

## WHO Position Paper on Influenza Vaccines: Selected references

The following list includes some of the references that have been consulted during preparation of the most recent WHO position paper on Influenza Vaccines (Wkly Epidemiol Record 2005; 33 (19 Aug) 279-287). This position paper replaces the previous paper on this topic (WER 2002; 28 (12 Jul) 230-239).

Both these position papers are dealing mainly with seasonal influenza and the public health impact of yearly influenza vaccination. For authoritative information on pandemics, see <http://www.who.int/influenza>.

Whereas most of the background information and policy statements remain the same in the two position papers, the 2005 paper emphasises developments during the period 2002-2005 especially in the fields of:

1. vaccination of children
2. live, attenuated influenza vaccines for nasal application
3. the epidemiology of influenza in developing countries
4. utilization of influenza vaccines among the elderly
5. the problem of vaccine supply in case of an influenza pandemic
6. safety and efficacy
7. pharmaco-economics.

Suggestions for further reading in the field of vaccination policy are provided.

### 1: Vaccination of children

Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Pietrantoni C Di. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. *Lancet*. 2005 Feb 26-Mar 4;365(9461):773-80.

*BACKGROUND: We aimed to assess evidence of efficacy and effectiveness of live attenuated and inactivated influenza vaccines in children up to 16 years of age. METHODS: We searched the Cochrane Library, MEDLINE, EMBASE Biological Abstracts, and Science Citation Index to June, 2004, in any language, and contacted vaccine manufacturers and authors of relevant studies to identify additional data. We included randomised, cohort, and case-control studies comparing efficacy of vaccines against influenza (reduction in laboratory-confirmed cases), effectiveness of vaccines against influenza-like illness (reduction in symptomatic cases), or both, with placebo or no intervention. We analysed the following outcomes: influenza, influenza-like illness, admissions, school absences, complications, and secondary transmission. FINDINGS: We included 14 randomised controlled trials, eight cohort studies, one case-control study, and one randomised controlled trial of intraepidemic use of the vaccines. Live attenuated influenza vaccines had 79% efficacy and 38% effectiveness in children older than 2 years compared with placebo or no immunisation. Inactivated vaccines had lower efficacy (65%) than live attenuated vaccines, and in children aged 2 years or younger they had similar effects to placebo. Effectiveness of inactivated vaccines was about 28% in children older than 2 years. Vaccines were effective in reducing long school absences (relative risk 0.14 [95% CI 0.07-0.27]). Studies assessing the effects of vaccines against secondary cases, lower-respiratory tract disease, acute otitis media, and hospital stay suggested no difference with placebo or standard care, but lacked statistical power. INTERPRETATION: Influenza vaccines (especially two-dose live attenuated vaccines) are efficacious in children older than 2 years. Efficacy and effectiveness of the vaccines differed strikingly. Only two small studies assessed the effects of influenza vaccines on hospital admissions and no studies assessed reductions in mortality, serious complications, and community transmission of influenza. If influenza immunisation in children is to be*

*recommended as public-health policy, large-scale studies assessing such important outcomes and undertaking direct comparisons of vaccines are urgently needed.*

Zangwill KM, Belshe RB. Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new area of routine vaccination. *Pediatr Infect Dis J.* 2004 Mar;23(3):189-97.

*Increasing use of influenza vaccine in children is expected as this important virus becomes more widely recognized as a major cause of morbidity in young children. Clinicians and third party payers must consider the implications of national vaccine use recommendations, with their current focus on young children, on their practices and on the community at large. Two influenza vaccines are available in the United States, an inactivated, trivalent intramuscular formulation (TIV) which is approved for use among children > or =6 months of age; and a live, attenuated intranasal trivalent preparation (LAIV) indicated for healthy persons 5 to 49 years of age. This review summarizes available data regarding the safety and efficacy of TIV, in comparison with LAIV, with particular attention to children <9 years of age, the population for whom two doses of vaccine are recommended for first time vaccination. It is apparent that relatively few data are available on the safety of TIV in young children, that important age-specific differences in TIV vaccine efficacy exist and that LAIV appears similar to TIV with regard to safety and efficacy in younger children, but no head-to-head comparison of these two licensed products is available.*

Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, Colborn DK, Kurs-Lasky M, Haralam MA, Byers CJ, Zoffel LM, Fabian IA, Bernard BS, Kerr JD. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA.* 2003 Sep 24;290(12):1608-16.

