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Review Article

# Influenza vaccines: an Asia–Pacific perspective

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This article provides an overview of some aspects of seasonal, pre-pandemic and pandemic influenza vaccines and initiatives aimed to increase influenza vaccine use within the Asia–Pacific region. Expanding the use of influenza vaccines in the Asia–Pacific region faces many challenges. Despite the recent regional history for the emergence of novel viruses, SARS, the H5N1 and H7N9, and the generation of and global seeding of seasonal influenza viruses and initiatives by WHO and other organisations to expand influenza awareness, the use of seasonal influenza vaccines remains low. The improvement in current vaccine technologies with the licensing of quadrivalent, live-attenuated, cell culture-based, adjuvanted and the first recombinant influenza vaccine is an important step. The development of novel influenza vaccines able to provide improved protection and with improved manufacturing capacity is also advancing rapidly. However, of ongoing concern are seasonal influenza impact and the low use of seasonal influenza vaccines in the Asia–Pacific region. Improved influenza control strategies and their implementation in the region are needed. Initiatives by the World Health Organization (WHO), and specifically the Western Pacific Regional Office of WHO, are focusing on consistent vaccine policies and guidelines in countries in the region. The Asian-Pacific Alliance for the Control of Influenza (APACI) is contributing through the coordination of influenza advocacy initiates.

**Keywords** APACI, influenza, pandemic, seasonal, vaccine advocacy, vaccine strategies.

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## Introduction

Expanding the use of seasonal influenza vaccines in the Asia–Pacific region faces many challenges. The size of the greater region, containing an estimated 52% of the world's population, the diverse climatic zones, some with the year-round circulation of influenza viruses, the absence of data on the burden of disease from influenza in some countries and poor definition of influenza at-risk groups along with individual countries differing health priorities have all contributed to the low levels of seasonal influenza vaccine use by most countries in the region.[1] However, there is evidence of increasing awareness of the importance of human influenza in the region.[2–5]

The disease burden from influenza in tropical and subtropical climatic zones has been shown to be similar to that observed in temperate zones. In Singapore, a tropical zone, and Hong Kong, a subtropical zone country, influenza-associated circulatory and respiratory mortality rates per 100 000 population among those at greatest risk from influenza (65 years and older: 155·4 and 102·0, respectively) and for all age groups (11·9 and 12·4, respectively) have been shown to be similar to the United States (65 years and older: 96·3 and for all ages: 13·6), a temperate zone country.[6–9] Similar mortality rates have also been observed in both northern (temperate zone) and southern (subtropical zone) cities in China.[10] Understanding the disease burden in individual countries is needed for influenza policy development and vaccine introduction.[5]

The World Health Organization's (WHO) pandemic preparedness initiatives, focused on the strengthening of laboratory capacity to support both virological and disease surveillance along with the strengthening of influenza vaccine supply through the establishment of manufacturing capacity, are steadily building regional capacity.[11–13] The region has long been recognised as an important source of novel influenza viruses and for the generation of seasonal influenza viruses, followed by their global circulation.[14–16] The emergence and then subsequent spread of the avian influenza H5N1 virus in domestic poultry and the associated human infections, from late in 2003,[17] along with the more recent emergence of the avian H7N9 virus in Eastern China in 2013,[18] reinforce the importance of ongoing initiatives to understand and control influenza in the region.

This article addresses aspects of seasonal, pre-pandemic and pandemic influenza vaccines and initiatives aimed to increase influenza vaccine use within the Asia–Pacific region. It was presented in part at the combined ISIRV and ISIRV

Antiviral Group Conference on Severe Influenza: Burden, Pathogenesis and Management, held in Hanoi, Viet Nam 29th–31st October 2012.

