Influenza Asian Focus

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Welcome to the tenth 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.

Amid the ongoing media focus on avian influenza and pandemic planning, the severe morbidity and mortality associated with seasonal influenza often goes unreported. This may be especially true in Asia, where the seasonality and burden of influenza remain poorly defined. In this issue of *Influenza – Asian Focus*, we review the increasing body of evidence documenting the burden of seasonal influenza in Asia and highlight the need for further research, along with an enhanced regional focus on vaccination. The national influenza control initiatives being undertaken across Asia demonstrate that governments, ministries of health and other relevant bodies in the region are indeed making progress towards these goals. While the details vary between countries, all emphasise the importance of raising awareness of the seasonal influenza burden, strengthening influenza surveillance and promoting the use of influenza vaccination. These issues are further explored elsewhere in the newsletter, with articles discussing the epidemiological techniques used to measure disease burden and the role of antivirals and vaccines in combating seasonal influenza.

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Advisory Committee Members

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The role of the Asia-Pacific Advisory Committee on Influenza

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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
  - participating in regional and international congresses
- providing educational resources to support influenza awareness activities:
  - healthcare professional's resource package
  - case management guidelines
  - speaker's kit
  - APACI website (www.apaci-flu.org)
- 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
  - hosting press conferences to raise awareness of influenza-related issues
- identifying and developing activities that complement the WHO Global Agenda on Influenza Surveillance and Control.

Meeting highlights

Hanoi, Vietnam, was the setting for the 12th APACI meeting held on 8–9 March 2007. The meeting focused on current initiatives to fight seasonal influenza in Asia, with highlights including seminars by Fred Hayden of the WHO's Global Influenza Programme and Arnold Monto from the University of Michigan, USA. Fred Hayden discussed the use of antiviral agents in seasonal influenza, while Arnold Monto reviewed the role of vaccination and gave an overview of new epidemiological research from around the world.

Throughout the two-day meeting, APACI members updated the group on the current vaccine recommendations, influenza awareness initiatives and surveillance data in their countries. Local experts Nguyen Tran Hien and Nguyen Thu Van described Vietnam's current control initiatives and reported on influenza vaccine research. Lalit Kant and Prasert Thongcharoen updated delegates on recent Influenza Foundation activities in India and Thailand, respectively, while Ilina Isahak reported on the formation of a national influenza advisory group in Malaysia.

At the now traditional post-meeting press conference, Chair Lance Jennings urged the governments of member countries to make influenza prevention and control a priority. He emphasised the importance of raising awareness as well as increasing the uptake of influenza vaccination during inter-pandemic periods in order to prepare for a pandemic.

Measuring the impact of influenza

Dr Arnold Monto, Professor of Epidemiology at the University of Michigan, discusses recent epidemiological studies illustrating the techniques used to measure the seasonal influenza burden.

Seasonal influenza causes substantial morbidity and mortality. Estimating this disease burden is important for identifying at-risk groups, differentiating the impact of various influenza types or subtypes and recognising time trends, all of which contribute to the evidence base needed to guide health policy and resource planning.

Estimating the influenza burden

Quantifying the impact of influenza is challenging. Most influenza infections are not confirmed virologically and severe or fatal illness – the readily measurable part of the influenza burden – frequently results from secondary complications that occur when the virus is no longer detectable. In addition, the epidemiological techniques used to estimate the burden of influenza typically rely on the presence of a well-defined seasonal influenza peak, limiting their application to temperate regions. In tropical areas, influenza seasonality remains poorly understood and epidemiological techniques have only recently been applied.

Mortality

Estimates of influenza-related mortality rely on establishing an expected baseline, then calculating excess deaths for periods during which the influenza virus is circulating.[1] Influenza epidemics are linked to increases in hospitalisation and mortality for congestive heart failure, chronic obstructive pulmonary disease and bacterial superinfections, as well as pneumonia and influenza.[2] Both the number of excess deaths and the distribution of deaths by cause during the influenza season fluctuates from year to year.[3] The prevailing influenza virus type is one factor contributing to this variation.

Who is at risk?

Elderly individuals are disproportionately affected by influenza-related mortality.[2] In the USA, the influenza-associated mortality rate per 100,000 person-years from underlying pneumonia and influenza deaths was 22.1 in individuals aged 65 years and above, compared with 3.1 for all ages. Individuals aged 85 years and above were also 32 times more likely than those aged 65–69 years to die of an influenza-associated pneumonia or influenza death.[2]

Influenza deaths are uncommon among children in the developed world. However, 153 fatal cases occurred in children aged from 2 weeks to 17 years (median 3 years) during the 2003–2004 influenza season in the USA; 47% of those who died were previously healthy.[4] Influenza may similarly contribute to childhood mortality in resource-poor countries.

Morbidity

While the elderly are at highest risk for influenza mortality, morbidity is greatest in children and young adults. Hospitalisation is the major quantifiable outcome and community studies have substantially contributed to the body of knowledge in this area.

