Influenza Asian Focus

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Welcome to the 15th 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.

This issue of *Influenza – Asian Focus* looks at the impact of the novel, swine-origin influenza A(H1N1) pandemic in 2009 and beyond. We review the important contribution of antivirals prior to the availability of a pandemic vaccine (page 2). Pandemic 2009 H1N1 vaccines were available within months of the pandemic being declared, due to a coordinated effort by the World Health Organization (WHO), vaccine manufacturers, governments and regulatory bodies. We invited vaccine manufacturers to share their perspectives on the challenges of pandemic vaccine development (page 3). In addition, we discuss the role of school-age children in transmitting the influenza virus, and the need to prioritise vaccination of this group during a pandemic (page 4). In most regions, the 2009 H1N1 virus rapidly became the dominant circulating strain, raising interesting questions about the future of the seasonal H1 virus (page 5). Lastly, our APACI members discuss the effect of the pandemic in the Asia-Pacific region based on observations from their respective countries (page 6).

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Antivirals and the 2009 pandemic

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The use of antiviral drugs during the early stages of an influenza pandemic can slow the spread of infection and reduce morbidity and mortality until adequate vaccine supplies become available.[1] Neuraminidase inhibitors (NIs), including oral oseltamivir and inhaled zanamivir, were extensively used in the early stages of the current 2009 H1N1 pandemic; this was made possible by the ready availability of antivirals in many countries due to stockpiling by governments in response to the threat of influenza A(H5N1).

The WHO recommends immediate initiation of antiviral treatment in patients who have, or are at risk for, severe disease.[2] In addition to oseltamivir and zanamivir, an investigational NI, peramivir, may be administered intravenously to certain hospitalised patients in the USA following an Emergency Use Authorisation issued in October 2009.[3]

Benefits of early treatment

Consistent with clinical experience in seasonal influenza,[4,5] early antiviral treatment is associated with improved survival in patients hospitalised with severe 2009 H1N1 influenza.[6,7] Among critically ill patients in Mexico, the odds ratio for survival with NI treatment versus no treatment was 8.5 (95% CI, 1.2–62.8).[6] Early treatment initiation is of critical importance. Two studies reported that patients hospitalised due to 2009 H1N1 who received antiviral treatment within 2 days of symptom onset were less likely than those who received delayed treatment to be admitted to an intensive care unit or to die,[7] and spent less time in hospital (median 2 days versus 3 days; p = 0.03).[8] Conversely, delaying antiviral treatment beyond 2 days after symptom onset was associated with a 4.3-fold increase in the risk of admission to intensive care or death in pregnant women hospitalised with 2009 H1N1,[9] and was an independent predictor of respiratory failure in Taiwanese patients hospitalised with pneumonia and 2009 H1N1 influenza (odds ratio, 16.1).[10]

The desirability of early treatment initiation means that the decision should not be delayed while awaiting the results of laboratory tests. This is especially pertinent for pandemic influenza, as the rapid tests are too insensitive to exclude the infection and it soon emerged that even polymerase chain reaction (PCR) tests miss some patients if performed only on upper respiratory tract samples. The optimal dosage and treatment duration for patients with lower respiratory tract infection, especially severely ill and/or immunocompromised patients, was unclear; many received increased doses and/or prolonged therapy based on limited previous experience, but definitive guidelines are not yet available.[11,12]

Antiviral resistance

The development of NI resistance was of concern prior to the current pandemic, as widespread use of NIs was anticipated. However, the vast majority of circulating pandemic viruses remain sensitive to both oseltamivir and zanamivir, and there has been no evidence of reassortment between the 2009 H1N1 virus and the seasonal H1N1 strain. As of 3 February 2010, 225 cases of oseltamivir-resistant 2009 H1N1 virus had been confirmed from over 20,000 specimens tested.[13] All resistant isolates had the same neuraminidase gene mutation, H275Y, and remained sensitive to zanamivir.[13] Many of the oseltamivir-resistant viruses were identified in severely immunocompromised patients, with two clusters reported within hospital wards.[13] Although such person-to-person transmission is very rare, it highlights the need for active surveillance and prompt reporting of any resistant cases.

