Influenza Asian Focus

Volume 3, Issue 1, March 2007

Welcome to the ninth 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 evolution of influenza viruses calls for continuous surveillance to identify new vaccine candidate strains and sustained efforts to produce improved vaccines. In this issue of *Influenza – Asian Focus*, the evolution of influenza viruses and new developments in influenza vaccines are discussed. National influenza pandemic plans have been prepared across the Asia-Pacific region and this issue focuses on some of these. Surveillance and biosafety continue to be primary concerns within the context of epidemic and pandemic influenza control, and we present an overview of influenza surveillance in China, an update on the avian influenza situation in Indonesia and news about the Singapore–Indonesia bilateral venture in biosafety. Given the global variation in the prevalence of influenza disease, our attention is drawn to the importance of pre-travel vaccination. This issue also includes a review of the revised recommendations on paediatric vaccination from the US Advisory Committee on Immunization Practices (ACIP).

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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

Dr Lance Jennings

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

Dr Ai Ee Ling

Ai Ee Ling is Director of the Virology Section, Department of Pathology and a Senior Consultant at the Singapore General Hospital. She is responsible for the National Influenza Centre and the National HIV Reference Laboratory in Singapore.

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 (formerly Chiron Vaccines), Roche, Sanofi Pasteur and Solvay Pharmaceuticals.

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

Objectives

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

Activities

Activities include:

- promoting influenza awareness to healthcare professionals in the region:
  - identifying country-specific key opinion leaders (KOLs)
  - publishing a regular newsletter (*Influenza – Asian Focus*)
  - producing peer-reviewed publications
- providing educational resources to support influenza awareness activities:
  - healthcare professional's resource package
  - case management guidelines
  - speaker's kit
  - continuing medical education programme
- assisting the process of establishing or reviewing country-specific recommendations for influenza prevention and control:
  - to establish a list of existing recommendations
  - to evaluate international recommendations in the Asia-Pacific context
  - to facilitate development of consensus statements and information exchange
- assisting the development of country-specific public awareness programmes:
  - identifying country-specific requirements
  - developing a strategy to increase country-specific public awareness
  - media kit
  - media training for KOLs
- identifying and developing activities that complement the WHO Global Agenda on Influenza Surveillance and Control.

Meeting highlights

The 11th APACI meeting was held in Beijing, China, on 16–17 September 2006. The meeting featured presentations on the evolution of influenza viruses by Alan Hampson, former Deputy Director of the WHO Collaborating Centre for Reference and Research in Influenza in Melbourne, Australia, and Professor Malik Peiris, expert on the epidemiology, evolution and pathogenesis of influenza at the Department of Microbiology, The University of Hong Kong, Hong Kong SAR, China. Alan Hampson also gave an update on new influenza vaccines for pandemic and epidemic control.

Surveillance and pandemic planning were once again prominent on the agenda, with APACI members giving an overview of individual country influenza pandemic preparedness plans.

Professor Prasert Thongcharoen presented results of a study evaluating the efficacy and safety of an intradermal reduced-dose influenza vaccine in healthy adults. The seasonality of influenza in the Asia-Pacific region was also discussed.

The board meeting was followed by a press conference to publicise meeting outcomes to local journalists. Chair Lance Jennings and Yuelong Shu spoke on APACI initiatives in the Asia-Pacific region and the influenza control measures currently in place in China, while Alan Hampson answered media questions on vaccine-related issues.

Evolution of influenza viruses

The rapid evolution of influenza viruses has had dramatic consequences for global health. Alan Hampson and Malik Peiris discuss the mechanisms involved in viral evolution.

The genome of influenza viruses A and B consists of eight segments of single-stranded RNA, each segment coding for a different component (Figure 1).[1] There are two principle surface antigens, the haemagglutinin and neuraminidase glycoproteins, which are primarily responsible for eliciting antibodies after infection or vaccination. Sixteen haemagglutinin and nine neuraminidase subtypes have been detected in birds.

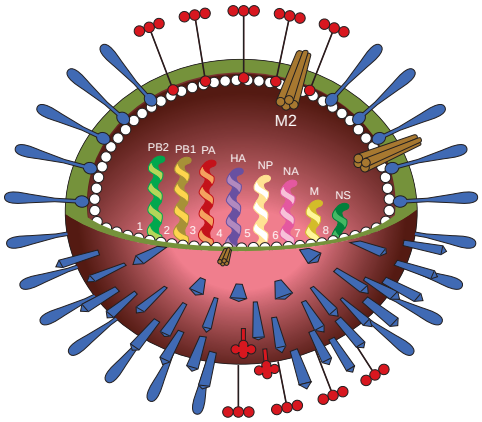

Figure 1. *Influenza virus.*

Causes of variation

Variation results from antigenic drift and antigenic shift. Antigenic drift occurs by point mutations in both the haemagglutinin and neuraminidase glycoproteins, leading to new strains that differ from previous circulating strains; this potentially results in seasonal influenza epidemics. Antigenic drift occurs for both influenza A and B viruses, and is directional, particularly for influenza A. Antigenic shift results from genetic reassortment between avian and human influenza viruses; for example, when a host is infected by both an avian and a human virus and RNA segments are exchanged by reassortment, resulting in a completely changed haemagglutinin in the human population, with or without a changed neuraminidase.