*CONTEXT: Acute otitis media (AOM) frequently complicates influenza infection. Previous studies have found influenza vaccine effective in reducing the occurrence of AOM in children mainly older than 2 years. OBJECTIVE: To evaluate the effectiveness of inactivated influenza vaccine in preventing AOM in children aged 6 to 24 months. DESIGN, SETTING, AND PATIENTS: Randomized, double-blind, placebo-controlled trial of 786 children aged 6 to 24 months enrolled at Children's Hospital of Pittsburgh before the 1999-2000 (411 children) and 2000-2001 (375 children) respiratory seasons (defined as December 1 through March 31 of the respective following year). Children received influenza vaccine or placebo in a 2:1 ratio. The first cohort was observed for 1 year and the second cohort until the end of the ensuing respiratory season. INTERVENTION: Two doses (0.25 mL each) of inactivated trivalent subvirion influenza vaccine or placebo were administered intramuscularly approximately 4 weeks apart. MAIN OUTCOME MEASURES: Proportion of children who developed AOM, monthly occurrence rate of AOM, estimated proportion of time with middle ear effusion, and utilization of selected health care and related resources. RESULTS: Of the 66 children in the vaccine group from whom serum samples were collected, seroconversion against strains in the vaccine formulations developed in 88.6% to 96.8%, depending on the specific strain. The efficacy of the vaccine against culture-confirmed influenza was 66% (95% confidence interval [CI], 34%-82%) in 1999-2000 and -7% (95% CI, -247% to 67%) in 2000-2001; however, influenza attack rates differed between these 2 periods (in the placebo group, 15.9% and 3.3%, respectively). Compared with placebo, influenza vaccine did not reduce the proportion of children who had at least 1 episode of AOM during the respiratory season (in the first cohort: vaccine, 49.2% vs placebo, 52.2%;  $P = .56$ ); in the second cohort: vaccine, 55.8% vs placebo, 48.3%;  $P = .17$ ). The vaccine also did not reduce the monthly rate of AOM; the estimated proportion of time with middle ear effusion; or the utilization of selected health care and related resources. There were also no differences between the vaccine and placebo groups regarding any of these outcomes during peak influenza periods. The vaccines administered to both cohorts of children were well tolerated. CONCLUSION: Administration of inactivated trivalent influenza vaccine to children aged 6 to 24 months did not reduce their burden of AOM or their utilization of selected health care and related resources.*

Principi N, Esposito S. Are we ready for the universal influenza vaccination in paediatrics? *Lancet Infect Dis* 2004;4:75-83

*Recent studies have suggested that paediatric influenza is a greater medical problem than usually thought because it can cause excess hospitalisations, medical visits, and antibiotic prescriptions even in healthy children, especially those under 2 years. Furthermore, influenza in otherwise healthy children may have substantial socioeconomic consequences for the children and their household contacts. These findings have led many experts to encourage the more widespread use of influenza vaccine in childhood. Although the immunogenicity of the available vaccines is good and they are safe, well-tolerated, and highly effective in preventing influenza and its complications, economic data support universal vaccination only when indirect effectiveness is considered. However, infants aged 6-23 months, children with recurrent acute otitis media or respiratory-tract infections, and healthy children attending day-care centres or elementary schools should be included among the paediatric groups requiring vaccination.*

## 2: Live attenuated influenza vaccine

Ghendon YZ, Markushin SG, Akopova II, Koptiaeva IB, Nechaeva EA, Mazurkova LA, Radaeva IF, Kolokoltseva TD. Development of cell cultured (MDCK) live cold-adapted (CA) attenuated influenza vaccine. *Vaccine*. 2005 Sep 7;23(38):4678-84.