Antiviral agents in clinical development

In January 2010, Biocryst Pharmaceuticals' **peramivir** was approved for the outpatient treatment of seasonal influenza in Japan (where it is licensed to Shionogi) and a New Drug Application was filed in South Korea (licensee Green Cross Corporation). **Intravenous zanamivir** was also used on a compassionate basis for a number of cases in 2009.[14] Other antivirals in clinical development for influenza include a long-acting inhaled NI, **laninamivir** (CS-8958; Daiichi Sankyo); **favipiravir** (Toyama Chemical); and **DAS181** (FluDase®; NexBio), a sialidase fusion protein that targets host cell receptors. If approved, these new drugs may provide additional treatment options if the H1N1 virus mutates, or they may pave the way for new combination therapies.

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Pandemic vaccine development: the manufacturer's perspective

The first vaccines targeting swine-origin influenza A(H1N1) received regulatory approval only 3 months after the WHO's pandemic declaration, an achievement reflecting years of investment in influenza vaccine research and development. We invited several vaccine manufacturers to share their experiences and perspectives on the challenges of developing a pandemic influenza vaccine.

What challenges did manufacturers face in developing a vaccine against pandemic 2009 H1N1?

Key challenges included the time until availability of the parent seed, the yield of the virus and its adaptation to egg/cell-culture processes, the use of an accelerated regulatory process to expedite vaccine production, and uncertainty over whether one or two doses of the vaccine would suffice.

Why was a monovalent 2009 H1N1 vaccine produced instead of a combined vaccine incorporating seasonal strains?

As the epidemiology of the pandemic virus was unknown at the start of the outbreak, the priority was to produce as many doses as possible of pandemic vaccine. This focus did limit the production of the Southern Hemisphere seasonal vaccine. However, it is important to note the link between the uptake and production capacity of seasonal influenza vaccine and readiness to scale up production in a pandemic situation. Global implementation of the existing recommendations for seasonal vaccination would help to increase the production capacity for pandemic vaccine.

Has the unpredictable demand for the pandemic vaccine caused difficulties for manufacturers?

Vaccine manufacturers have worked with governments to ensure appropriate allocation of the 2009 H1N1 pandemic vaccine and to fulfil existing contractual arrangements in a timely manner. Initially, manufacturers followed WHO guidance and proceeded with vaccine production prior to the establishment of purchase agreements.

Regarding vaccine safety, were there any particular concerns relating to pandemic vaccines (e.g., Guillain-Barré syndrome)?

No. The pandemic vaccine used existing platforms and technologies and was similar to developing a vaccine for any new influenza strain. Millions of people have now received 2009 H1N1 vaccines (both adjuvanted and non-adjuvanted) in both clinical and field settings. Vaccine manufacturers, in conjunction with regulatory authorities, continue to monitor and evaluate safety. The adverse events reported in large-scale immunisation programmes will include a combination of true vaccine side-effects and adverse events that are coincidental or result from underlying medical conditions. To date, the most common adverse events have included headache, arthralgia, myalgia, injection-site reactions, fever and fatigue.

What lessons can be learned from the 2009 H1N1 pandemic and what issues need to be addressed before a more severe pandemic occurs?

Pandemic preparedness planning (through the Influenza Vaccine Supply International Task Force and by individual vaccine manufacturers) helped to enable rapid vaccine development. The severity of the outbreak was not foreseeable and comments made with the benefit of hindsight are not useful. However, the current outbreak has revealed too many insufficiencies that would result in social unrest and a catastrophic impact in the event of a severe pandemic. The current outbreak should be treated as a test case and used to make improvements prior to a more severe outbreak.

- Overall, public (non-vaccine) preparedness needs to be drastically improved, and improved cooperation, action plans and implementation are needed from governments and other authorities.
- Communication could be improved (e.g., to address confusion over the distinction between global spread versus severity in a pandemic), but this is primarily the task of the WHO and health authorities.
- There is a need for greater international coordination to ensure an equitable distribution of pandemic vaccine supplies. Central purchasing by a consortium could be one way to achieve this, but is probably not feasible at this stage.

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Paediatric vaccination: lessons from the pandemic

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The 2009 H1N1 pandemic has reinforced the important role of children in influenza epidemiology and the potential societal benefits of universal paediatric vaccination.