Phylogenetic analyses demonstrate that avian viruses can be transmitted to new, non-avian hosts and displace previous strains.[2] It has been suggested that a shift in the receptor-binding specificity of the avian virus haemagglutinin is a prerequisite for the generation of human pandemic viruses, and that only one or two amino acid mutations in the avian virus haemagglutinin are required for this shift.[3]

There are multiple subtypes of influenza A, distinct both genetically and antigenically, and a single continuous lineage of influenza B. Influenza A haemagglutinin displays true Darwinian evolution and evolves along a single dominant lineage. Influenza B haemagglutinin, on the other hand, shows less evidence of selection, and there are often coexisting evolutionary lineages. Influenza B evolves at a slower rate than influenza A. Influenza C shows no evidence of directional evolution and is antigenically more stable than human influenza A virus.

Influenza A evolution in non-human hosts

The rates of change in the haemagglutinins and neuraminidase of influenza A in pigs and domestic poultry are similar to those in humans, but there is little antigenic drift with the pig virus. There is some evidence of antigenic drift and immunological pressure in horse influenza A. The recent influenza A(H5N1) outbreaks may indicate an immunological drift in domestic poultry.

Evolution of H5N1 viruses

H5N1 is antigenically and genetically heterogeneous, and has evolved into geographically distinct groups. Within endemic countries, these viruses spread within domestic poultry and have evolved into distinct regional clades.[4,5] Some genetic mutations are associated with amantadine resistance. More than 95% of the viruses isolated in Vietnam and Thailand contained resistant mutations, although these were less commonly found in Indonesia and China.[6]

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Professor 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.

Dr Nguyen Thi Hong Hanh

Nguyen Thi Hong Hanh is the Head of the Department of Virology and Vice-director of the National Institute of Hygiene and Epidemiology in Hanoi, Vietnam.

National influenza pandemic plans

In 2005, WHO updated its global influenza preparedness plan and published a checklist to facilitate preparedness planning. Because of concerns about the possibility of an influenza pandemic originating in the Asia-Pacific region, many countries in this region have developed individual strategic influenza pandemic plans.[1] A number of these plans were described at the APACI meeting held in Beijing.

Plans generally cover prevention and preparedness measures, such as surveillance in humans and animals, development of vaccination strategies, stockpiling and production of antiviral drugs and medical supplies, communication, training relevant personnel, simulation exercises and impact mitigation. Early containment measures are a priority, as is the provision for international and national multi-sector cooperation, in particular between the human and animal health sectors.

Taiwan

National surveillance includes a sentinel physician system that reports cases of influenza-like illness (ILI) and regional reference laboratories spread throughout Taiwan. Surveillance includes the detection of novel virulent strains of influenza and animal surveillance of wild birds as well as domestic pigs and chickens. Influenza with complications is a reportable disease in Taiwan.

In the event of a pandemic, public health interventions would include the stockpiling of personal protective equipment and antiviral agents, travel restrictions, social distancing, isolation and quarantine, and measures to ensure supply of influenza vaccine. Free vaccination is currently offered to those > 65 years and < 24 months of age, and to workers in poultry and swine industries. The Taiwanese influenza committee for strain selection determines vaccine composition by analysing information, characterising local influenza strains and predicting circulating strains in the coming season.

Taiwan actively participates in international control programmes. In the event of a pandemic, fever monitoring and quarantine would occur at international ports, with surveillance of travellers from affected areas. Infection control measures in hospitals have been enhanced since the SARS epidemic, and there is a healthcare network for epidemic control. The closing of schools and restrictions on public gatherings might also be enforced to minimise infection during a pandemic. More information can be found at the Centers for Disease Control (Taiwan) website at www.cdc.gov.tw.

Malaysia

The National Influenza Pandemic Preparedness Plan (NIPPP) in Malaysia contains specific advice and actions to be undertaken by the Ministry of Health, other government departments and agencies and non-government organisations. The components of the plan can be categorised into organisational, public health, medical or laboratory responses. The public health response includes surveillance measures and use of antiviral drugs, vaccines and personal protective equipment. Control measures to prevent disease spread include active case detection, screening travellers, isolation and quarantine, hand hygiene, disinfection and the use of facemasks. Staff training and protection, and work safety in hospitals, laboratories and in the field are also a priority.

The medical response involves case definition, notification/reporting of cases, triage and initial assessment, clinical management, hospital admission policies and resource management for health facilities. The national reference laboratory for human influenza is responsible for surveillance and is a key component of the laboratory response. Guidelines for sample collection and handling have been prepared. Supplies and procurement of essential items, logistics and risk communication are also considered in the NIPPP. The level of pandemic alert will determine the actions taken. Further information is available on the Malaysian Ministry of Health website at www.dph.gov.my/survelans.