## WHO vaccine initiatives

The WHO has established a Global Action Plan for Influenza Vaccines (GAP) and conducted GAP-I and GAP-II consultations.[19] The first objective of the GAP is to increase seasonal vaccine use. As part of this, in 2012, the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) reviewed the 2005 WHO Influenza Vaccine Recommendations and re-endorsed the safety and effectiveness of seasonal influenza vaccines.[20] Five target groups were prioritised for annual influenza immunisation: pregnant women, healthcare workers, children 2–5 years, children 5 months to 2 years, the elderly and individuals with specific underlying health conditions.[13] Although it is recommended that countries with existing vaccination programmes that target all or only some of these groups continue such programmes, but also ensure they include pregnant women as the highest priority group, these recommendations imply simply by their order, an order of risk-group priority for the focus of vaccination strategies.

The second GAP objective is to increase influenza vaccine production capacity. Vaccine manufacturing capacity has existed in the region in Australia, China and Japan. Through the WHO Technology Transfer Initiative, helping developing countries to develop vaccine manufacturing capabilities and capacity for pandemic preparedness, financial and technical assistance has been provided from 2007 to India, Indonesia, Thailand, Vietnam, South Korea and China.[21–25] Following the emergence of the A(H1N1)pdm2009 virus, the WHO initiated a pandemic influenza A(H1N1) vaccine deployment and donation initiative. Within the WHO Western Pacific Region (WPR), 16 countries received a total of over 8 million doses of H1N1 vaccine. Vaccine utilisation by a further 10 countries or territories not receiving WHO donated vaccine in the region was 285 million doses.[26]

## Influenza vaccine use in the Asia–Pacific

Comprehensive initiatives to document influenza vaccine use and vaccine recommendations in the region are recent. Initial data collection attempts were made by the Macroepidemiology of Influenza Vaccination (MIV) Study Group from some countries in the region for 1997–2003.[27] Two International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Influenza Vaccine Supply (IVS) International Task Force surveys obtained data on vaccine distribution from the periods 2003–2007 and 2008–2009, which included 19 countries in the region including India and South Korea, identified substantial increases, although from low baselines in vaccine supply in three countries: Thailand, China and Japan.[28] The WHO has conducted two surveys: in 2010 the Global Mapping of Seasonal Influenza Vaccine Supply Survey, with 35 countries from the WHO South East Asian region (SEAR) and WPR[29] and in 2011, the survey conducted by the WPRO to describe seasonal influenza vaccination policies, recommendations and use in the Western Pacific Region.[4,29] This latter study collected data from 36 (97%) of 37 countries or areas in the region. A total of 18 (50%), comprising 93% of the Western Pacific Region population, had established seasonal influenza vaccination policies and a further 7 (19%) provide influenza vaccination recommendations only for risk groups. In 2011, seasonal influenza vaccines were available through public funding and/or from the private market in 26 (72%) of these countries or areas, although only enough vaccine was purchased to cover <25% of their populations (range 0·3% to 99·7%). However, 11 (30%) reported having no seasonal influenza vaccination policies or recommendations in place. Countries with no policies in place were largely island nations, but included Cambodia, Lao People's Democratic Republic, Viet Nam and Papua New Guinea; however, they comprise only a small proportion of the total Western Pacific Region population.

## Vaccination during pregnancy

Influenza is a significant cause of illness and death in pregnant women and infants. A global pooled analysis of risk factors for severe outcomes following influenza A(H1N1) pdm2009 infection during pregnancy found a relative risk of 6·8 (4·5–12·3) for hospitalisation and 1·9 (0·0–2·6) for death.[30] Although vaccination during pregnancy is safe, protection of children <6 months by vaccination is not possible as current vaccines are not licensed for this age group. Evidence from the Mother's Gift Project in Bangladesh (2004–5), a randomised controlled trial, suggests that maternal influenza vaccination protected infants during the first 6 months of life, reducing febrile influenza-like illness in infants by 29%, and among the mothers themselves by 36%.[31,32] Other observational studies have also demonstrated infant protection with a 45–48% reduction in infant hospitalisation,[33] 41% reduction in laboratory confirmed influenza[34] and a 91·5% reduction in hospitalised infants with laboratory confirmed influenza.[35] Prevention of seasonal influenza also influences intra-uterine growth. Influenza immunisation of pregnant women in Bangladesh was associated with a lower risk of small growth for age (SGA) infants (a 34% reduction) and an increase in mean birth weights (200 g).[32] Similar infant benefits have been seen in other observational studies.[36–38] Currently under way in Mali, Nepal and South Africa are prospective, randomised studies of trivalent influenza vaccine (TIV) in pregnant