During the initial stages of the outbreak in the USA, 60% of 642 confirmed cases were aged 18 years or younger.[1] The median age of individuals with laboratory-confirmed infections to the end of July 2009 was 12 years.[2] High transmission rates in school-age children helped to drive the spread of the pandemic, with school outbreaks identified as a common source of early community transmission.[3–5] Potential reasons for high transmission rates in children could include lack of pre-existing immunity, the high probability of exposure in schools, or case-detection bias due to higher testing rates in young febrile patients.[6,7] However, a study investigating the household transmission of 2009 H1N1 found that household contacts aged 18 years or younger were twice as likely to develop an acute respiratory illness as those aged 19–50 years, who were in turn more likely to become ill than adults aged over 50 years, suggesting that case-detection bias and community risk cannot adequately explain the observed age distribution.[7]

Severe complications more frequent

Although the majority of 2009 H1N1 influenza cases have been self-limiting, severe complications leading to hospitalisation have occurred more frequently in children than is expected with seasonal influenza (Figure 1).[2,8] Cumulative hospitalisation rates were highest in children aged under 5 years and generally declined with age.[9,10] A total of 236 paediatric deaths associated with laboratory-confirmed influenza were reported in the USA from the beginning of the 2009–2010 influenza season to early January 2010, compared with a mean of 74 paediatric deaths during the previous three influenza seasons.[9] Although the hospitalisation rate was highest for preschoolers, approximately 70% of paediatric deaths in the 2009–2010 influenza season occurred in children aged 5–17 years.[9] In Argentina, the paediatric death rate from 2009 H1N1 influenza was 10 times higher than the rate for seasonal influenza in 2007, with infants the most likely to die.[8]

Underlying medical conditions were reported in 60% of US children hospitalised with 2009 H1N1 influenza, compared with previously reported rates of 31–43% among children hospitalised with seasonal influenza.[6] Neurological conditions and chronic lung disease were associated with an increased risk of severe illness leading to hospitalisation or death.[6,8]

Vaccinating school children

The high transmission rates in school-age children and the risk of severe illness support the use of targeted public health interventions, including school closure and immunisation. Children and young people aged from 6 months to 24 years were recognised as one of five initial priority groups for 2009 H1N1 vaccination in the USA.[2] Furthermore, modelling suggests that targeting school-age children for vaccination is a key to mitigating the severity of an epidemic.[11–13]

Two doses of pandemic vaccine are recommended for children aged 6 months to 9 years and one dose in older children.[14] Two recent trials have suggested that a single dose may be adequate in younger children.[15,16] In an Australian trial, one 15 μg dose of unadjuvanted vaccine was immunogenic in 92.5% of infants and children,[15] and a single 7.5 μg dose with adjuvant was immunogenic in 92% of Costa Rican children aged 3–8 years.[16] However, the current recommendations are consistent with the results of a US study and two large Chinese studies supporting the use of two doses of pandemic vaccine in children aged younger than 12 years.[17–19]

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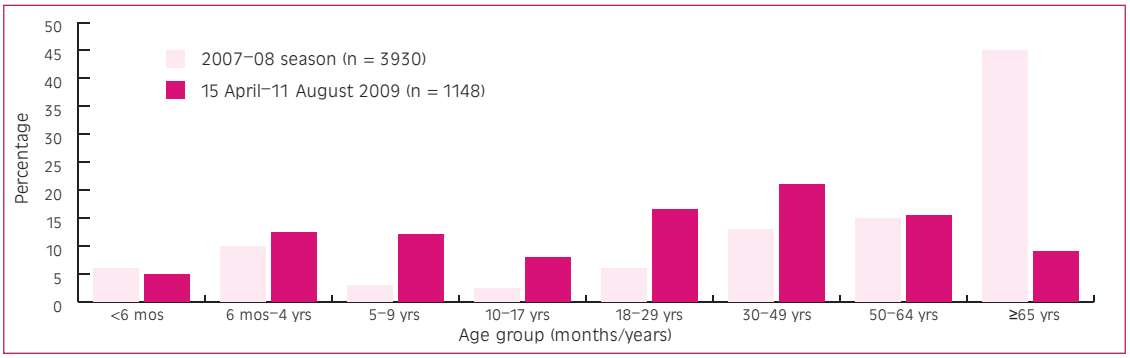

Figure 1. Age distribution of individuals hospitalised with laboratory-confirmed influenza in the USA during the 2007–08 winter influenza season and from 15 April to 11 August 2009.[2]

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What is the future for seasonal H1?