Vietnam

In the event of a pandemic, an increased capacity to ensure rapid detection and response would be essential. Human and animal surveillance would be enhanced, with more collaboration between the human and animal health sectors. Measures for preventing and containing epidemics in poultry are to be strengthened; for example, by maintaining regular influenza vaccination in poultry.

Considerations include deploying supplies of antiviral drugs for post-exposure and possibly pre-exposure prophylaxis of those individuals most likely to be exposed to the animal virus, promoting vaccination with seasonal influenza vaccine and reviewing strategies for vaccine use. Steps would be taken to prevent nosocomial transmission and laboratory infections, such as increasing awareness of healthcare workers. Rapid communication among health authorities, other relevant government departments, partner organisations and the general public would be facilitated.

There is a strong political commitment in Vietnam to the response measures. Activities promoting the prevention and control of avian influenza include strengthening disease surveillance, improving diagnostic capabilities, sharing information between human and animal health sectors in surveillance and detection, outbreak containment, destruction of infected birds, disinfection of poultry premises and control of poultry movement.

Singapore

In Singapore's planned response to an influenza pandemic, both external and internal surveillance will be important to rapidly detect the importation or in-country occurrence of disease. Singapore is working on the establishment of a vaccine plant in order to have ready

access to needed vaccines and to vaccinate the entire population. A colour-coded approach to risk management has been developed using green for animal disease; yellow for inefficient human-to-human transmission and small clusters; orange for larger clusters and more efficient human-to-human transmission (although still limited); red for pandemic, widespread infection; and black for high morbidity and mortality.

The Ministry of Health will respond to a pandemic by organising the healthcare system to deliver effective care. The stockpiling of oseltamivir and smaller amounts of zanamivir in the event of resistance to oseltamivir is one strategy to enable treatment of those providing essential services. Appropriate social distancing measures will be implemented and, if the situation deteriorates, the closing of borders may have to be considered. A large influenza pandemic readiness drill, Exercise Sparrowhawk II, has been recently conducted to test the responses of border authorities, health institutions and schools in the event of a pandemic.

More information about Singapore's influenza pandemic planning is available at www.flu.gov.sg and www.moh.gov.sg.

Hong Kong

In Hong Kong, government departments, healthcare professionals and the community are required to collaborate in the emergency response to an influenza pandemic. The command structure, objectives and response will be determined by the severity of the situation. At the alert response level, the goal is to prevent importation of disease; at the serious response level, to limit transmission and prevent exportation; and, at the emergency level, to minimise morbidity and mortality. Risk reduction measures relating to poultry include vaccination of chickens, banning of backyard poultry and infection control training for livestock workers.

An early warning system has been put in place that involves statutory notification; sentinel physician, laboratory and hospital surveillance; and outbreak reporting. Border health measures include temperature checks at borders and ports, and travel health information being given to industry. Infection control training has been provided to healthcare professionals, and treatment guidelines for doctors have been prepared. There are defined virology laboratory testing strategies for each alert level.

Community preparedness measures include the preparation of educational material (see www.chp.gov.hk) and the implementation of several pandemic preparedness exercises.

Australia

The strategy underlying Australia's pandemic preparedness plan is to delay the entry of any pandemic strains into Australia, and to slow the spread and lessen the impact once the strain enters. Initial containment measures would be followed by strategies to maintain social functioning. Measures include border surveillance and testing, restrictions on travel to Australia from affected countries, thermal screening of disembarking passengers and transfer of arriving travellers with flu-like symptoms to a centre for further assessment. Within the community, containment measures include the adoption of good infection control practices, 'seek and contain' measures for new cases of infection, quarantine and isolation of proven or suspect cases. Contact tracing, social distancing, special hospital arrangements for flu patients, possible restrictions on movement within Australia, closing schools and encouraging people to stay home from work might all be considered.

As a priority, antiviral medicines would be made available to individuals who provide essential services for the community and whose work puts them at high risk of exposure to the virus. Vaccines would be used when available. A national medical stockpile is accumulating items such as antiviral drugs, personal protective equipment, thermal imaging scanners, needles and syringes, medical ventilators and negative pressure units. Large businesses and government organisations may have additional stockpiles.

A pandemic readiness exercise (Exercise Cumpston) has been recently held to validate the capacity and capability of the Australian response to a pandemic. Further information can be found on the Australian Department of Health and Ageing website at www.health.gov.au.

New Zealand

New Zealand's Influenza Pandemic Action Plan (NZIPAP) is based on an established strategy to deal with outbreaks of infectious disease and forms part of the New Zealand National Health Emergency Plan. The NZIPAP summarises possible scenarios and responses, and has taken a 'whole of government' approach. Although strongly patient focused, it also emphasises business continuity planning and workforce management through to community involvement.