In a large US study, children aged under 5 years had a similar hospitalisation rate to those aged 50–64 years.[5] The rate of excess hospitalisation during the influenza season is inversely related to age in healthy children.[6,7] Healthy infants under 12 months of age have hospitalisation rates similar to those of high-risk adults.[7] A study in Hong Kong found that influenza hospitalisation rates among children in 1998–1999 were substantially higher than corresponding rates reported in temperate regions, even exceeding those reported for high-risk patients in the USA.[8] This was in spite of the clear separation of respiratory syncytial virus (RSV) and influenza activity in Hong Kong during the period studied. In temperate climates, the assessment of influenza morbidity in children is complicated by co-circulation of RSV during the winter seasonal peak, whereas RSV circulates during the summer in Hong Kong and the influenza season varies.

Influenza-related morbidity that does not result in hospitalisation is more difficult to quantify. Relevant outcome measures in children may include excess respiratory illnesses, healthcare visits, analgesic use, school days missed and work days missed by parents during the influenza season.[9] Vaccine probe studies and rapid antigen tests may also be of value in evaluating influenza-related morbidity.

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Regional focus on vaccination needed

The WHO strongly emphasises the benefits of influenza vaccination and recommends it for various target groups to reduce the incidence of severe influenza and its complications, including premature death.[1] Although influenza vaccine production has increased at an annual rate of approximately 5% over recent years, no country fully implements the WHO vaccine recommendations[1] and the use of influenza vaccination varies widely across the Asia-Pacific region.[2]

Barriers to vaccination

Several factors may hinder the implementation of influenza vaccination. Inadequate data on the seasonality and disease burden of influenza in tropical and subtropical regions are a major obstacle, especially in resource-poor countries.

Influenza seasonality in the tropics

In contrast to the well-defined influenza peaks that occur during winter in temperate countries, the seasonality of influenza – and therefore the most effective timing for vaccination – is unknown in most areas of the Asia-Pacific region. In tropical countries, influenza activity continues year-round, with peaks coinciding with the rainy season in some countries.[3]

A recent report from the Multinational Influenza Seasonal Mortality Study (MISMS) on influenza transmission in Brazil shed light on the relationship between latitude and influenza seasonality.[4] Brazil is of interest as it crosses both the equatorial and southern tropic lines. Seasonal influenza was found to travel from equatorial regions to more densely populated subtropical regions, suggesting that the Northern Hemisphere vaccine formulation may be more appropriate for Southern Hemisphere countries situated near the equator[4] and vice versa. For example, analysis of seasonality data in the Philippines recently led to revised recommendations for the use of the Southern Hemisphere vaccine formulation.

The observed differences in the seasonality of influenza between temperate and tropical regions raise the question of whether epidemiological results from temperate countries are applicable to the tropics; for example, different modelling techniques are needed to estimate excess deaths from influenza against a background of year-round transmission.[3] Accurate modelling also requires the availability of reliable virus surveillance data over a number of years.[3]

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Resourcing is another key issue. Developing countries may not view influenza as a health priority, while inadequate public health infrastructure and limited health budgets may compound the severity of influenza infection due to factors such as malnutrition and the limited availability of antibiotics and hospital care.[3] These factors may combine to restrict access to vaccines. Low demand for seasonal influenza vaccines in developing countries then presents a challenge for vaccine manufacturers, who need to ensure that production increases are sustainable.

Burden of influenza in Asia

Despite these difficulties, considerable progress is apparent with respect to the availability of published data on the influenza burden in Asia, and increasing vaccination rates in many countries (discussed below). In fact, a growing body of evidence suggests that the burden of influenza in tropical and subtropical regions is greater than previously thought and at least comparable to that in temperate countries.

Data from Hong Kong show that influenza in this subtropical city is associated with hospitalisation and mortality rates similar to, or higher than, rates in temperate countries;[5–7] in particular, a study in children found a much higher influenza-associated hospitalisation rate than published rates for the USA.[8] Comparable data on influenza-associated deaths have been obtained in Singapore,[9] and influenza has been found to be associated with a substantial economic burden in Thailand, a middle-income country.[10] Influenza surveillance results have also been published for India,[11] Indonesia,[12] Korea[13] and Vietnam.[14]

Influenza vaccination in Asia-Pacific countries

Information on influenza vaccine distribution in the region is becoming more readily available and shows an encouraging increase in vaccine uptake in several areas. A report by the Macroepidemiology of Influenza Vaccination (MIV) Study Group, which comprises representatives of academic institutions or government health departments from over 50 countries, presented data on influenza vaccine distribution in 56 countries for the years 1997–2003.[2]