*Optimal conditions are determined for growing cold-adapted reassortant strains of a live influenza vaccine in MDCK cell line cultivated in a fermenter with a serum-free medium and microcarriers. The studied MDCK cell line meet all national and WHO requirements for the finite cell lines used for the production of biological preparations. CA reassortant vaccine strains grown in such conditions which fully preserve its mutations and the mutations lead to amino acid substitution in all genome segments of the studied CA reassortants. Under optimal cultivation conditions, the output of a monovalent live CA influenza vaccine in a 10-l fermenter may reach 100,000 doses.*

Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, Walker R, Hessel C, Cordova J, Mendelman PM. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatr Infect Dis J*. 2004 Feb;23(2):138-44.

*OBJECTIVE: To determine the safety of cold-adapted trivalent intranasal influenza virus vaccine (CAIV) in children and adolescents. STUDY DESIGN: A randomized, double blind, placebo-controlled safety trial in healthy children age 12 months to 17 years given CAIV (FluMist; MedImmune Vaccines, Inc.) or placebo (randomization, 2:1). Children <9 years of age received a second dose of CAIV or placebo 28 to 42 days after the first dose. Enrolled children were then followed for 42 days after each vaccination for all medically attended events. Prespecified outcomes included 4 prespecified diagnostic groups and 170 observed individual diagnostic categories. The relative risk and the 2-sided 90% confidence interval were calculated for each diagnostic group and individual category by clinical setting, dose and age. More than 1500 relative risk analyses were performed. RESULTS: A total of 9689 evaluable children were enrolled in the study. Of the 4 prespecified diagnostic categories (acute respiratory tract events, systemic bacterial infection, acute gastrointestinal tract events and rare events potentially associated with wild-type influenza), none was associated with vaccine. Of the biologically plausible individual diagnostic categories, 3, acute gastrointestinal events, acute respiratory events and abdominal pain, had different analyses that demonstrated increased and decreased relative risks, making their association with the vaccine unlikely. For reactive airway disease a significant increased relative risk was observed in children 18 to 35 months of age with a relative risk of 4.06 (90% confidence interval, 1.29 to 17.86) in this age group. The individual diagnostic categories of upper respiratory infection, musculoskeletal pain, otitis media with effusion and adenitis/adenopathy had at least one analysis that achieved a significant increased risk ratio. All of these events were infrequent. CONCLUSION: CAIV was generally safe in children and adolescents. The observation of an increased risk of asthma/reactive airway disease in children <36 months of age is of potential concern. Further studies are planned to evaluate the risk of asthma/reactive airway disease after vaccine.*

### 3: Influenza in developing countries

Van Essen GA, Palache AM, Forleo E, Fedson DS. Influenza vaccination in 2000: recommendations and vaccine use in 50 developed and rapidly developing countries. *Vaccine*. 2003 May 1;21(16):1780-5.

*Influenza vaccination is becoming an increasingly important aspect of public health programs in developed and rapidly developing countries. In 2000, most of these countries had national recommendations to vaccinate elderly people and those with high-risk conditions. Levels of vaccine use, however, varied widely and several rapidly developing countries had higher levels than those seen in many developed countries. More than one-third of all influenza vaccinations occurred in countries outside North America, western Europe and Australia and New Zealand. With increasing vaccine use, all countries will be better prepared for the next pandemic. Nonetheless, those countries that use but do not produce influenza vaccine will find it difficult to obtain supplies of pandemic vaccine.*

Wkly Epidemiol Rec. 2002 Nov 15;77(46):381-4. Outbreak of influenza, Madagascar, July-August 2002.

Comment: *The outbreak which was apparently caused by A(H3N2) involved more than 30 000 clinical cases and 754 deaths, mainly in the Fianarantsoa province. In some highland areas, the attack rate reached 67% and the case/fatality rate 2%. (No summary provided by the WER).*

Chiu SS, Lau YL, Chau KH, Wong WHS, Peiris JSK. Influenza related hospitalizations among children in Hong Kong. *N Engl J Med*. 2002 Dec 26;347(26):2097-103.