Primary and secondary healthcare considerations include identifying patients at risk and streaming patients to three levels of care according to the severity of their illness and needs: home care, core primary care and hospital care. Various ways of assessing illness have been identified, from self-assessment to hospital triage, with phone assessment and support systems also available. A care map describing symptoms and suggested treatments for different levels of illness has been devised.

Protection and prevention measures include education about respiratory hygiene, particularly in schools and preschools, and about the measures that can be taken to prevent spread, including the concept of social distancing. The New Zealand Government has prepared a national fact sheet that is intended to facilitate the communication of infection risks to healthcare sectors and a poster for healthcare providers with the theme 'protect and prevent' has also been produced.

For more information on New Zealand's pandemic planning, see the New Zealand Ministry of Health website at www.moh.govt.nz/pandemicinfluenza.

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US ACIP recommendations for paediatric vaccination – an update

Professor Li-Min Huang

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

The US Advisory Committee on Immunization Practices (ACIP) now recommends universal vaccination with the inactivated influenza vaccine for children aged 6–59 months. Children aged 6–24 months are at an increased risk for severe complications from influenza, and children aged 24–59 months are at an increased risk for influenza-associated clinic, emergency department or hospital visits, particularly if they have a high-risk medical condition.

Babies < 6 months of age are at greatest risk of influenza-related complications, but the current influenza vaccines are not approved by the US Food and Drug Administration (FDA) for this age group. However, the vaccination of the out-of-home caregivers and household contacts of these babies is recommended because it may decrease the risk that the unvaccinated babies they care for will suffer influenza virus infection. (Either inactivated or live attenuated vaccines may be used to vaccinate adult caregivers and household contacts, unless contraindicated.)

All children aged 6 months to 9 years who have not received a previous influenza vaccination should receive two doses of vaccine. If children receive trivalent inactivated influenza vaccine (TIV), they should be given a booster dose of TIV at least 1 month after the initial dose. If they received influenza vaccine for the first time during a previous season but did not receive a second dose of vaccine within the same season, only one dose of vaccine should be administered. Children aged 5–9 years who receive live attenuated influenza vaccine (LAIV) should have a second dose of LAIV 6–10 weeks after the initial dose. Vaccination should be given before the start of the influenza season, if possible.

The WHO recommended composition of influenza vaccines for use in the 2007 Southern Hemisphere winter is:

- A/New Caledonia/20/99(H1N1)-like virus
- A/Wisconsin/67/2005(H3N2)-like virus
- B/Malaysia/2506/2004-like virus

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Singapore–Indonesia cooperation for avian influenza preparedness

Professor Ilina Isahak

Ilina Isahak is Head of the Department of Medical Microbiology and Immunology at 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.

In November 2005, Indonesian President Susilo Bambang Yudhoyono, US President George Bush and Singapore's Prime Minister Lee Hsien Loong agreed to embark on a pilot project for the prevention and control of avian influenza within a designated area in Indonesia. This project, known as Project Red Lory, was developed in collaboration with the WHO, the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health. Based in the Tangerang municipality, the preparation for and implementation of the avian influenza pilot project began in February 2006. The project will continue for 2 years, at which point, it will undergo a 6-month evaluation.

The project focuses include establishing improved disease-control measures in animals, enhancing case-management systems in humans and implementing strategies for the protection of high-risk groups. Education, communication and information strategies are to be developed, including the implementation of public and farmer awareness programmes, and the provision of training initiatives for medical and laboratory personnel. The pilot project will also aim to improve avian influenza surveillance systems – a goal that will involve the provision of laboratory equipment to allow early detection, improve reporting systems and integrate information into a national surveillance system. It is hoped that successful implementation of this pilot project will provide a useful model that could help Indonesia and other affected countries in their fight against avian influenza.

Influenza seasonality in the Asia-Pacific region

In appreciation of the importance of influenza surveillance, members of APACI have contributed data on influenza seasonality from their respective countries to support a paper on seasonality in the region.

The oscillations in influenza incidence concentrate the mortality and morbidity burden of the disease into a few months each year. This predictable pattern allows health authorities to set protocols in place to protect the public against infection. By studying influenza seasonality, patterns of initiation and spread can be determined, as well as morbidity and mortality burden, and appropriate measures can be taken to ensure that infection is minimised in the general population.

Because of large year-to-year variations in influenza incidence, several years' worth of data are necessary to accurately determine patterns of virus activity. Surveillance should be supported by laboratory capacity to ensure that sufficient viral isolates are obtained to identify circulating influenza virus strains and provide timely access to potential vaccine strains. Several countries in the Asia-Pacific region have now established influenza virus surveillance systems to contribute to information on influenza infections. At present, most studies are of short duration and collection of viral surveillance data must be increased and improved throughout the region.