women supported by the Bill & Melinda Gates Foundation which will provide additional information on influenza vaccine efficacy, safety during pregnancy and benefits to both mothers and infants.[13] In the 2011 WPRO survey, of the 25 countries or areas with national vaccine policies or recommendations, 19 (76%) recommended vaccinating pregnant women, suggesting that many countries are yet to recognise pregnant women as a the highest priority group to receive influenza vaccination.[4]

## Vaccination of healthcare workers

Healthcare workers are frequently implicated as a source of influenza infection in healthcare settings, leading to nosocomial infections and staff absenteeism.[39] Nosocomial infections have been shown to be associated with patient mortality, as high as 27%, especially in those with co-morbidities. The vaccination of healthcare workers can reduce the risk to patients with associated reduced patient morbidity and mortality.[40,41] Most countries recommend immunisation of healthcare workers; however, rates are often low with uptakes frequently <50%, even though the vaccination of healthy working adults is moderately effective. In a meta-analysis, the pooled vaccine efficacy in 10 randomised controlled trials, conducted in adults 18–65 years, was 59%.[42] Since 2004, there have been moves towards the mandatory vaccination of healthcare workers in the United States to address the low uptake rates.[43–45] These initiatives have resulted in high coverage rates of over 96% in some health facilities. Healthcare systems have an ethical and moral responsibility to protect vulnerable patients from vaccine preventable infections; thus, calls for mandatory influenza vaccination on healthcare settings, consistent with accepted professional ethics, are likely to benefit those at greatest risk because they are patients in hospital and contribute to reduced staff absenteeism and pandemic preparedness.[46]

Evidence from a Japanese long-term care facility suggests the protective benefits of healthcare worker vaccination.[47] Little information is available on healthcare worker coverage in Asian-Pacific countries, although high coverage has been achieved in several countries: 78% was reported in South Korea[48] and 98% in Singapore.[49] In the WPRO 2011 survey, of the 25 countries with national vaccine policies or recommendations, healthcare workers were recommended for vaccination in 24 (96%), the most frequently recommended group.[4] A history of influenza vaccination is the most reliable predictor of vaccine receipt in the next season.[39] However, in the wider Asia–Pacific region, many countries will be starting from negligible or low baseline levels of vaccination amongst healthcare workers; thus, successful healthcare worker vaccination programmes will need to be followed[39] and new initiates for the education of healthcare workers about influenza introduced.[2]

## Vaccination of children

Children have a high burden of disease and are important disseminators of influenza in the household and community, thus a priority group for vaccination. Younger children of 6 months to 2 years are the highest risk group for severe influenza or hospitalisation, while older children over 2 years of age have significantly increased outpatient attendances, antibiotic usage and absenteeism form school. Vaccination is problematic in children as initially two doses of vaccine are required, and the immune response to inactivated seasonal vaccines by children under 2 years is not as good as older children. TIVs are not licensed for children <6 months, and live-attenuated influenza vaccines (LAIV) licensed for use from 2 years of age. Further, it is also recognised that the vaccine match with the circulating influenza strains is a key driver for vaccine effectiveness in young children. A recent trial has shown promising results, where a TIV was compared with an adjuvanted (MF59) trivalent influenza vaccine (ATIV) over two influenza seasons.[50] The adjuvanted vaccine was demonstrated to be efficacious against reverse transcription-polymerase chain reaction (RT-PCR) confirmed influenza and to be superior to TIV in children 6 months to 3 years and over 3 years of age. Although LAIVs have been widely used in Russia (for individuals aged ≥3 years) and the United States, and now in the Asia–Pacific region, through the WHO technology transfer programme, they are licensed and in use in India only. A study in 2006 suggested that influenza vaccination was a priority in some countries in the Asia–Pacific region,[51] however the more recent survey, with only 19 of 36 countries or areas in the Western Pacific Region to include policies or recommendations for the vaccination of children,[4] clearly suggests childhood vaccination remains a low priority in most countries.