*BACKGROUND: It has been difficult to define the burden of influenza in children because of confounding by the cocirculation of respiratory syncytial virus (RSV). In Hong Kong, China, the influenza and RSV infection seasons sometimes do not overlap, thus providing an opportunity to estimate the rate of influenza-related hospitalization in a defined population, free from the effects of RSV. METHODS: In a retrospective, population-based study, we estimated the influenza-associated excess rate of hospitalization among children 15 years old or younger in the Hong Kong Special Administrative Region from 1997 to 1999. Data from a single hospital with intensive use of virologic analyses for diagnosis were obtained to define and adjust for underestimation of the model. RESULTS: Peaks of influenza and RSV infection activity were well separated in 1998 and 1999 but overlapped in 1997. The adjusted rates of excess hospitalization for acute respiratory disease that were attributable to influenza were 278.5 and 288.2 per 10,000 children less than 1 year of age in 1998 and 1999, respectively; 218.4 and 209.3 per 10,000 children 1 to less than 2 years of age; 125.6 and 77.3 per 10,000 children 2 to less than 5 years of age; 57.3 and 20.9 per 10,000 children 5 to less than 10 years of age; and 16.4 and 8.1 per 10,000 children 10 to 15 years of age. CONCLUSIONS: In the subtropics, influenza is an important cause of hospitalization among children, with rates exceeding those reported for temperate regions. Copyright 2002 Massachusetts Medical Society*

### 4: Utilization of influenza vaccines among the elderly

Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet*. 2005 Oct 1;366(9492):1165-74.

*BACKGROUND: Influenza vaccination of elderly individuals is recommended worldwide. Our aim was to review the evidence of efficacy and effectiveness of influenza vaccines in individuals aged 65 years or older. METHODS: We searched five electronic databases to December, 2004, in any language, for randomised (n=5), cohort (n=49), and case-control (n=10) studies, assessing efficacy against influenza (reduction in laboratory-confirmed cases) or effectiveness against influenza-like illness (reduction in symptomatic cases). We expressed*

vaccine efficacy or effectiveness as a proportion, using the formula  $VE = 1 - \text{relative risk (RR)}$  or  $VE^* = 1 - \text{odds ratio (OR)}$ . We analysed the following outcomes: influenza, influenza-like illness, hospital admissions, complications, and deaths. **FINDINGS:** In homes for elderly individuals (with good vaccine match and high viral circulation) the effectiveness of vaccines against influenza-like illness was 23% (95% CI 6-36) and non-significant against influenza (RR 1.04, 0.43-2.51). Well matched vaccines prevented pneumonia (VE 46%, 30-58) and hospital admission (VE 45%, 16-64) for and deaths from influenza or pneumonia (VE 42%, 17-59), and reduced all-cause mortality (VE 60%, 23-79). In elderly individuals living in the community, vaccines were not significantly effective against influenza (RR 0.19, 0.02-2.01), influenza-like illness (RR 1.05, 0.58-1.89), or pneumonia (RR 0.88, 0.64-1.20). Well matched vaccines prevented hospital admission for influenza and pneumonia (VE 26%, 12-38) and all-cause mortality (VE 42%, 24-55). After adjustment for confounders, vaccine performance was improved for admissions to hospital for influenza or pneumonia (VE\* 27%, 21-33), respiratory diseases (VE\* 22%, 15-28), and cardiac disease (VE\* 24%, 18-30), and for all-cause mortality (VE\* 47%, 39-54). **INTERPRETATION:** In long-term care facilities, where vaccination is most effective against complications, the aims of the vaccination campaign are fulfilled, at least in part. However, according to reliable evidence the usefulness of vaccines in the community is modest.

Gravenstein S, Davidson HE. Current strategies for management of influenza in the elderly population. *Clin infect dis* 2002; 35:729-37.