The APACI recognises the importance of enhanced surveillance and the need to strengthen this capacity at national and international levels. It encourages the discussion and exchange of information on influenza and its surveillance, and supports the WHO initiative in building laboratory capacity and surveillance in the Asia-Pacific region.

Governments are urged to give high priority to the establishment and continued support of influenza surveillance systems, so that epidemiological data on influenza activity and seasonality can aid in making informed decisions about influenza prevention and control, including vaccine policy.

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.

New developments in the avian influenza situation in Indonesia

Indonesia reported its first poultry influenza A(H5N1) outbreak in early 2004 and its first human case in July 2005.[1] Figures from late 2006 showed that poultry infection had then been reported in 29 of the 33 Indonesian provinces and was endemic in 28. Eight provinces and 23 districts had reported confirmed human H5N1 disease, and approximately 75% of human cases reported had a history of contact with infected fowls. Clusters of avian influenza had been reported in Tangerang (July 2005, November 2005), Bintaro (September 2005), Lampung (October 2005), Indramayu (January 2006), Karo (May 2006) and Bandung (June 2006).

As of 6 February 2007, a total of 81 human H5N1 cases have been confirmed in Indonesia, 63 of which were fatal (78% mortality). The most recently confirmed case was that of a 6-year-old girl from Magelang District in Central Java Province. Initial investigations into the origins of her infection have been suggestive of exposure to dead poultry.[2]

A central government commitment to pandemic planning has now been achieved, and avian influenza surveillance has improved. However, programme implementation at a village level is still weak, and there seems to be little sense of the crisis situation at hand among the general public. Poor control of fowl traffic, limited stockpiling of oseltamivir and a limited budget available to compensate farmers for culled poultry are some of the obstacles encountered in trying to contain avian influenza outbreaks in Indonesia. Improved coordination and communication is required with regard to disease surveillance and reporting, ongoing pandemic planning and the implementation of disease control measures.

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Professor 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.

Influenza surveillance in China

The diversity of geographical regions throughout China leads to differences in influenza prevalence and seasonality patterns throughout the country. In Southern China, the occurrence of influenza-like illness (ILI) follows a seasonal pattern, peaking in the colder months. However, in Northern China, ILI is starting to show less seasonal variation, particularly over the recent 2005–06 period, when the occurrence of ILI was similar year round.

Influenza surveillance initiatives have been operating in China since the 1950s. The China National Influenza Center (NIC) was founded in 1957 and China re-joined the WHO Global Influenza Surveillance Network in 1980. The current Chinese influenza surveillance network (Figure 1) is based on the US Centers for Disease Control and Prevention (CDC) system and has involvement from four tiers: the WHO, the Chinese Ministry of Health, the Chinese CDC and various provincial, prefecture and county CDCs. There is close cooperation with the US CDC and, at present, 197 hospitals and 63 laboratories across China collect data to contribute to the national influenza surveillance system.

The implementation of a new human influenza surveillance information system has helped to collate data and provide statistics regarding epidemiological and virological influenza patterns across China. This system provides year-round surveillance in Southern China and half-yearly surveillance in Northern China. Between 2002 and 2006, the proportion of ILI in outpatients in Mainland China decreased steadily, but despite this, the number of confirmed influenza virus isolates has increased. The increased detection of isolates may be attributed to greater surveillance.

The Chinese influenza surveillance information system has also helped provide important and beneficial insights into the patterns and demographics of the recent human influenza A(H5N1) outbreak. Data show that between January 2005 and October 2006, there were 20 confirmed human H5N1 cases in Mainland China, with most of them occurring in the south. Of these cases, 13 (65%) were female and seven (35%) were male, and the median patient age was 26 years (age range 6–62 years). The median time between initial exposure and onset of symptoms was 7 days, although only six patients were sure of the time of first exposure. All patients experienced fever. Following pyrexia, the most common symptoms were cough (94.4%), sputum (77.8%) and dyspnoea/wheeze (77.8%). With regard to exposure history, 10 patients had been exposed to dead poultry in their own or a neighbour's home (nine cases versus one case, respectively), two patients had a history of contact with apparently healthy poultry and five had a history of market exposure only. The remaining three patients had no history of direct contact with dead poultry or market exposure, but had been exposed to an environment where dead poultry may have been present.

Ongoing influenza surveillance and reporting is required to build further understanding of both established and changing patterns of influenza in China.