During an influenza pandemic, the new virus may replace previously circulating seasonal strains, as occurred after the 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2) pandemics. However, whereas H2 strains have not circulated in humans since the late 1960s, H1N1 reappeared in 1977 in an outbreak predominantly affecting young people.[1,2] Since 1977, both H1N1 and H3N2 have contributed to seasonal epidemics, although H3N2 has remained the dominant subtype.[3]

The emergence in 2009 of a novel, swine-origin H1N1 influenza raised several important questions, including whether the new virus would displace or co-circulate with the current seasonal strains.[3,4] The situation differs from previous pandemics in that 2009 H1N1 does not represent a classic antigen shift (since human H1N1 viruses have circulated continuously since 1977).[3] The presence of H3N2 further complicates the picture. In theory, 2009 H1N1 could replace both seasonal H1N1 and H3N2. Then again, the possibility of all three subtypes persisting cannot be excluded, as the reason for the switch from one to two circulating influenza A subtypes after 1977 remains uncertain. Reassortment of 2009 H1N1 with the H3 influenza virus to generate a new variant is a further possibility,[4] and it is unknown whether antigenic drift will increase the virulence of 2009 H1N1.[1]

Implications of viral replacement

The prospect of 2009 H1N1 replacing one or both seasonal strains has several potential implications. As 2009 H1N1 has predominantly affected children and young adults,[3] a shift in the influenza burden from the elderly to younger individuals might be expected. From a public health perspective, this could be beneficial as most deaths attributable to seasonal influenza occur in the elderly, and younger individuals typically have a stronger immune response to vaccination. Replacement of seasonal H1N1 with the pandemic virus might also reduce the problem of antiviral resistance, at least temporarily. The emerging seasonal pattern is an important consideration for vaccine development, as co-circulation of 2009 H1N1 with the existing seasonal strains would increase the cost of vaccine production.[1]

Early impact of 2009 H1N1

The initial impact of 2009 H1N1 is now clear. The pandemic strain proved to be the dominant circulating influenza virus in both hemispheres, with rapid and near-complete displacement of seasonal H1N1 during the completed influenza season. In the USA, data from 30 August 2009 to 9 January 2010 showed that 2009 H1N1 accounted for 99.4% (61,332 of 61,726) of subtyped influenza A viruses, compared to under 0.1% each for seasonal H1N1 and H3.[5] As of February 2010, seasonal H3N2 and B viruses were circulating at low levels in parts of Asia and Africa,[6] while influenza B became predominant in China by January 2010.[7]

The WHO now expects that the 2009 H1N1 pandemic strain will co-circulate with H3N2 and B viruses in the 2010–2011 northern hemisphere season, with 2009 H1N1 likely to predominate.[7] Accordingly (and consistent with the previous southern hemisphere recommendations), the seasonal H1N1 virus has been dropped from the recommended vaccine strains.[7] Despite these findings, the notoriously unpredictable nature of influenza A viral evolution means that there can be no certainty regarding the future of seasonal H1N1 and its swine-origin counterpart, and emerging trends will be followed with interest.

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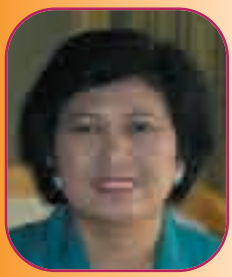

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Impact of the 2009 H1N1 virus in the Asia-Pacific region

APACI members provide updates on the impact of the 2009 H1N1 influenza pandemic in their respective countries.

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Australia (David Smith)

Pandemic H1N1 09 was first reported in Australia on 12 May 2009. By late November, there had been nearly 40,000 cases and 191 laboratory-confirmed deaths. Australia was one of the first countries to experience the pandemic during its usual influenza season and without the benefit of a vaccine; it therefore provided a valuable learning opportunity and several reports have already been published.[1–3]

Data on population infection rates are now emerging, with post-pandemic infection rates of 25–50% in children and around 15% in pregnant women, similar to rates in the UK and Europe. Influenza-like illness (ILI) rates were similar to previous seasons, although those presenting with an ILI tended to be sicker than in past seasons. However, the major difference from previous seasons was in the number and type of people becoming seriously ill. Despite the early reports from Mexico, it quickly became clear that this virus was not behaving like the 1918 H1N1 pandemic strain. Still, about 13% of cases were hospitalised and 13% of these were admitted to intensive care units (ICUs). Major hospitals and ICUs experienced an extremely heavy load, with hospitalisation rates increased in all age groups except the very elderly. The greatest increase occurred in those aged 20–60 years; for example, hospitalisation rates in the 50–59-year age group were 4–6 times higher than the 2004–2007 average. Pregnancy increased the risk of hospitalisation and ICU admission more than 5-fold, as did indigenous status.

Although fatality rates were low, the pattern of mortality was dramatically different from seasonal influenza: instead of the expected peaks in the very young and the elderly, the peaks occurred in young and middle-aged adults. Of note, the dominant problem in those with serious illness was a primary viral pneumonia, whereas secondary bacterial infections played a much smaller role. Severe cases often required prolonged periods in ICU and heroic measures, including extracorporeal membrane oxygenation. Fortunately, transmission to healthcare workers did not occur to any significant extent and oseltamivir-resistant strains remain very uncommon.