*Influenza virus remains among the most important pathogens infecting elderly people. Vaccination is the most cost-effective strategy to reduce morbidity and mortality due to influenza. For persons who are not vaccinated or for whom vaccines fail to prevent influenza, there are 2 classes of efficacious drugs for treatment or chemoprophylaxis: M2 channel inhibitors and neuraminidase inhibitors. Effective treatment, however, must commence within 48 h of the onset of symptoms, which can create problems for patients who wait to see whether their symptoms worsen or improve. Older adults who have relocated to the congregate housing environments of assisted living and long-term care facilities deserve special consideration, because influenza exposure risks are different for this group. Strategies for control of influenza must combine preventive approaches, such as vaccination, educational approaches, and the introduction of policies that allow health care professionals anticipate, identify, and efficiently respond to influenza outbreaks.*

## 5: Problems of influenza vaccine supply in case of a pandemic

Stephenson J, Nicholson KG, Wood JM, Zambon M, Katz JM. Confronting the avian influenza threat: vaccine development for a potential pandemic. *Lancet Infect Dis*. 2004 Aug;4 (8): 499-509.

*Sporadic human infection with avian influenza viruses has raised concern that reassortment between human and avian subtypes could generate viruses of pandemic potential. Vaccination is the principal means to combat the impact of influenza. During an influenza pandemic the immune status of the population would differ from that which exists during interpandemic periods. An emerging pandemic virus will create a surge in worldwide vaccine demand and new approaches in immunisation strategies may be needed to ensure optimum protection of unprimed individuals when vaccine antigen may be limited. The manufacture of vaccines from pathogenic avian influenza viruses by traditional methods is not feasible for safety reasons as well as technical issues. Strategies adopted to overcome these issues include the use of reverse genetic systems to generate reassortant strains, the use of baculovirus-expressed haemagglutinin or related non-pathogenic avian influenza strains, and the use of adjuvants to enhance immunogenicity. In clinical trials, conventional surface-antigen influenza virus vaccines produced from avian viruses have proved poorly immunogenic in immunologically naive populations. Adjuvanted or whole-virus preparations may improve immunogenicity and allow sparing of antigen.*

Fedson DS. Vaccination for pandemic influenza: a six point agenda for interpandemic years. *Pediatr Infect Dis J* 2004; 23: S74-7.

**BACKGROUND:** The demand for influenza vaccine is driven by recognition of its health and economic benefits. Vaccine reduces all cause mortality in the elderly by 30 to 50% and prevents > or =30% of hospital admissions for influenza-related respiratory disease, heart disease and stroke. However, because most influenza vaccine (85%) is produced in only eight countries, adequate production and equitable distribution of vaccine throughout the world will pose a serious challenge when the next influenza pandemic appears. **METHODS:** This article reviews a six point agenda for pandemic vaccination that should be undertaken during interpandemic years. The agenda includes preparing vaccine seed strains using reverse genetics, determining the characteristics of a pandemic vaccine and vaccination schedule, considering global registration of pandemic vaccines, increasing vaccination in interpandemic years, documenting the epidemiology of vaccine use and addressing political issues that will affect the global supply of pandemic vaccines. **CONCLUSIONS:** Planning for pandemic vaccination must begin during the interpandemic period to ensure a vaccine supply that will be adequate to meet demand in all countries. This will require the skills not only of experts in virology, epidemiology and public health but also those in politics, economics and law. The task will be complex, but its promised benefits will be immense.

Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. *N Engl J Med* 2004; 351: 2295-301.

