts, antiviral treatment is advised.

A balance needs to be maintained between maximising clinical benefit and minimising the risk of escalating drug resistance. The recommended flow chart should be useful when deciding whether to respond to influenza-like symptoms with antiviral therapy. Additionally, there should be some awareness of factors affecting local clinical practice; for example, it should be noted that patients in the Asia-Pacific region sometimes struggle to reach their GPs within the 48-hour timeframe of greatest neuraminidase inhibitor efficacy. Issues such as neuraminidase inhibitor access and affordability vary widely in the Asia-Pacific region and these should also be taken into consideration.

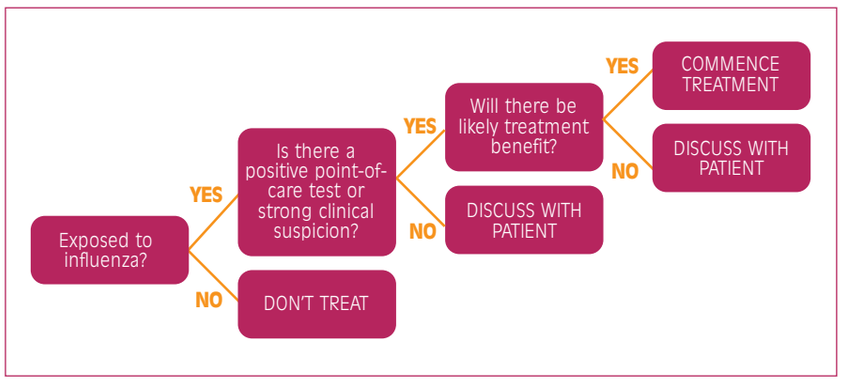

Figure 1. APACI guidelines for prescription of neuraminidase inhibitors.

Reference

1. Weitzel T, Schnabel E, Dieckmann S, Börner U, Schweiger B. Evaluation of a new point-of-care test for influenza A and B virus in travellers with influenza-like symptoms. *Clin Microbiol Infect* 2007; 13: 665–9.

The Chinese influenza vaccine alliance

China has a low rate of influenza vaccination for reasons that include a lack of awareness of the risks associated with influenza, the absence of government funding, inadequate health policy and guidelines, and deficits in doctor education. Although a growing number of vaccine manufacturers have entered the Chinese market, the number of influenza vaccine doses administered has remained constant at approximately 20 million doses each year. In 2007, over 30 million doses were made available by 14 companies but 10 million were returned, highlighting the inefficient use of resources and unnecessary duplication of expenses by vaccine manufacturers. To address these concerns, local and international influenza vaccine manufacturers in China have formed an alliance to promote influenza vaccine awareness and to improve the prevention and control of influenza. Preliminary meetings were held in the fourth quarter of 2007, and a charter and action plan were established in the first half of 2008.

The alliance is to be hosted by the Chinese Preventive Medicine Association (CPMA), which has a close relationship with government departments. One role of the alliance is to facilitate communication between alliance members and the Chinese government, both to ensure that members are aware of government policies and regulations and to promote government support for influenza vaccination. A permanent liaison office will be established within the CPMA. The alliance's regular activities will include international conferences and round-table discussions to focus on policy and strategy, together with public education campaigns to increase awareness and understanding of the importance of influenza vaccination. Long-term projects will include conducting research into the influenza disease burden, gathering data on influenza vaccination and education programmes for doctors.

Objectives of the alliance

- To formulate and coordinate a common strategic approach to developing the influenza vaccine market in China.
- To promote influenza vaccination policy through dialogue with the government.
- To organise conferences, workshops and media programmes to raise awareness of influenza vaccination.
- To provide scientific research and educational resources to government departments to enhance decision-making.
- To share vaccine distribution information between alliance members.

Paediatric influenza case study: Australia

Prof Woo-Joo Kim

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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.

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.

Clinical Associate Professor David Smith, PathWest Western Australia Division of Microbiology and Infectious Diseases Clinical Director, and Dr Paul van Buynder from the Communicable Disease Control Directorate, Department of Health, reported on the appearance of a cluster of influenza-related childhood deaths in Western Australia.

At the end of June 2007, Perth in Western Australia experienced a unique and tragic cluster of deaths in healthy children under 5 years of age. At the time, winter seasonal influenza had begun circulating in Australia but was still at very low levels in Perth. Over a period of 1 week, three previously healthy children died after an initial mild febrile illness rapidly progressed to severe illness and death over a period of 12 hours or less.