Data obtained from several Asia-Pacific countries (see Figure 1) showed notably high vaccine distribution in Korea, which in 2003 had the highest distribution rate of any country except for Canada.[2] The distribution rates for Japan and Australia were also in the top five of all countries. Distribution rates in Hong Kong increased by more than sevenfold from 1999 (the first year of available data) to 2003, elevating Hong Kong to tenth position, while New Zealand and Taiwan had similar distribution rates to those in a number of Western European countries. Although Singapore had a substantially lower distribution rate, it also showed a particularly large increase from 2002 to 2003 (from 7 to 90 doses per 1000 total population).[2] There was no apparent relationship between vaccine use and a country's level of economic development, but the availability of public reimbursement for vaccination seemed to be

important among countries with a similar economic development level.[2]

The MIV authors also compared their results with those of a second report examining the global distribution of influenza vaccine. The Influenza Vaccine Supply (IVS) International Task Force (a specialised group of the International Federation of Pharmaceutical Manufacturers and Associations), submitted a report to the WHO containing influenza distribution data for 2000–2003 by region, along with limited data for individual countries.[15] A comparison of 2003 data showed that the MIV figures were generally lower than those in the IVS Task Force report. The degree of correspondence varied by region: nearly 90% of doses in the IVS report were also documented by the MIV study for the Western Pacific region, compared with only 33% of doses in South-East Asia.[2] However, South-East Asia accounted for less than 1% of the global vaccine distribution reported by the IVS Task Force.[2]

Priorities for regional influenza control

Surveillance to identify seasonality and studies to define the disease burden are prerequisites for a well-designed vaccination strategy and are therefore priorities for improving influenza control in the Asia-Pacific region. More developed countries in the region may be able to assist developing countries with areas such as training personnel, conducting clinical trials, setting up laboratory testing, quality assurance and information technology. In addition to reducing the burden of seasonal influenza, these steps will enhance preparedness for an influenza pandemic.

Surveillance to identify seasonality and studies to define the disease burden are prerequisites for a well-designed vaccination strategy

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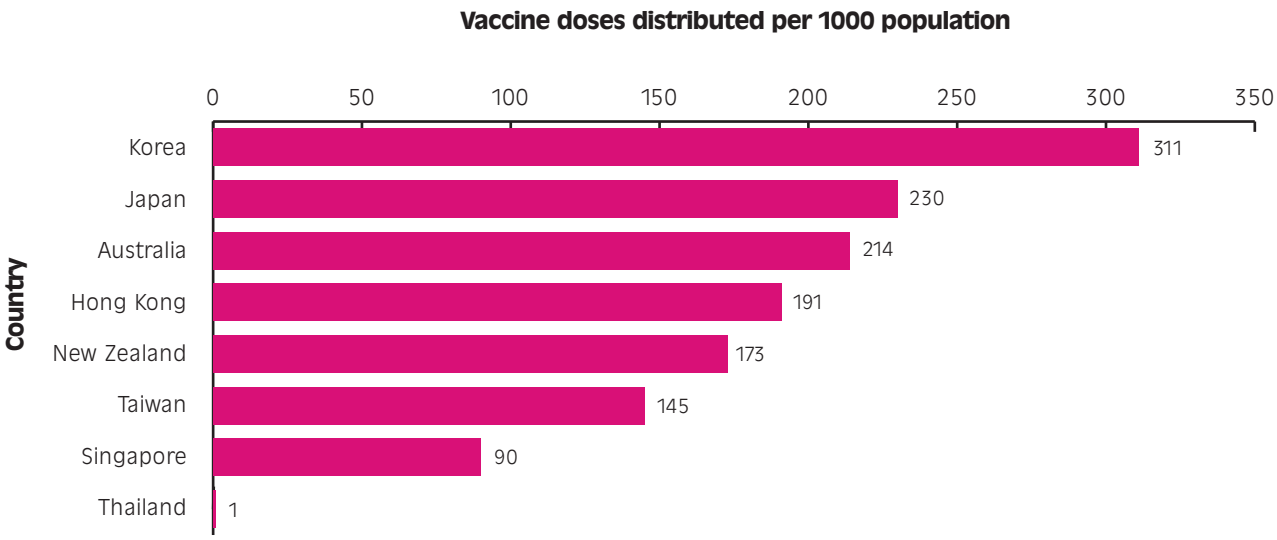

Figure 1. Influenza vaccine distribution in the Asia-Pacific region, 2003.[2]

Antivirals and vaccines in seasonal influenza

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Antivirals and vaccines have an essential role in minimising the significant morbidity and mortality associated with seasonal influenza. Dr Arnold Monto, Professor of Epidemiology at the University of Michigan, reviews the benefits of influenza vaccination, while Dr Fred Hayden, member of the WHO Global Influenza Programme and Professor of Internal Medicine and Pathology at the University of Virginia, discusses antivirals as prophylaxis or treatment for seasonal influenza.

Vaccines

Influenza vaccination aims to reduce influenza-associated morbidity – highest in children and young adults – and mortality – highest in the elderly and people with high-risk medical conditions.