## Vaccination of the elderly

Influenza contributes to substantial morbidity and mortality in the elderly;[6] It is likely that the mortality from influenza in the elderly in the Asia–Pacific region is similar to that in other countries.[7,8] Influenza vaccines are less effective in the elderly than in young adults, with effectiveness estimates ranging from 20% to 80%, depending on the population studied, circulating strains and outcomes being measured.[13,52] Studies carried out in the Asia–Pacific region in tropical countries are limited.[5,53,54] In the WPRO 2011 survey, of the 25 countries or areas in the Western Pacific Region with national vaccine policies or recommendations, the elderly were recommended for vaccination in 24 (96%), along with healthcare workers being the most frequently

recommended group.[4] However, with the Asia–Pacific region containing a large proportion of the world's population, and with an increasing proportion of this population being over 65 years of age, influenza control initiatives need to become a high priority.[10]

## Vaccination of other risk groups

Individuals with specific underlying chronic diseases, including chronic respiratory, cardiac disease, compromised immune status or metabolic disease, are at high risk from influenza and are more likely to develop severe outcomes following influenza compared with healthy individuals in the same age group.[13] There are little data on these groups in the Asia–Pacific Region, although 6 (60%) countries in South-East Asia had guidelines for persons with underlying medical conditions were reported in 2011,[3] and 18 (72%) countries in the Western Pacific Region had recommendations for vaccinating people with chronic illness in 2012.[4] Other groups at risk from influenza are pilgrims to the Hajj, and Malaysia and Indonesia have recommendations for their vaccination.[3,21]

## Improvement in current vaccine technologies

The use of egg-based influenza vaccines was first reported in 1948.[55] Even though influenza vaccination has been recognised as the most effective way to prevent seasonal influenza and its severe outcomes,[13,56,57] the development of vaccines with improved immunogenicity and cross-reactivity is only now gaining momentum.

### Quadrivalent vaccines

Since the late 1970s, two influenza B lineages, B/Victoria and B/Yamagata, have been co-circulating globally causing seasonal epidemics every 2–4 years. There is little cross-reactive protection between the influenza B lineages, which means that good protection against the circulating lineage relies on predicting which influenza B lineage is likely to be prevalent in any season. However, the heterogeneity of lineage circulation between seasons and regions means prediction is usually no better than chance.[58,59] The WHO SAGE have endorsed a move towards the use of quadrivalent influenza vaccines (QIV), and from 2012 WHO has included in its seasonal vaccine strain recommendations, influenza B strains from each lineage. QIVs have safety and effectiveness profiles, essentially similar to TIVs. One estimate of 2 684 145 total cases averted over a decade through the use of QIV[58] has been used in a Monte Carlo simulation model to determine the economic value of QIV compared with TIV.[60,61] By adding a second B strain, assuming the QIV cost was the same as TIV, there would be cost-savings of USD1148 per case and third-party cost-savings of USD108 per case. Both Q/LAIV and inactivated QIVs received FDA licensure in 2012. The FluMist Quadrivalent (MedImmune, LLC, US) LAIV was licensed for healthy individuals 2–49 years, while Flurarix Quadrivalent (GlaxoSmithKline, Germany) for those 3 years and older, and in 2013, Fluzone Quadrivalent (Sanofi Pasteur, US) for children 6 months and older. The first country in the Asia–Pacific region to register a QIV in 2013 is likely to be Taiwan.