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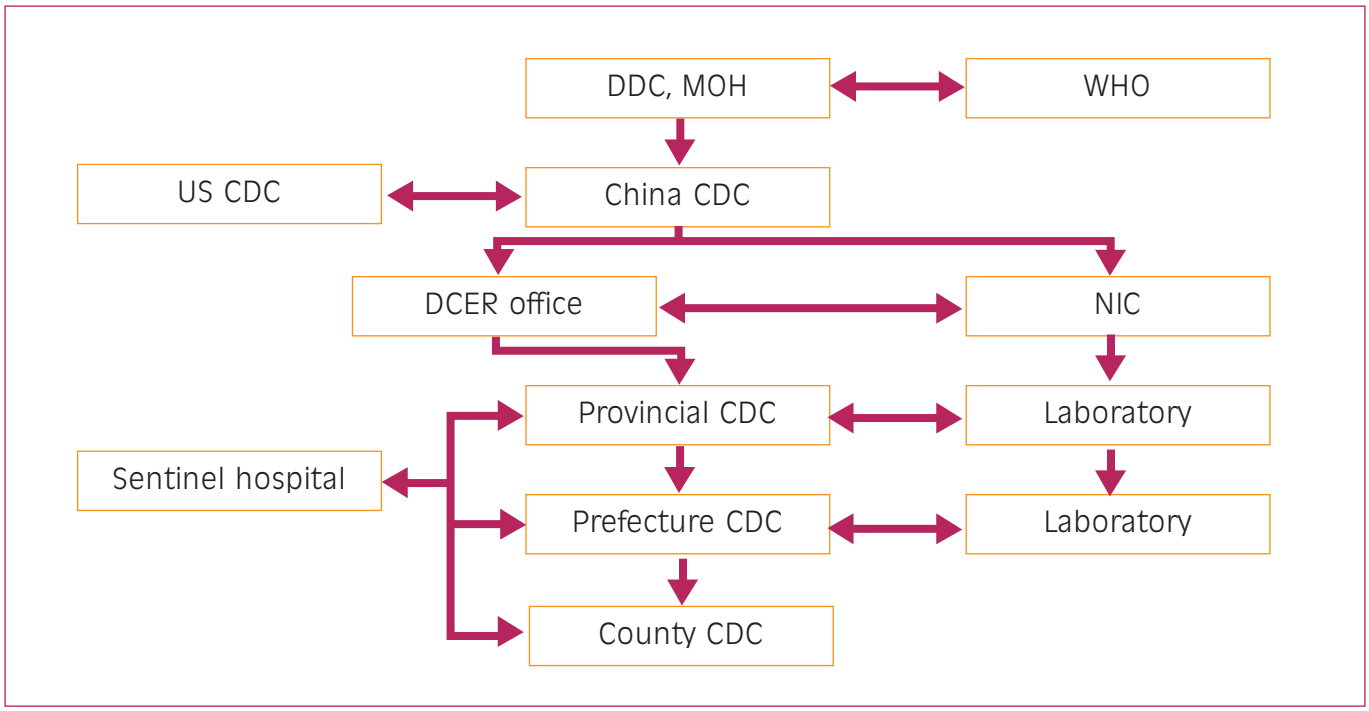

Figure 1. Influenza surveillance network in China.
DDC, MOH: Department of Disease Control, Ministry of Health; NIC: National Influenza Center.

New influenza vaccines

The changing nature of influenza viruses, the high viral mutation rate and the imperfect protection given by existing vaccines creates a continuing need for new vaccines. Alan Hampson discusses the progress towards new and improved influenza vaccines.

Protection against infection with influenza is primarily mediated by anti-haemagglutinin antibodies, and is subtype specific and largely strain specific. Anti-neuraminidase immunity is not protective, although it has a sparing effect. There may be short-term mucosal immunity and possibly low-level immunity across subtypes that is reinforced by multiple infections.

Current vaccines

At present, influenza vaccines are grown in eggs and purified by filtration plus zonal centrifuge or chromatography. The virus may be disrupted to give subvirion or subunit preparations, which are then purified. The antigen content is standardised by immunological testing. The WHO makes recommendations for vaccine composition based on the circulating influenza strains identified by its global surveillance system, and vaccines are updated annually based on these recommendations.

Disadvantages of the current vaccines include the need for well-matched strains, short-lived immunity, dependence on an adequate supply of suitable eggs and a long lead time for vaccine production. Global production capacity is currently limited to around 400 million doses of trivalent vaccine per year. There is a poor response in unprimed individuals, and also an inferior response to split vaccines compared with whole cell vaccines.

Problems related to H5N1 vaccines

Early human trials with influenza AH5 vaccines showed poor response in comparison to conventional vaccines. The recent H5N1 viruses are unsuitable for vaccine production because of the danger to workers involved in production and because the viruses kill the egg embryos used in vaccines. Strains must be engineered genetically to make them suitable and, as they may then be considered genetically modified organisms, registration difficulties may occur in some countries.

Approaches to vaccine improvements

New vaccines are being developed with the aims of:

- increasing potency and ability to cope with antigenic drift
- improving production methods
- producing broadly protective vaccines.

Potency could be improved by the use of live vaccines, adjuvants and improved delivery systems. Live attenuated vaccines have broader and possibly stronger immunity than subunit vaccines. They may offer protection against drift variants, and there is evidence of herd immunity through the vaccination of children.[1] However, subunit vaccines are safer and their side-effects (e.g. temperature elevation) are less severe.