Producing the vaccines

Influenza vaccines are produced annually and contain three influenza strains: type A(H3N2), type A(H1N1) and type B. Separate formulations of inactivated vaccine are prepared for the Northern and Southern Hemispheres; the strains are selected from those submitted to the WHO through its global surveillance system, based on the potential for spread. The live attenuated vaccine FluMist® (MedImmune Vaccines Inc., Maryland, USA) comprises cold-adapted, temperature-sensitive virus strains with reduced virulence; this vaccine is only licensed for use in the USA. Both vaccines are currently grown in the allantoic sac of embryonated chicken eggs.

FluMist® is given intranasally, with protective immunity dependent on infection and replication of cells in the nasopharynx. However, FluMist® is only approved for administration to those aged 5–49 years without high-risk medical conditions. It should probably not be given to healthcare workers in close contact with immunosuppressed individuals, due to the uncertain potential for viral transmission.

Efficacy in adults...

Despite studies demonstrating the clear benefits of influenza vaccination, questions surround the efficacy of vaccination in the elderly, possibly due to the observational nature of many studies in this population.[1] Notwithstanding, influenza vaccination in the elderly reduces hospitalisation and mortality rates, as well as reduces influenza outbreaks in nursing home settings.[2,3]

Inactivated vaccines appear to be more efficacious than the live attenuated vaccine in older adults.

...and schoolchildren

Live attenuated vaccines may, however, be more effective than inactivated preparations in children. A placebo-controlled Russian study compared the vaccines over a 2-year period in children aged 7–14 years. Although both vaccines significantly reduced the number of children with influenza illness, the live vaccine was significantly more effective than its inactivated counterpart.[4]

Vaccinating children may provide indirect protection for at-risk individuals. In Japan, vaccination of schoolchildren was implemented as an influenza control strategy from 1962 to 1987. Researchers who analysed mortality during the mass immunisation programme concluded that 37,000–49,000 excess all-cause deaths were averted annually, and that vaccination of schoolchildren reduced mortality from influenza in unvaccinated older persons.[5]

Antivirals

Useful for prophylaxis

In the past, prophylaxis with M2 ion channel or neuraminidase (NA) inhibitors has been effective for seasonal influenza (see Figure 1). Administered rapidly and in a socially targeted fashion, prophylaxis is useful for outbreak control and associated with reductions in secondary influenza illness. However, the anti-influenza spectrum of antivirals varies, as do their pharmacokinetics, tolerability and resistance profile. In particular, resistance can now limit the use of M2 inhibitors.[6,7] It should also be noted that long-term prophylaxis is an inefficient use of limited drug supplies.

Prophylaxis with either inhaled zanamivir or oral rimantadine was compared in 482 nursing home residents between 1997 and 2000. In this multicentre trial, residents were randomised to receive zanamivir or standard-of-care (comprising rimantadine 100 mg for influenza A or placebo for influenza B) following a declaration of influenza outbreak; treatment was

administered once daily for 14 days. Symptomatic, laboratory-confirmed influenza was recorded in 3% of zanamivir and 8% of rimantadine recipients overall, and influenza A was responsible for 95% of outbreaks. Zanamivir produced a significantly greater protective effect than rimantadine and, in contrast to rimantadine, no antiviral-resistant isolates were detected in zanamivir recipients.[8]

Post-exposure prophylaxis (PEP) also proved effective in reducing secondary influenza illness in a household setting. During the 2000–2001 influenza season, 277 households in Europe and North America were included in an open-label study comparing oseltamivir PEP with oseltamivir treatment at the time of developing illness. In the intent-to-treat population, oseltamivir PEP of householders in contact with an influenza-positive index case reduced secondary influenza illness by 62.7%.[9]

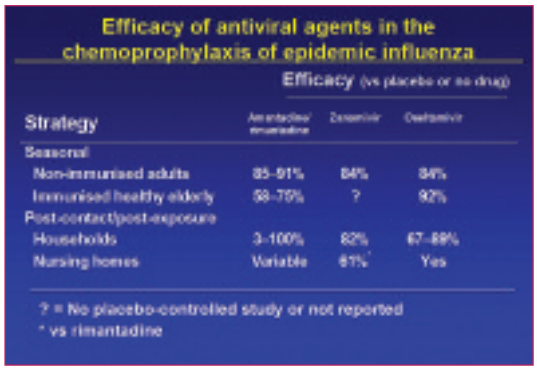

Figure 1. Efficacy of antiviral agents in the chemoprophylaxis of epidemic influenza.