Debriefing exercises have now taken place and there is little doubt that the investment in pandemic planning provided a good preparation. Nevertheless, things did not go exactly as anticipated and the experience taught us that flexibility is an important part of the response capacity. Lessons have been learned. The monovalent pandemic vaccine was not available until after the pandemic peak and uptake was poor, with only 20% of adults receiving the vaccine. However, it is included in the trivalent vaccine for 2010. Hopefully, the combination of pre-existing immunity due to natural exposure and the impact of the vaccine will ensure that Australia will be spared another season like 2009.

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Hong Kong (Paul Chan)

The first wave of pandemic influenza A(H1N1) infection in Hong Kong started in June 2009 and peaked in late September, when over 2800 laboratory-confirmed cases were recorded per week. The infection then declined and remained at a low level from November until the time of writing in early February 2010. As of 3 February 2010, the cumulative number of patients who tested positive for 2009 H1N1 was 35,330 and the median age of patients was 14 years (ranging from 10 days to 95 years). A total of 65 fatal cases were recorded.

In late December 2009, the Hong Kong SAR government launched a campaign promoting vaccination against pandemic influenza. The target groups for free or subsidised vaccination are healthcare workers, persons at higher risk of death and complications due to pre-existing medical conditions, pregnant women, children aged 6 months to under 6 years, elderly persons aged 65 years and above, pig farmers and slaughterhouse workers.

Hong Kong has two influenza peaks occurring in winter/spring and the summer months. The winter/spring peak is expected in late February and early March, thus a second wave of pandemic influenza is imminent. It is hoped that the availability of an effective vaccine will minimise the impact of this pandemic virus.

Indonesia (Cissy Kartasasmita)

The first case of novel H1N1 in Indonesia was identified in May 2009. Thereafter, it spread rapidly to 25 provinces in Indonesia. A total of 1097 cases of positive H1N1 occurred up to September 2009; 590 (54%) were male and most cases (1031; 94%) were Indonesian citizens. In 163 patients (15%) there was a history of travelling abroad, while 10 patients (1%) had confirmed contact with H1N1 patients. Figure 2 shows the distribution of cases by age. The highest prevalence was in children and adolescents. Ten patients died, giving a case fatality rate of 0.91%.

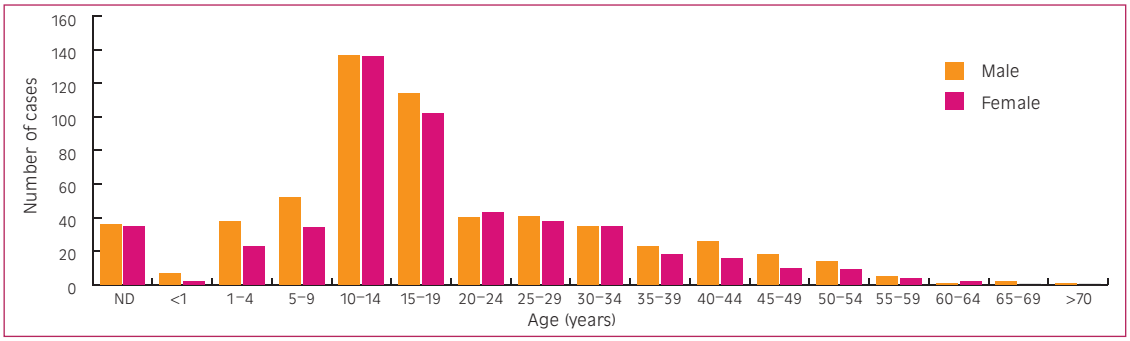

Figure 2. Age distribution of novel H1N1 influenza in Indonesia, 2009 (n = 1097).

The Philippines (Shelley de la Vega)

" Pacquiao knocks out swine flu "

The Philippines was one of the last countries to be affected by swine flu, which appeared around the time when the boxing great Manny Pacquiao won his match against Ricky Hatton. In an informal Google survey, I identified 37,200 swine flu blogs from the Philippines. However, Pacquiao features in 750,000 Philippine blogs! An advanced search on 'swine flu' combined with the Filipino word *gamut* (medicine) resulted in 51,000 hits, including 2760 hits on prevention.