The conventional aluminium adjuvant adds little or no benefit to seasonal influenza vaccines, but there are indications of benefit against new influenza subtypes. Studies on a subunit vaccine with the MF59 adjuvant, an oil in water emulsion, show an improved immune response to an influenza A(H9N2) virus.[2] An H5N1 vaccine for humans manufactured by GlaxoSmithKline has proven to mount an immune response in clinical tests. This new vaccine uses only small doses of active ingredient, and it is claimed it could be mass-produced in 2007, subject to receiving regulatory approval.

Cell culture is an alternative to culturing vaccine in eggs, although cost and difficulties in scaling up production may be limiting factors. Vaccines using recombinant haemagglutinin antigen have also been tested.[3] Data show that the H5 influenza vaccine produced using this technique is immunogenic, can be produced and administered in high doses, does not involve the dangers of live virus and is effective in poultry. A third approach is for whole haemagglutinin antigen to be delivered via DNA expression. This has the potential for improved response, and such H5 and trivalent interpandemic vaccines are now in pre-clinical development.

Approaches to producing broadly protective vaccines with immunity across subtypes include using conserved epitopes as recombinant proteins or synthetic proteins from the M-protein ectodomain, nucleoprotein or haemagglutinin. These approaches can be combined with improved delivery systems; for example, using bacterial flagellae, artificial virus-like particles, living viral vectors or lipidated peptides. DNA delivery, including conjugation to immunostimulatory DNA sequences, is another promising technique for improving vaccine efficacy.

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Pre-travel vaccination against influenza

Professor 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.

Professor 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.

The risk to travellers of contracting influenza depends on the destination and the time of year. In the tropics, influenza can occur throughout the year, while in temperate regions, influenza is more prevalent during the winter months. Travellers can also be exposed to influenza virus if they travel as part of a large organised group and encounter people from regions where influenza viruses are circulating.[1]

Risk of influenza in Hajj and Umrah pilgrims

During the annual Hajj pilgrimage, over 2 million people travel to Mecca and Medina, Saudi Arabia, and converge on a relatively small, confined area. The exact date of the Hajj varies from year to year, as it is determined by a lunar calendar rather than the Gregorian calendar.[2–4] The congestion of people during this time increases health risks from infectious diseases, of which respiratory tract infection is the most commonly transmitted during this period.[2]

A 2003 study suggests a high incidence of influenza as a cause of upper respiratory tract infection among pilgrims, with an estimated 24,000 cases per Hajj season, excluding those who become ill from contact with Hajj pilgrims returning home.[2] Studies indicate a very low influenza vaccination rate as well as poor knowledge of the existence of the vaccine.[2]

The Umrah pilgrimage also involves visiting Mecca, with the option of travelling to Medina as well, but can occur at any time of the year and therefore the numbers are not as great at any one time as during the Hajj.

Vaccination recommendations for Hajj pilgrims

Pilgrims travelling to Mecca and Medina for the Hajj should consider influenza vaccination as a high priority.[2] A case-control study in Malaysia found that the adjusted vaccine effectiveness against clinic visits for influenza-like illness (ILI) was 77% (95% CI, 69–83), and the authors concluded that influenza vaccine was effective in preventing clinic visits for ILI and antibiotic use.[5]

Because influenza is highly contagious, it is important to increase awareness and uptake of influenza vaccine, particularly among pilgrims aged > 65 years who are at greater risk of serious illness because of their age. People who have pre-existing medical conditions that predispose them to respiratory illness should also be aware of the benefits of vaccination against influenza.[6]

The Saudi Ministry of Health recommends that Hajj and Umrah pilgrims, particularly those at greater risk, should be vaccinated against influenza before travel. It is intensifying influenza surveillance in pilgrims arriving from the most affected countries, including Indonesia, Cambodia, Thailand and Vietnam. Health officials at ports of entry will report suspected cases for confirmation of diagnosis, isolation and administration of antiviral medication.[7]

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Flu review

Kroll ME *et al.* Childhood leukemia incidence in Britain, 1974–2000: time trends and possible relation to influenza epidemics. *J Natl Cancer Inst* 2006; 98: 417–20.

This study investigated time trends in childhood leukaemia by using Poisson regression methods to analyse data from the National Registry of Childhood Tumours in Britain. During 1974–2000, the average annual change in rate of childhood acute lymphoblastic leukaemia (ALL) was 0.7% (95% CI, 0.4–1.0). Small peaks in ALL incidence occurred in 1976 and 1990, immediately following influenza epidemics, suggesting that some childhood leukaemia may be triggered by contact with influenza occurring close to the time of leukaemia diagnosis, particularly in conditions of low herd immunity to influenza.

Shinya K *et al.* Avian flu: influenza virus receptors in the human airway. *Nature* 2006; 440: 435–6.