Oseltamivir beneficial for influenza infections

Treatment of seasonal influenza with oseltamivir is associated with reductions in the occurrence of functional disabilities and lower respiratory tract infections.[10] Early administration also appears to reduce antibiotic use, hospitalisations and mortality,[11] although, in young children, oseltamivir may be less effective against influenza B than influenza A infections.[12] Oseltamivir treatment of sick index cases may reduce transmission of the virus to household contacts, but further study is required.[13]

Differing resistance profiles

While resistance can emerge during treatment with either M2 or NA inhibitors, NA inhibitors are rarely associated with primary resistance, and the overall frequency of emerging resistance during treatment is substantially higher with M2 inhibitors. M2 inhibitor resistance also confers resistance to the entire class, whereas patterns of resistance to NA inhibitors vary by virus type and subtype. Dual resistance to both M2 and NA inhibitors is uncommon, and usually occurs only in immunocompromised hosts; generally, one drug class will be effective against variants resistant to the other class. Drug resistance appears to emerge more commonly in children than adults.[14]

Resistance to oseltamivir was evaluated using Japanese data from the 2003–2004 influenza season. Despite substantial oseltamivir use – approximately 6 million treatment courses – only three of 1180 (0.25%) influenza A(H3N2) isolates had mutations previously shown to confer resistance to oseltamivir.[15] Nonetheless, continued monitoring of resistance patterns in both human and animal viruses is essential.

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National influenza control initiatives

Members of the APACI provide an update on seasonal influenza control initiatives in their respective countries.

Hong Kong

Influenza occurs year-round in Hong Kong, with seasonal peaks occurring during February/March and sometimes in July/August. The influenza surveillance system in Hong Kong includes influenza-like illness (ILI) surveillance by private clinics and general outpatient clinics, together with laboratory surveillance. In addition, a sentinel surveillance system for fever covering more than 40 sentinel childcare centres and over 50 residential care homes for the elderly has been in place since 2005. *Flu Express* – a weekly report summarising local and global influenza surveillance activities over the influenza season – is available on the Centre for Health Protection website at www.chp.gov.hk. This regularly updated website has an influenza page containing extensive information intended for the public, the media and health professionals. The groups targeted for influenza vaccination in Hong Kong include individuals aged over 65 years, people living or working in residential care homes, children aged 6–23 months, pregnant women and workers who have contact with poultry. Vaccination coverage rates are approximately 93% for residents in homes for the elderly or disabled, 66–71% for staff in residential care homes and 40–70% for healthcare workers in public hospitals.

India

The Influenza Foundation of India (IFI) was established by the Indian Council of Medical Research (ICMR) in late 2005 in response to calls from influenza experts. The IFI aims to increase knowledge of influenza and its epidemiology in India, produce unbiased scientific and educational materials for the medical community and the general public, promote influenza pandemic-preparedness activities, and provide a link between private practice and the government. The IFI has established a panel of expert advisors and working groups focusing on virology, paediatric influenza, at-risk groups, research, pandemic preparedness and public health, and industry. To date, the IFI has met on three occasions and produced the inaugural issue of its official newsletter, *Influenza – Indian Focus*. The ICMR's influenza surveillance network is also expanding, with 10 new centres to be added during 2007–2008, subject to a favourable assessment of each centre's proficiency in sample collection and virus isolation following initial training. Funding for the expansion of the surveillance network will come from the World Bank.

Indonesia

Indonesia has a high potential for widespread transmission of influenza and other respiratory infections. Steps taken to address this issue include epidemiological and virological surveillance performed in partnership with the US Centers for Disease Control and Prevention (CDC) and the US Naval Medical Research Unit No. 2 (NAMRU-2) in Jakarta, and an increased focus on vaccination. A total of 300,000 influenza vaccine doses were distributed in 2006, representing a 40% increase on the 2005 total. This increase was in part due to the Hajj pilgrimage, which accounted for 105,000 doses, while other reasons for the increase included new influenza vaccination recommendations from the Indonesian Society of Gerontology and the Indonesian Society of Pediatricians, and concerns about avian influenza.

Malaysia

A national influenza advisory group for Malaysia was launched on 30 March 2007. The group includes an epidemiologist, virologist, respiratory paediatrician, respiratory physician, public health officers and industry representatives. Recent initiatives to increase public awareness of influenza have included radio talks, newspaper articles and media briefings at medical conferences. Meanwhile, the national influenza surveillance network has been expanded to include the states of Terengganu, Wilayah Persekutuan, Selangor, Johor and Negeri Sembilan. Malaysian guidelines recommend influenza vaccination for various target groups, including large groups of pilgrims.

The Philippines

Influenza is among the top five causes of morbidity in the Philippines. The Technical Working Group for Influenza (TWGI) is responsible for formulating national guidelines for influenza prevention and control, strengthening the existing influenza surveillance network, promoting influenza pandemic preparedness, and disseminating guidelines to health practitioners and the public. Vaccination is recommended for a range of target groups, including all individuals aged 50 years and over, children aged 6–23 months and women in the second and third trimesters of pregnancy who have not been vaccinated within the past 12 months. An analysis of influenza surveillance data led to a revised recommendation in 2004 to begin using the Southern Hemisphere vaccine formulation.