**BACKGROUND:** The loss of half the U.S. supply of influenza vaccine due to contamination has created a critical shortage. Dose-sparing strategies that use intradermal delivery of vaccines may be one approach to consider. **METHODS:** We conducted a randomized, open-label trial outside the influenza season in 100 healthy adults 18 to 40 years of age to compare the immunogenicity and safety of intradermal immunization with influenza vaccine with standard intramuscular immunization. Subjects were randomly assigned to receive either a single intramuscular dose of 0.5 ml of trivalent influenza vaccine, containing at least 15 microg of hemagglutinin per strain, by means of a prefilled syringe or a single intradermal dose of 0.1 ml, containing at least 3 microg of hemagglutinin per strain, by means of a fine-gauge needle; both injections were in the deltoid region. Changes in the hemagglutination-inhibition (HAI) antibody titer were assessed by comparing geometric mean titers and fold increases relative to baseline values and by comparing changes in the seroconversion and seroprotection rates. Local and systemic adverse events were assessed after both types of vaccination. **RESULTS:** Subjects who received an intradermal injection with one fifth the standard dose of influenza vaccine had increases in the geometric mean HAI titer by a factor of 15.2 for the H1N1 strain in the vaccine, 19.0 for the H3N2 strain, and 12.4 for the B strain on day 21, as compared with respective increases by a factor of 14.9, 7.1, and 15.3 for the intramuscular injection of the standard dose. Seroconversion and seroprotection rates were similar in the two groups on day 21, ranging from 66 to 82 percent and 84 to 100 percent, respectively. Local reactions were significantly more frequent among recipients of intradermal injections than among recipients of intramuscular injections, but such reactions were mild and transient. **CONCLUSIONS:** In this study of young adults, intradermal administration of one fifth the standard intramuscular dose of an influenza vaccine elicited immunogenicity that was similar to or better than that elicited by intramuscular injection. Intradermal administration could be used to expand the supplies of influenza vaccine, but further studies are needed before this strategy can be recommended for routine use.

## 6: Efficacy and safety

Langley JM, Faughnan ME. Prevention of influenza in the general population: recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ*. 2004 Nov 9;171(10):1213-22.

**BACKGROUND:** Although all jurisdictions in Canada offer annual influenza immunization to people at high risk of complications, only Ontario has provided universal annual immunization of healthy adults and children. Use of chemotherapy (amantadine, neuraminidase inhibitors) to prevent influenza varies among provinces. We sought to systematically review the evidence for the prevention of influenza infection in the general population. **METHODS:** The interventions reviewed were influenza vaccination and prophylactic use of neuraminidase inhibitors. The health outcomes of interest were rates of laboratory-confirmed influenza infection, clinical definitions of influenza-like illness and work absenteeism. **MEDLINE** and **Cochrane** databases were searched for relevant articles published between 1966 and March 2003. Only randomized controlled trials (RCTs) were

selected. Evidence was appraised using the methodology of the Canadian Task Force on Preventive Health Care. **RESULTS:** Eighteen trials involving more than 33,000 healthy adults were identified that met the inclusion criteria; of these, 15 showed that influenza vaccination with either live-attenuated and inactivated vaccines was efficacious. Eleven trials were considered to be of "good" quality, and 7 were considered to be of "fair" quality. The relative risk reduction (RRR) associated with influenza immunization in adults ranged from 0% to 91%. Fifteen RCTs involving more than 45,000 healthy children aged 6 months to 19 years were identified, of which 9 were considered to contain "good" evidence and 6 "fair" evidence. Results from 12 of these trials showed protection against influenza. The RRR ranged from 0% to 93%. There were 6 RCTs of "good" quality showing that neuraminidase inhibitors are effective in preventing influenza infection. Side effects from both influenza vaccination and neuraminidase inhibitor administration were mild. **INTERPRETATION:** There are numerous RCTs of good quality in large populations that have consistently shown that influenza vaccination, using inactivated or live-attenuated vaccines, is moderately effective in preventing influenza in the general population (healthy adults and children over 6 months of age). There is good evidence that neuraminidase inhibitor prophylaxis in contacts given within 36 to 48 hours of symptom onset of the household index case is effective; appropriate use of this prevention method requires access to rapid diagnostic methods. Decisions about introduction of routine immunization programs must take into account the cost and cost-effectiveness of a universal program and the burden of illness associated with influenza in each jurisdiction.

Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Pietrantoni C Di. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. *Lancet*. 2005 Feb 26-Mar 4;365(9461):773-80.