### Live-attenuated vaccines

LAIVs have a theoretical advantage in that their intranasal replication is closer to natural influenza infection than the injection of inactivated vaccines. One is licensed for intranasal spray administration of non-pregnant and healthy individuals either 2–49 years of age in the United States (FluMist, MedImmune, US) or 2–18 years of age in Europe (Fluenz, AstraZeneca, UK). Paediatric studies show a high protective efficacy and greater protection against drift variants with LAIV than TIV.[62,63] However, LAIV appears to have lower efficacy than TIV in adults in some seasons.[64–67] However, concern remains for their use in a pre-pandemic setting because of a perceived risk of reassortment with seasonal viruses.[68] Initiatives to produce seasonal, H1N1pdm09 and H5N1 vaccines with improved immunogenicity and cross-protection, while retaining attenuation and growth characteristics by exploring the differences in use of the cold-adapted backbone viruses (A/AnnArbor/6/60 in the United States and A/Leningrad/134/17/57 in Russia) and both 6-2 reassortant and 5-3 reassortant viruses are promising.[69,70]

### Adjuvanted vaccines

Adjuvants have been used with inactivated vaccines to potentiate immune responses. The oil in water adjuvant MF59 increases the immune response to seasonal TIVs in infants;[50] however, the same benefit has not been seen consistently in healthy adults, the elderly and immunocompromised.[71,72] The addition of adjuvants MF59, AS03 and AF03 to pre-pandemic H5N1 and H1N1pdm09 vaccines has led to antigen-sparing to achieve presumed protective humoral immune responses, while the use of alum has not consistently improved responses. With H5N1 adjuvanted vaccines, doses as low as 3·8 μg of haemagglutinin (HA) have been shown to produce neutralising antibodies which are vaccine strain specific and cross-reactive to heterologous H5N1 viruses in other clades.[68] Other adjuvants and routes of administration are also under development.[73]

### Cell culture vaccines

Cell culture-based vaccine production has a number of advantages over egg-based vaccines.[74] Pre-pandemic H5N1 and H1N1pdm09 vaccines using cells for production have

been licensed.[75] Trials with H5N1 whole-virus vaccines in adults and the elderly have shown that they are well tolerated and demonstrated both antigen-sparing and induction of cross-reactive responses.[68] In 2009, Celvapan (H1N1)v (Baxter AG, Austria), the first H1N1pdm09 vaccine, was available within 12 weeks following availability of the pandemic seed strain, demonstrating pandemic responsiveness superior to existing egg-based vaccines. Seasonal TIVs produced in cell culture are also licensed for use in a number of countries. These vaccines have shown efficacy against matched and mis-matched seasonal strains.[76–78] Cell culture-based vaccines are currently increasing the global influenza vaccine supply and potentially offer the faster availability of a pandemic vaccine.

## New approaches

### Towards a Universal Vaccine

One of the enigmas of influenza is that despite repeated infections, most humans do not develop protection against novel influenza strains. The usual immune response is to make neutralising antibodies to epitopes on the globular head of the influenza HA glycoprotein, which is continually 'drifting'. One of the newer vaccine approaches is to elicit broadly neutralising antibodies to the highly conserved stem regions of the HA.[79] A range of monoclonal antibodies have been developed for potential therapeutic use, some of which are effective against group 1 or 2 influenza type A subtypes (16 HA subtypes divided into phylogenetic groups 1 and 2) and at least one inhibitory across both A and B viruses.[80] High doses of these antibodies protect against lethal influenza infections in animal models.[80] It is possible that immunogens may be engineered from the HA stem to induce similar antibodies that may result in wider protection than current vaccines.[68]