Insights gained from a pilot 'preventive geriatrics' outpatient clinic run by the Philippine General Hospital have prompted a recommendation that influenza vaccination be incorporated as part of a holistic focus on 'wellness'. The clinic provided free influenza vaccination

together with osteoporosis screening, free vision testing and monthly Tai-Chi exercises in addition to the usual clinical services. The clinic serves the over-60 age group, with the majority of its patients aged between 70 and 79 years. A survey explored the knowledge, attitudes and practices of older individuals with regard to influenza vaccination, after which the benefits of vaccination were discussed in a patient forum. Feedback has been positive and demand for influenza vaccination has increased; since 2003, a mean 44% of the clinic's outpatients have been vaccinated each year.

Taiwan

Taiwan has a well-established influenza surveillance network comprising sentinel physician, laboratory and animal surveillance, along with detection of novel virulent strains by passive reporting of severe cases and surveillance for acute neurological or respiratory syndromes. The elements of this network have been in place since 1999, enabling the analysis of time trends such as phylogenetic changes and the development of amantadine-resistant strains. Influenza vaccination rates in Taiwan increased rapidly between 1998 and 2005 (see Figure 1). The vaccination rate in people aged over 65 years was 59.1% in 2005, down from a high of 68.4% in 2003. Priority groups for influenza vaccination in 2006–2007 include individuals aged over 65 years, children aged 6–23 months, people who live or work in nursing homes and long-term residential care facilities, healthcare workers and individuals working with poultry and swine. As part of its influenza pandemic plan, Taiwan will develop the technology to produce its own vaccine.

Thailand

Since 2004, the Influenza Foundation (Thailand) (IFT) has conducted seminars and workshops covering topics ranging from influenza vaccination guidelines to pandemic-preparedness planning. The IFT's website, www.ift2004.org, details its objectives and activities. Influenza surveillance in Thailand is ongoing in wild birds, farm animals and humans, with human surveillance being conducted by the Ministry of Public Health and the Department of Disease Control. There are five surveillance centres (strategically located on the borders with Laos, Myanmar, Cambodia and Malaysia), 12 regional laboratory centres and two mobile units capable of processing real-time polymerase chain reaction (PCR) assays. The Department of Medical Sciences and the National Influenza Center complete the Thai influenza network.

Vietnam

The epidemic waves of influenza A(H5N1) that occurred in Vietnam from December 2003 to November 2005 provided the impetus for strengthening influenza surveillance, which encompasses ILI, severe viral pneumonia and avian influenza. As the Vietnamese climate ranges from subtropical in the north to tropical in the south, it is important to ensure a nationwide distribution of sentinel surveillance sites. The surveillance network continues to expand; five additional sites were included from May 2006 and a further three sites from May 2007, bringing the total to 15. The sentinel sites report to regional centres or, in some cases, directly to the National Institute of Hygiene and Epidemiology (NIHE). The NIHE submits national data to the WHO Global Influenza Surveillance Network through FluNet and has many additional responsibilities, including submitting viral isolates to the WHO and advising the Ministry of Health on influenza control and prevention. In 2006, the Vietnamese surveillance network reported a total of 691,006 consultations, with consultations for ILI accounting for 18.0% of this total.