Influenza A was detected by PCR in post-mortem samples of all three children. Testing at the National Influenza Centre at PathWest in Western Australia quickly identified the virus as influenza A(H3N2), which was the subtype known to be circulating in the region at the time, and excluded the possibility of a new haemagglutinin subtype. None of the children had been vaccinated, nor were there any epidemiological links between them.

These events caused immense concern to the health department due to the potential for further severe infections or deaths, and alerts were sent to doctors, hospitals and the public. Paediatric emergency departments and GPs were flooded with children brought in by concerned parents, but fortunately no further cases of severe illness or death in young children occurred. The influenza season in 2007 turned out to be the worst experienced in Western Australia since 2003, with influenza A(H3N2) early in the season, and both A(H3N2) and A(H1N1) later in the season.

Early post-mortem findings revealed that the children did not die from either a primary viral or a secondary bacterial pneumonia. Each of the children had a range of streptococcal species isolated from their lungs, but there was no common single bacterium; neither was there any evidence of a myocarditis that may have explained these deaths. Sequencing of the influenza viruses was carried out at the WHO Collaborating Centre in Melbourne after confirmation that the viruses were identical to those already known to be circulating in the community. Furthermore, in each case, the siblings of the dead children had also been infected with the same influenza viruses, but they had had a typical mild influenza illness. There was also no evidence that Perth had a particularly virulent strain of influenza A(H3N2). As a result, discussions were initiated with Australian colleagues at the US Centers for Disease Control and Prevention (CDC) in Atlanta and at Columbia University in New York, and a number of further investigations were undertaken. No single organism other than influenza has so far been identified in all of the cases, and the investigation of the cause of death in these children continues.

Influenza is known to be a serious illness in children and fulminant illness leading to death has been described in the past. However, such deaths have usually occurred as sporadic cases at a time of high influenza activity,[1] and a cluster of three cases occurring at a time of low influenza activity in Perth is a rare occurrence. Further studies are being undertaken to determine the cause of these fatalities and to gain a better understanding of why children die suddenly from influenza, as well as to find clues about potential intervention strategies. In addition, it has reminded us of the potential severity of influenza in children if precautionary measures are not taken.

The Government of Western Australia has supported the introduction of free influenza vaccination in 2008 for children aged 6 months to 4 years. This will be combined with a study to measure the community burden attributable to paediatric influenza and the cost-effectiveness of universal paediatric vaccination. The study is supported by CSL and Sanofi Pasteur, and should provide important information about the value of paediatric vaccination.

Reference

1. Bhat N, Wright JG, Broder KR *et al.*; Influenza Special Investigations Team. Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med* 2005; 353: 2559–67.

Flu review

Isahak I, Mahayiddin AA, Ismail R. Effectiveness of influenza vaccine prevention of influenza-like illness among inhabitants of old folk homes. *Southeast Asian J Trop Med Public Health* 2007; 38: 841–8.

Influenza vaccination significantly reduces the incidence of influenza-like-illness (ILI) among rest home inhabitants in a tropical environment, researchers in Malaysia have observed. A non-randomised, single-blind placebo-controlled study of 527 subjects was conducted from June 2003 to February 2004. Influenza vaccination was associated with a 14–45% risk reduction in contracting ILI compared to the placebo group.

Vaccine recipients also had fewer episodes of fever, cough, muscle aches and runny nose during follow-up (81 morbidity symptoms in the treatment group versus 234 in the control group), and experienced fewer sick days due to respiratory illness. Only 10% of subjects in the vaccine group required more than 3 days to recover, compared to 49% in the control group. The results of this study support those from studies conducted in temperate climates.

Russell CA, Jones TC, Barr IG *et al.* The global circulation of seasonal influenza A (H3N2) viruses. *Science* 2008; 320: 340–6.

Influenza A(H3N2) outbreaks are seeded by viruses originating in East and South-East Asia, a finding that may lead to improved influenza vaccines, say researchers from Cambridge University.