Although influenza A(H5N1) viruses can replicate efficiently in human lungs, human-to-human transmission of H5N1 influenza is rare. The molecular barriers limiting human-to-human transmission have not yet been identified, although it is known that H5N1 viruses preferentially bind to sialic acid linked to galactose by an α-2,3 linkage (SAα2,3Gal) and human influenza viruses preferentially bind to sialic acid linked to galactose by an α-2,6 linkage (SAα2,6Gal). This study demonstrates the different distribution of these binding molecules in the human airway. The authors suggest that this may provide a explanation as to why H5N1 viruses at present rarely infect and spread between humans.

Atmar RL *et al.* Safety and immunogenicity of nonadjuvanted and MF59-adjuvanted influenza A/H9N2 vaccine preparations. *Clin Infect Dis* 2006; 43: 1135–42.

A 2-dose schedule of an inactivated influenza A/chicken/Hong Kong/G9/97 (H9N2) subunit vaccine with MF59 adjuvant was evaluated in a phase I, randomised trial in 96 adults aged 18–34 years. Four dose levels of haemagglutinin were used. Immunogenicity was measured using serum haemagglutination inhibition (HAI) and microneutralisation (MNt) antibody assays, and safety was assessed with a diary and blood tests. The adjuvanted vaccine was associated with improved immune responses to the influenza A/H9N2 virus, and mean serum HAI and MNt antibody titres were significantly higher on days 28 and 56 for the adjuvanted vaccine groups than for groups given non-adjuvanted vaccine. Other measures of immunogenicity were also higher in the adjuvanted vaccine groups. Adverse effects were generally mild. The adjuvanted vaccine was immunogenic even after a single dose; this suggests a single dose vaccination strategy may be feasible with this adjuvanted vaccine.

Clinical Associate Professor 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 updates

Funding to combat avian influenza

Approximately US$475 million was pledged to the UN Food and Agriculture Organization (FAO) at an international donor conference in Mali in late 2006 to combat H5N1 avian influenza virus. The FAO Assistant Director-General stated at the conference that avian flu remains a "potent threat around the world".[1] During 2006, there were a total of 114 confirmed cases, and 79 deaths attributed to avian influenza worldwide. Of these, 55 cases occurred in Indonesia, 12 in China, three in Thailand and two in Cambodia.[2] Although no human deaths have been reported from the UK, an avian influenza outbreak killed 2500 turkeys at a farm in Suffolk in early February 2007. Subsequently, all 159,000 birds at the farm were slaughtered. The virus strain is identical to one found among geese in Hungary in January 2007.[3]

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Advances in vaccine development

An adjuvanted avian flu vaccine for humans, which uses only a very low dose of active ingredient and has proved effective in clinical trials, could be mass-produced in 2007.[1] (See page 9.)

Analysis of newly isolated viruses from both animals and humans indicates that H5 haemagglutinin genes are genetically distinguishable from the H5N1 viruses that have previously been selected for vaccine development and there is evidence of antigenic variation among the recent viruses. Consequently, WHO Collaborating Centres and H5 Reference Laboratories have been developing new recombinant H5N1 vaccine viruses.[2]

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Professor 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.

Dr Luningning Villa

Luningning Villa is National Program Manager for the Emerging Infections Control Program and Medical Specialist IV at the National Center for Disease Prevention and Control at the Department of Health (DOH) in the Philippines. She is also a member of the DOH Task Force for Avian and Pandemic Influenza Prevention and Control.

Professor 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

World Vaccine Congress 2007
Washington DC, USA — 19–22 March 2007
www.terrapinn.com/2007/wvc_DC/index.stm

20th International Conference on Antiviral Research
Palm Springs, USA — 29 April–3 May 2007
www.meetingassistant.com/icar2007/

25th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID)
Porto, Portugal — 2–4 May 2007
www.kenes.com/espid/

6th Options for the Control of Influenza Conference
Toronto, Canada — 17–23 June 2007
www.optionsviconference.com/

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

Regional

ISSAR 2007: the 6th International Symposium on Antimicrobial Agents and Resistance
Singapore — 7–9 March 2007
www.isaar.org/index.asp

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

Next APACI meeting

The next APACI meeting will be held in Hanoi, Vietnam, on 8–9 March 2007.

In the next issue ...

- Focus on Vietnam:
  - Influenza control initiatives in Vietnam
  - Raising influenza awareness in Vietnam
- Seasonal influenza: the role of vaccines and antiviral drugs
- Country report: current influenza awareness initiatives

Produced and published by In Vivo Communications (Asia) Pte Limited, 103 Beach Road #06-01/02, Premier Centre, Singapore 189707.

On behalf of GlaxoSmithKline, 150 Beach Road, Gateway West #22-00, Singapore 189720; Novartis Vaccines, PO Box 1630, 35006 Marburg, Germany; F Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland; Sanofi Pasteur, the vaccines business of sanofi-aventis Group, 2 Avenue Pont Pasteur, 69007 Lyon, France; and Solvay Pharmaceuticals, CJ van Houtenlaan 36, 1381 CP, WEESP, The Netherlands.

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