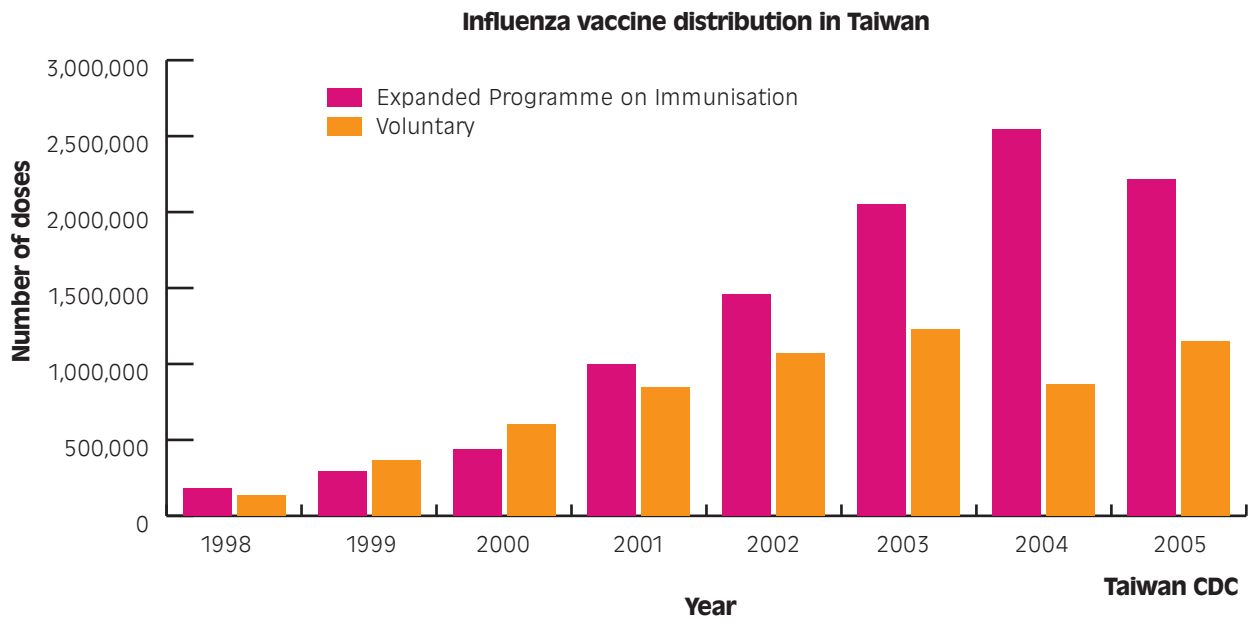

Figure 1. Influenza vaccine distribution in Taiwan, 1998–2005.

SEA Influenza Clinical Research Network

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.

The SEA Influenza Clinical Research Network was established to advance the scientific knowledge and clinical management of human influenza. The Network consists of hospitals and institutions in Indonesia, Thailand and Vietnam in association with the WHO and the following international partners: the Wellcome Trust, the University of Oxford, the US National Institute of Allergy and Infectious Diseases (NIAID) and the NIAID Center for International Research Assistance and Support (CIRAS). One of the Network's key objectives is to conduct protocol-based, multicentre studies that will generate high-quality evidence to guide health policies and clinical practice. To achieve this, the Network employs a multi-lateral, collaborative approach focused on enhancing the research capabilities of its members and sharing of information and samples (subject to approval from the relevant national authorities). The NIAID and the Wellcome Trust are currently the principal sources of financial support. Full details of the Network's aims and organisational structure are available on its website www.seaclinicalresearch.org.

Several clinical trials are under way or in the planning stages. SEA-001 is a randomised, phase II study comparing standard- and high-dose oseltamivir in approximately 600 patients hospitalised with severe human or avian influenza. SEA-002, initiated in November 2006, is a phase I study investigating the pharmacokinetics and tolerability of increasing loading doses of oseltamivir, as well as the effects of concomitant probenecid administration, in healthy Thai volunteers. A second phase I trial, SEA-003, will investigate the pharmacokinetics of oseltamivir and intravenous zanamivir in volunteers. Additional studies are planned.

In memoriam – Aileen Plant

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.

It is with great sadness that APACI notes the sudden death of Aileen Plant at the age of 58. Professor Plant will have been known by many in the Asia-Pacific region for her long and very distinguished career in the epidemiology and control of infectious diseases and as one of the most valued and most widely travelled WHO experts.

She was Professor of International Health at Curtin University of Technology and Deputy Chief Executive Officer of the Australian Biosecurity Cooperative Research Centre for Emerging Infectious Diseases.

To many in the region, she will also be remembered for her work on behalf of the World Bank, AusAID and numerous other bodies, in addition to her WHO roles. From her early work with tuberculosis in Vietnam and outbreaks of HIV in the developing world, she was more recently involved in the control of the SARS epidemic and avian influenza. Professor Plant was one of the leaders of the response to SARS in Vietnam, and her death at Jakarta airport followed her invited speech at a pivotal avian influenza meeting in that city.

Testimonials have been received from people around the world, ranging from the many students Professor Plant taught to international experts she worked with, including the Director-General of the WHO. The impact of her death has been felt so widely because she was a person of great knowledge, energy and enthusiasm. She was generous with her time and had the ability to identify the important bits in complex problems. Everyone was treated with goodwill and respect, and she had a knack for bringing people together.

In an article in *The Australian* newspaper in 2004 about the personal threats she faced in dealing with new infectious diseases, Professor Plant was quoted as saying, "It would be a nuisance to die and I'm not planning it."

None of those diseases claimed her life, but she did die while helping the world fight its newest threat. For those of us who worked with her and knew her personally, we have lost both an invaluable colleague and a great friend.

David Smith

The Western Australian Centre for Pathology and Medical Research, Nedlands, Australia

Flu review

Madjid M *et al.* Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34, 892 subjects. *Eur Heart J* 2007; 28: 1205–10.

This study analysed the relationship between influenza epidemics and deaths due to coronary heart disease using autopsies conducted between 1993 and 2000 in St Petersburg, Russia. Weekly autopsy-confirmed deaths from acute myocardial infarction (AMI) or chronic ischaemic heart disease (IHD) were plotted against weekly acute respiratory disease counts and influenza epidemics. Overall, there were 11,892 deaths from AMI and 23,000 from chronic IHD. Compared with influenza off-season weeks, the odds for AMI and chronic IHD death increased during influenza epidemic weeks by 30% and 10%, respectively. The authors advocate influenza vaccination for high-risk patients with coronary heart disease.

Grijalva CG, Poehling KA, Edwards KM *et al.* Accuracy and interpretation of rapid influenza tests in children. *Pediatrics* 2007; 119: e6–11.