In partnership with scientists from the WHO Global Influenza Surveillance Network, they analysed haemagglutinin from 13,000 A(H3N2) samples collected from six continents between 2002 and 2007. The results showed that new strains emerged each year from a viral circulation network spanning tropical, subtropical and temperate areas of East and South-East Asia, then spread to Oceania, North America and Europe, and later to South America. The year-round circulation of the influenza virus in Asia reflects the presence of overlapping epidemics caused by variations in the timing of the rainy season, as well as winter epidemics in temperate areas. The authors propose that focusing on influenza surveillance in Asia may increase the ability to forecast strains likely to cause epidemics, and thereby to improve the selection of vaccine strains.

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.

Avian influenza: recent developments

Suspected person-to-person transmission of influenza A(H5N1)

A 52-year-old Chinese man most likely caught H5N1 avian influenza from unprotected bedside contact with his dying son while in hospital in December 2007. The older man recovered after a blood plasma transfusion from a woman who had received an H5N1 vaccine in a phase I clinical trial, suggesting the possibility that vaccine-induced antibodies in the plasma played a role in his recovery. High-dose oseltamivir was also administered. The man had no known exposure to the virus other than that from his son, and serum samples from 91 contacts of the index case showed no evidence of H5N1 antibodies, raising the possibility of some genetic susceptibility to the virus.

Reference

Wang H, Feng Z, Shu Y *et al.* Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. *Lancet* 2008; 371: 1427–34.

Indonesia runs avian influenza pandemic drill

Thousands of villagers, health workers and government officials in Bali, Indonesia, participated in a large-scale drill simulating an outbreak of avian influenza with human-to-human transmission in April 2008. Held over a 3-day period, the exercise was orchestrated by the Indonesian Ministry of Health Director of Communicable Diseases, Nyoman Kandun, in a rehearsal for a potential pandemic situation. The drill began in the Bali village of Tukaddaya, starting with a simulated index patient presenting at the village clinic with symptoms of avian influenza. The scripted scenario increased in gravity when the patient revealed to doctors that he had not been in contact with sick or dead birds. Health officials and military forces were involved in practising containment procedures, such as slaughtering birds in the vicinity and isolating other infected humans. The pandemic drill led all the way to preventing supposedly infected passengers from boarding planes at the international airport. Health experts estimate that up to 60 million Indonesians could become infected if the avian influenza virus begins spreading from person to person.

Reference

Paddock C. Indonesia runs large scale bird flu drill. *Medical News Today*, 25 April 2008. Available at: www.medicalnewstoday.com/articles/105412.php. Accessed: 13 May 2008.

Dr Paul Anantharajah Tambyah

Paul Tambyah is Associate Professor and Head of the Division of Infectious Diseases at the National University of Singapore. He is an editorial consultant to the *Singapore Medical Journal* and serves as Vice Chair of the Chapter of Infectious Disease Physicians in Singapore.

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

3rd European Influenza Conference
Vilamoura, Portugal — 14–17 September 2008
www.eswiconference.org/

48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/ Infectious Diseases Society of America (ISDA) 46th Annual Meeting (joint meeting)
Washington, DC, USA — 25–28 October 2008
www.icaacidsa2008.org/

7th Louis Pasteur Conference on Infectious Diseases. *Understanding and controlling infectious diseases: an agenda for the 21st century*
Paris, France — 11–13 November 2008
www.pasteur.fr/infosci/conf/sb/clp7/

Influenza Vaccines for the World – IVW 2009
Cannes Cedex, France — 27–30 April 2009
www.meetingsmanagement.com/ivw_2009/index.htm

6th World Congress of the World Society for Paediatric Infectious Diseases (WSPID)
Buenos Aires, Argentina — 19–22 November 2009
www.kenes.com/wspid/

Regional

International Symposium on Tropical Medicine and Hygiene
Karachi, Pakistan — 10–13 November 2008
www.aku.edu/news/seminars/rstmh/

8th Asia Pacific Conference for Medical Virology (APCMV)
Hong Kong, China — 25–28 February 2009
www.apsmv.org

ISAAR 2009: the 7th International Symposium on Antimicrobial Agents and Resistance
Bangkok, Thailand — 18–20 March 2009
www.isaar.org/

Australasian Society for Infectious Diseases (ASID) Annual Scientific Conference
Hunter Valley, Australia — 25–28 March 2009
www.asid.net.au/

Next APACI meeting

The next APACI meeting will be held in Delhi, India, on 4–5 October 2008.

In the next issue ...

- Highlights from the APACI Clinician Symposium in Delhi
- The use of Northern Hemisphere vs. Southern Hemisphere strain vaccines in tropical countries
- A progress report on the APACI influenza disease burden study.

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