**BACKGROUND:** We aimed to assess evidence of efficacy and effectiveness of live attenuated and inactivated influenza vaccines in children up to 16 years of age. **METHODS:** We searched the Cochrane Library, MEDLINE, EMBASE Biological Abstracts, and Science Citation Index to June, 2004, in any language, and contacted vaccine manufacturers and authors of relevant studies to identify additional data. We included randomised, cohort, and case-control studies comparing efficacy of vaccines against influenza (reduction in laboratory-confirmed cases), effectiveness of vaccines against influenza-like illness (reduction in symptomatic cases), or both, with placebo or no intervention. We analysed the following outcomes: influenza, influenza-like illness, admissions, school absences, complications, and secondary transmission. **FINDINGS:** We included 14 randomised controlled trials, eight cohort studies, one case-control study, and one randomised controlled trial of intraepidemic use of the vaccines. Live attenuated influenza vaccines had 79% efficacy and 38% effectiveness in children older than 2 years compared with placebo or no immunisation. Inactivated vaccines had lower efficacy (65%) than live attenuated vaccines, and in children aged 2 years or younger they had similar effects to placebo. Effectiveness of inactivated vaccines was about 28% in children older than 2 years. Vaccines were effective in reducing long school absences (relative risk 0.14 [95% CI 0.07-0.27]). Studies assessing the effects of vaccines against secondary cases, lower-respiratory tract disease, acute otitis media, and hospital stay suggested no difference with placebo or standard care, but lacked statistical power. **INTERPRETATION:** Influenza vaccines (especially two-dose live attenuated vaccines) are efficacious in children older than 2 years. Efficacy and effectiveness of the vaccines differed strikingly. Only two small studies assessed the effects of influenza vaccines on hospital admissions and no studies assessed reductions in mortality, serious complications, and community transmission of influenza. If influenza immunisation in children is to be recommended as public-health policy, large-scale studies assessing such important outcomes and undertaking direct comparisons of vaccines are urgently needed.

## 7: Pharmacoeconomics of influenza vaccination

Block SL. Role of influenza vaccine for healthy children in the US. *Paediatr Drugs*. 2004;6(4):199-209.

*Influenza infection is associated with significant morbidity and mortality in adults, but the highest attack rates for influenza regularly occur in children, particularly those in preschool and elementary school. The consequences of influenza in this younger population - increased rate of hospitalization in those younger than 2 years of age and serious associated morbidity - have been underestimated. Children are also the critical link for*

*spreading influenza in the community. Recent data suggest that mass influenza vaccination of healthy children would not only protect recipients, but also may reduce the burden of influenza throughout the community. During the past 3 decades, efforts to control influenza have focused on the use of an injectable trivalent inactivated vaccine (TIV) in high-risk persons. The vaccine is 'safe' and effective, but its acceptance and uptake by patients and healthcare providers have been modest at best. A new intranasal, live-attenuated, trivalent cold-adapted influenza virus vaccine (CAIV-T) [FluMist] is 'safe', well tolerated, immunogenic, and efficacious in preventing influenza illness in healthy children. Compared with TIV, CAIV-T is easier to administer and should be more readily acceptable, particularly for mass immunization campaigns. CAIV-T also induces a broader immune response and has demonstrated protection against at least three different variant influenza strains. This vaccine is particularly well suited for routine immunization of children and thus offers the potential for greatly improved control of influenza. However, the acquisition cost per single dose of FluMist for the 2003-4 season (approximate, equals 46 US dollars) significantly hampered its uptake both by practitioners and by managed care organizations, even despite a later approximate, equals 25 US dollars rebate offer. For the 2004-5 season, CAIV-T is likely to be only modestly more expensive (average wholesale price: 16.50 US dollars for non-returnable doses, 23 US dollars for returnable doses) than TIV. The practitioner must consider the benefits of FluMist compared with its likely higher vaccine cost and the issues of reimbursement among multiple insurers.*

Postma MJ, Jansema, P, van Genugten LL, et al. Pharmacoeconomics of influenza vaccination for healthy working adults. Reviewing the available evidence. *Drugs*. 2002;62(7):1013-24.