The effect of influenza prevalence on the predictive value of rapid influenza antigen detection tests was evaluated in children hospitalised with respiratory symptoms and fever in the USA. The study included 270 children aged under 5 years who were given rapid influenza tests between 2000 and 2004; test results were compared with the gold-standard viral culture and reverse-transcriptase (RT) PCR. Influenza was detected by viral culture or RT-PCR in 41 children, 63% of whom had a positive rapid influenza test. Of the 229 children who tested negative by viral culture or RT-PCR, 97% had a corresponding negative rapid test result. The researchers concluded that rapid antigen tests are useful when the influenza prevalence exceeds 10%, with a positive predictive value of ≥ 70% at this level.

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 updates

Human monoclonal antibodies protect mice from influenza A(H5N1)

Researchers have shown that fully human monoclonal antibodies (mAbs) isolated from the peripheral blood of survivors of H5N1 infections can neutralise the virus in a mouse model. In this study, B cells from Vietnamese adults who had recovered from infections with highly pathogenic avian influenza H5N1 viruses were immortalised using Epstein–Barr virus. Supernatants from B cell lines were screened in a virus neutralisation assay and those secreting neutralising antibodies were cloned and the mAbs purified. Cross-reactivity of the antibodies was tested in *in vitro* neutralisation assays and mice. Two mAbs, FLA3.14 and FLD20.19, neutralised both Clade I and Clade II H5N1 viruses, while two others, FLA5.10 and FLD21.140, neutralised Clade I only. FLA3.14 and FLA5.10 also conferred dose-dependent protection from lethality in mice challenged with A/Vietnam/1203/04 (H5N1). Also addition, prophylaxis with mAbs significantly reduced pulmonary virus titre and virus-associated lung inflammation, and restricted extrapulmonary virus dissemination. FLA3.14, FLA5.10, FLD20.19 and FLD21.140 all protected from lethality with A/Vietnam/1203/04 for ≥ 72 hours post-infection at therapeutic doses. The researchers concluded that neutralising mAbs can be rapidly generated from H5N1 survivors and such mAbs could be used for prophylaxis or adjunctive treatment of human H5N1 infections.

Reference

Simmons CP, Bernasconi NL, Suguitan AL *et al.* Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza. *PLoS Medicine* 2007; 4: e178.

Resolution on sharing reached

At the 60th WHO World Health Assembly held in May 2007, member states agreed on a resolution to assist countries to better prepare for the potential global public health threat of an influenza pandemic. The resolution, entitled "Sharing of Influenza viruses and access to vaccines and other benefits", emphasises the necessity of sharing and its downstream benefits. Moreover, it requests that the WHO establish an international stockpile of vaccines for H5N1 or other potential pandemic viruses, and formulate mechanisms and guidelines to ensure fair and equitable distribution of such vaccines at affordable prices in the event of a pandemic. An interdisciplinary working group has also been tasked with drawing up new terms of reference for the WHO Influenza Collaborating Centre Network and its H5 reference laboratories. The new terms will factor in the origin of shared virus samples and make their use more transparent.

Reference

WHO. World Health Assembly closes. 23 May 2007. Available at: www.who.int/mediacentre/news/releases/2007/wha02/en/index.html. Accessed 1 June 2007.

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

47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
Chicago, USA — 17–20 September 2007
www.icaac.org

World Vaccine Congress Lyon 2007
Lyon, France — 8–10 October 2007
www.lifescienceworld.com/2007/wvcl

Perspectives in Interpandemic Influenza
Madrid, Spain — 12–14 October 2007
www.perspectivesininfluenza.com

Modern Vaccines/Adjuvants Formulation (MVAF) 2007: Impact on Future Development
Dublin, Ireland — 12–14 November 2007
www.meetingsmanagement.com/mvaf_2007/index.htm

53rd International Respiratory Congress
Orlando, USA — 1–4 December 2007
www.aarc.org/education/meetings/#07_congress

Regional

5th World Congress of the World Society for Pediatric Infectious Diseases (WSPID)
Bangkok, Thailand — 15–18 November 2007
www.kenes.com/wspid

12th Congress of the Asian Pacific Society of Respirology (APSR)/ 2nd Joint Congress of the APSR and the American College of Chest Physicians (ACCP)
Gold Coast, Australia — 30 November–4 December 2007
www.apsr2007.org

Asia Pacific International Conference on Travel Medicine (APICTM) 2008
Melbourne, Australia — 24–27 February 2008
www.apictm.com

Next APACI meeting

The next APACI meeting will be held in Taipei, Taiwan, in September 2007.

In the next issue ...

Topics that will be covered in the next issue of *Influenza – Asian Focus* include:

- Pre-pandemic versus pandemic vaccines
- Guidelines on the use of antiviral medications
- Identifying the burden of influenza disease in the Asia-Pacific region.

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