### Recombinant vaccine

The first trivalent recombinant HA vaccine, FluBlok (Protein Sciences Corporation, US) produced in insect cells with a baculovirus expression vector system was licensed by the United States Food and Drug Administration (FDA) in January 2013, for intramuscular injection in adults 18–59 years old. The FDA recommended dosage is 45 μg HA/strain compared with 15 μg/strain for TIV. In young children, FluBlok is safe, however less immunogenic than TIV.[81] In healthy adults, FluBlok was safe and immunogenic and had a 44% efficacy in preventing culture-confirmed influenza, despite antigenic mismatch with the circulating viruses.[82] In adults older than the currently recommended age group, antibody responses to FluBlok were significantly higher against H1 and H3 antigens compared with TIV, with similar response to influenza B.[83] This vaccine production system has several advantages as it does not rely on the use of embryonated hens' eggs and or live virus, and with a 75-day production cycle, addresses some of the major issues with currently licensed technologies for a timely pandemic response.

### Vaccine advocacy

Targets for influenza vaccine coverage of all people at high risk from influenza, including the elderly and persons with underlying diseases, have been agreed to by countries in a World Health Assembly resolution, 28 May 2003 (resolution WHA56.19). However, the development of effective and targeted communication strategies to promote the uptake of seasonal influenza vaccines among the public and healthcare professionals has largely been left to individual countries. It is not surprising that countries in the temperate zones where annual seasonal influenza outbreaks are well defined, influenza control strategies are in place. In all countries, recommending influenza vaccination alone does not appear to be sufficient to encourage high levels of vaccine uptake, regardless of a countries economic status. However, reimbursement of the cost of vaccination and communication policies together may improve vaccine uptake irrespective of a countries development status.[28,51] Regional strategies run by non-government organisations include the European Scientific Working Group on Influenza (ESWI) established in Europe in 1992, National Influenza Summit in USA in 2000 and the Asia–Pacific Alliance for the Control of Influenza (APACI), established in 2002. APACI is a company limited by guarantee and registered in Hong Kong in April 2002 as a not-for-profit organisation (Charitable Trust), with a mission to reduce the burden of disease within the Asia–Pacific region.[2] Funding is received largely from the pharmaceutical industry; however, APACI maintains full control over all its activities and publications. The APACI model has identified and educated key opinion leaders in the region, whom have returned to their own countries to establish Influenza Foundations. Foundations have been established in Thailand (IFT), India (IIF) and Indonesia (IFI) and linkages established with the Philippine Foundation for Vaccination, the Australian Influenza Specialist Group (ISG) and the New Zealand Influenza Specialist Group (NISG). Regular online regional newsletters 'Influenza' and other translated influenza resources are available on the APACI website <www.apaci.asia>. This network continues to be extended focusing on influenza advocacy and information sharing throughout the Asia–Pacific region. It is achieving this by developing new regional collaborations through holding the first Asia–Pacific Influenza Summit followed by an antiviral forum in Bangkok in 2012 and a TEPIK/APACI International Influenza Workshop in Seoul in 2013.[2,84] Through these collaborative initiatives, healthcare professionals and other professional groups are

brought together, leading to improved policy and advocacy for vaccine uptake and best practices for the control of influenza in the region.

## Summary

Influenza vaccine use in the Asia–Pacific region has been limited; however, with the emergence of avian H5N1 and recently H7N9, and the A(H1N1)pdm09 viruses, along with WHO technology transfer and other initiatives, an expanding awareness of influenza in the region has lead to the increasing uptake of seasonal influenza vaccine in some countries. The past regional history of the emergence of novel viruses and postulated source for seasonal influenza virus circulation, and recent emergence of the H7N9 virus serve to highlight the global importance of the region. Lessons from A(H1N1) pdm2009 and pandemic vaccine production have highlighted the limitations of the current vaccine technology. H7N9 vaccines are in development, and despite many challenges still remaining,[85] the landscape for new vaccine development is active and rapidly evolving, suggesting that the response to another pandemic may be more timely with novel vaccines that protect most individuals. However, of ongoing concern are seasonal influenza and the low use of seasonal influenza vaccines in the Asia–Pacific region. Clearly there is a need for improved influenza control strategies and their implementation in the region.

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