Prevention blogs emphasise the importance of hygiene. Topics discussed include travel restrictions, school suspension, dietary restrictions on pork, and the economic effects of swine flu. Vaccines are covered favourably, with business continuity plans emphasising employee vaccination. Companies market swine flu masks and silver-laden cleaning solutions, while entrepreneurial bloggers advertise the virtues of vitamins C and D, spirulina, Lingzhi coffee, Camuvir barriera, glutathione and virgin coconut oil (VCO) for swine flu prevention. In one blog (www.talkph.net/index.php?topic=434.0), taking VCO, which is claimed to have natural immune-boosting properties, was likened to Pacquiao's training for the Hatton boxing match.

Blogs featuring both Pacquiao and swine flu yielded 127,000 hits – the flu awareness campaign would have triumphed if this champ had been hired to promote flu prevention. However, there was some negative buzz generated by Pacquiao's refusal to be quarantined. The Department of Health advised Pacquiao to observe self-quarantine returning from Las Vegas, but the boxing champ and his party chose to ignore this advice and arrived at the airport shaking hands and hugging fans. Could this fearless boxer possibly be taking VCO?

Flu review

Liang XF, Wang HQ, Wang JZ *et al.* Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2010; 375: 56–66.

Researchers affiliated with the Chinese Center for Disease Control and Prevention investigated the safety and immunogenicity of eight 2009 H1N1 vaccines from 10 Chinese manufacturers. A total of 12,691 children and adults were randomised in a double-blind manner to receive placebo, or one of eight vaccine formulations: a split-virion formulation containing 7.5 μg, 15 μg or 30 μg haemagglutinin per dose, each given with or without aluminium hydroxide adjuvant, and an adjuvanted, whole-virion formulation containing 5 μg or 10 μg haemagglutinin per dose. Two doses were given 3 weeks apart. The seroprotection rate 21 days after the first vaccine dose ranged from 69.5% (95% CI, 65.9–72.8%) to 92.8% (91.9–93.6%), compared with 9.8% (8.3–11.4%) in placebo recipients. A single dose of the 7.5 μg non-adjuvanted split-virion vaccine was seroprotective in all age groups, but the seroprotection rate in children aged 3 years to < 12 years increased from 76.7% (70.7–82.0%) after one dose to 97.7% (94.8–99.3%) after two doses, suggesting that two doses may be optimum in this group. Severe adverse events (most commonly fever) occurred in 0.6% of vaccine recipients.

Arguedas A, Soley C, Lindert K. Responses to 2009 H1N1 vaccine in children 3 to 17 years of age. *N Engl J Med* 2010; 362: 370–2.

A Costa Rican study compared the immune response to three regimens of a 2009 H1N1 vaccine in 194 children aged 3–8 years and 196 children aged 9–17 years. The children were randomised to receive one 7.5 μg dose with MF59 adjuvant, one 15 μg dose without adjuvant, or two 15 μg doses without adjuvant (total 30 μg). By day 22, all three regimens met the US Center for Biologics Evaluation and Research criteria for immunogenicity in the older children, but only the 7.5 μg adjuvanted dose met the criteria in the younger age group. Among children aged 3–8 years, haemagglutination-inhibition antibody titres were 1:40 or higher in 92% of the 7.5 μg adjuvanted vaccine group, compared with 72–75% of those who received up to 30 μg of non-adjuvanted vaccine.

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Upcoming meetings

International

20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
Vienna, Austria — 10–13 April 2010
www.congrex.ch/ECCMID2010

World Vaccine Congress 2010
Washington DC, USA — 19–22 April 2010
www.terrapinn.com/2010/wvcdc

28th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID 2010)
Nice, France — 4–8 May 2010
www.kenes.com/espid

American Thoracic Society (ATS) 2010 International Conference
New Orleans, USA — 14–19 May 2010
www.conference.thoracic.org

European Respiratory Society (ERS) Annual Congress
Barcelona, Spain — 18–22 September 2010
www.erscongress2010.org

Regional

Australasian Society for Infectious Diseases (ASID) Annual Scientific Conference 2010
Darwin, Australia — 26–29 May 2010
www.asid.net.au/meetings/index.asp

2nd International Forum on Pandemic Influenza (IFPI 2010)
Qingdao, China — 24–25 July 2010
www.ifpi2010.com

Options for the Control of Influenza VII
Hong Kong SAR, China — 3–7 September 2010
www.controlinfluenza.com

5th Asian Congress of Pediatric Infectious Diseases (ACPID)
Taipei, Taiwan — 23–26 September 2010
www.2010acpid.org

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