*A favourable pharmacoeconomic profile has been well established for influenza vaccination in the elderly. For employers relevant benefits seem to exist for vaccinating healthy working adults to avert absenteeism and related production losses. From a pharmacoeconomic point of view it is relevant to consider whether societal benefits of vaccination for healthy working adults is worthwhile given the costs of vaccination for the community. We searched Medline and Embase using the key words influenza (vaccination) in combination with cost, cost-benefit, cost-effectiveness, efficiency, economic evaluation, health-policy and pharmacoeconomics. From this primary search, we selected 11 studies concerned with the group of healthy working adults. We reviewed these studies according to several criteria: benefit-to-cost (B/C) ratio; vaccine effectiveness, influenza incidence, number of days of work absence due to illness; and relative cost of the vaccine. Three studies on vaccinating healthy working adults found costs exceeding the benefits (B/C-ratio <1). The remaining eight pharmacoeconomic studies found a B/C-ratio of almost two or more. Cost savings are strongly related to the inclusion of indirect benefits related to averted production losses. After exclusion of indirect costs and benefits of production gains/losses, only one of the eight studies remains cost saving. Considering the available pharmacoeconomic evidence, vaccination of healthy working adults in Western countries may be an intervention with favourable cost-effectiveness and cost-saving potentials if indirect benefits of averted production losses are included. Excluding indirect benefits and costs of production losses/gains, cost-saving potentials are limited. Recent international guidelines for pharmacoeconomic research advise the inclusion of production gains and losses in the preferred societal perspective. Hence, on the basis of the available evidence, influenza vaccination of healthy working adults may be recommended from pharmacoeconomic point of view. Pharmacoeconomics do, however, present only one argument for consideration aside from ethical issues, budgetary limits and psychosocial aspects.*

## Suggestions for further reading in the field of vaccination policy

Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Early release, *MMWR Recomm Rep*. 2005 Jul 29;54(RR-8):1-40. [Erratum published in *MMWR Morb Mortal Wkly Rep*. 2005 Aug 5;54(30):750.]

*This report updates the 2004 recommendations by the Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine and antiviral agents (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 2004;53[No. RR-6]:1-*

40). The 2005 recommendations include new or updated information regarding 1) vaccination of persons with conditions leading to compromise of the respiratory system; 2) vaccination of health-care workers; 3) clarification of the role of live, attenuated influenza vaccine (LAIV) in vaccine shortage situations; 4) the 2005-06 trivalent vaccine virus strains: A/California/7/2004 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like antigens (for the A/California/7/2004 [H3N2]-like antigen, manufacturers may use the antigenically equivalent A/New York/55/2004 virus, and for the B/Shanghai/361/2002-like antigen, manufacturers may use the antigenically equivalent B/Jilin/20/2003 virus or B/Jiangsu/10/2003 virus); and 5) the assessment of vaccine supply, timing of influenza vaccination, and prioritization of inactivated vaccine in shortage situations. A link to this report and other information can be accessed at <http://www.cdc.gov/flu>.

Longini Jr. IM, Halloran ME. Strategy for distribution of influenza vaccine to high-risk groups and children. *Am J Epidemiol* 2005; 161:303-306.

*Despite evidence that vaccinating schoolchildren against influenza is effective in limiting community-level transmission, the United States has had a long-standing government strategy of recommending that vaccine be concentrated primarily in high-risk groups and distributed to those people who keep the health system and social infrastructure operating. Because of this year's influenza vaccine shortage, a plan was enacted to distribute the limited vaccine stock to these groups first. This vaccination strategy, based on direct protection of those most at risk, has not been very effective in reducing influenza morbidity and mortality. Although it is too late to make changes this year, the current influenza vaccine crisis affords the opportunity to examine an alternative for future years. The alternative plan, supported by mathematical models and influenza field studies, would be to concentrate vaccine in schoolchildren, the population group most responsible for transmission, while also covering the reachable high-risk groups, who would also receive considerable indirect protection. In conjunction with a plan to ensure an adequate vaccine supply, this alternative influenza vaccination strategy would help control interpandemic influenza and be instrumental in preparing for pandemic influenza. The effectiveness of the alternative plan could be assessed through nationwide community studies.*