SSY Wong 黃世賢
KY Yuen 袁國勇

Influenza vaccination: options and issues

流行性感冒疫苗的選擇及問題

Currently available vaccines have similar efficacy if they are matched to the most prevalent circulating strains. They also have comparable adverse effect profiles. The choice of a specific preparation of vaccine therefore requires consideration of cost, purity of the vaccine preparation in terms of the amount of egg protein and endotoxin, allergy to different constituents of the vaccine, reactogenicity profiles, as well as the preferred route of administration. Intradermal injection of the vaccine appears to be a viable alternative to the traditional intramuscular administration with the additional benefit of requiring a smaller volume of vaccine. Despite the documented benefits in various community and institutional settings, influenza vaccination has been underutilised by most target groups. A major obstacle to broader coverage of vaccination is the perceived ineffectiveness of the vaccine and the relatively benign nature of the illness in most patients. Uptake of vaccine among target populations, especially health care workers, needs to be improved through a concerted effort between frontline clinicians and health authorities.

現時可使用的各種流行性感冒疫苗，如果與當時傳播最廣的病毒品種吻合，都可以發揮相近的效力，而各疫苗產生的副作用也相類似。因此，選擇使用哪一種疫苗製劑便需要從成本、疫苗純正度（雞蛋蛋白和內毒素的含量）、疫苗成份導致敏感的可能、反應原性概況和理想施藥方法各方面作考慮。除了傳統的肌內用藥外，另一個選擇是皮內注射，其好處是可以減少用藥量。儘管已有不同社區和機構的文獻證實接種流感疫苗的好處，大部分目標組別的接種率都偏低，主要原因是認為疫苗效果不顯著，而且大部分流感病人的病情並不嚴重。前線醫生和醫療當局須同心協力改善目標組別，特別是醫護人員注射疫苗的覆蓋率。

Key words:
Influenza;
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關鍵詞：
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Department of Microbiology, Centre of Infection, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong
SSY Wong, MRCPath, DTM&H
KY Yuen, FRCPath, MD

Correspondence to: Prof KY Yuen (e-mail: hkumicro@hkucc.hku.hk)

Introduction

Influenza is one of the most common infectious diseases and possesses high epidemic and pandemic potential. It is largely a vaccine-preventable disease. Influenza vaccine differs from other currently available vaccines in being a trivalent vaccine and in that the vaccine composition needs to be updated annually.

Orthomyxoviridae is a family of single-stranded minus-sense RNA viruses with a segmented genome. The three medically important genera are *Influenzavirus A, Influenzavirus B,* and *Influenzavirus C*. The eight RNA segments of the influenza A virus genome encode 10 proteins: polymerase proteins (PB1, PB2, and PA), nucleocapsid protein (NP), haemagglutinin protein (HA), neuraminidase (NA), matrix proteins (M1 and M2), and non-structural proteins (NS1 and NS2).[1] Currently, 16 HA and 9 NA types are recognised. The HA mediates viral attachment and

cellular entry and is the main viral target of protective humoral immunity. The antibody titre against HA is commonly used as a surrogate marker of immunity and to compare the immunogenicity of different vaccine preparations. Neuraminidase facilitates the spread of the virions in the host and is the target of NA inhibitors (oseltamivir and zanamivir) which are active against both influenza A and B viruses. The M2 protein serves as an ion channel. It is important in the uncoating of viruses in endosomes and in viral assembly, and is the target of amantadine and rimantadine.

Influenza A virus is prone to undergo antigenic variations (antigenic drift and antigenic shift). Antigenic drift occurs all the time and explains the need for yearly changes in vaccine composition. Antigenic shift results in the appearance of a novel combination of HA and NA for which the human population has little or no immunity, or when a virus acquires the ability to directly infect humans from their natural animal hosts, especially the avian species.

Properties of influenza vaccines

Vaccine strains

Most of the currently available influenza vaccines are inactivated vaccines. A live attenuated vaccine was approved by the United States Food and Drug Administration (FDA) in 2003. Recommendations on vaccine composition are based on the constant year-round global influenza surveillance coordinated by the World Health Organization (WHO). Two influenza A strains (currently H1N1 and H3N2) and one influenza B strain are chosen, based on their global prevalence. Every year in February (for the northern hemisphere), the WHO recommends the composition of influenza virus vaccines for use in the following influenza season (normally from November to April). Similar recommendations are made for the southern hemisphere in September every year for the forthcoming influenza season (from May to September in the following year). As an example, the vaccine to be used in the 2005 to 2006 season (northern hemisphere) contains an A/New Caledonia/20/99(H1N1)-like virus, an A/California/7/2004(H3N2)-like virus, and a B/Shanghai/361/2002-like virus.[2] In tropical countries, influenza occurs throughout the year and the choice of vaccine composition requires correlation with local epidemiology so that the most appropriate vaccine can be chosen. Some of the more commonly used vaccines are listed in Table 1.[3,4]

Inactivated vaccine production

Vaccine strains of influenza viruses are cultured in allantoic cavities of embryonated hens eggs. This conventional method of viral culture has disadvantages, including dependence on high-quality eggs, relatively cumbersome processing and disinfection, alteration in the antigenicity of the progeny viruses when grown in avian tissues, and potential adverse reactions when used in individuals with egg allergy. In recent years, attempts have been made to prepare influenza vaccines in mammalian cell lines, especially the Madin-Darby canine kidney (MDCK) and African green monkey kidney (Vero) cell lines.[5] Successful development of cell culture–derived vaccines may improve vaccine availability during pandemics. Cell culture–derived vaccines also preserve the antigenic properties of clinical isolates of influenza viruses better and elicit a stronger cell-mediated immunity than conventional egg-derived vaccines.[6]

Viral particles harvested from the growth substrate are inactivated by formalin or β-propiolactone. The virions are 'split' (using solvents to disrupt the viral envelope) to produce subvirions. These split-virion vaccines retain the immunogenicity of the virus, while the reactogenicity is reduced compared with whole-virus vaccines because of a lower quantity of non-viral components (eg egg proteins) and non-essential viral components (proteins and lipid membrane). Subunit vaccines are produced by further zonal centrifugation to separate the surface antigens from other viral proteins. The main immunogen of these vaccines is the HA. One adult dose of vaccine contains 15 μg of HA per viral strain.

Live attenuated vaccines

FluMist (MedImmune, Gaithersburg [MD], US) is the only FDA-approved live attenuated influenza vaccine available at present. It is delivered by intranasal spray to simulate a natural infection. A syringe-like applicator is used to produce large aerosols and delivers 0.25 mL of the vaccine into each nostril (total volume, 0.5 mL). Attenuation is achieved by cold-adaptation of master donor viruses, followed by reassortment with contemporary vaccine strains to produce the trivalent cold-adapted influenza vaccine (CAIV-T).[7] Cold-adapted viruses can only replicate in the upper respiratory epithelium at a temperature of about 32°C to 33°C. In contrast to inactivated vaccines, CAIV-T also stimulates the production of secretory immunoglobulin A (IgA) antibody and elicits cell-mediated immunity. The serum haemagglutinin antibody level achieved after vaccination with CAIV-T is lower than that of inactivated vaccines, despite similar efficacy between the two types of vaccines.[8]

Adjuvants

Two adjuvants have been used in inactivated vaccines to boost their immunogenicity. These are MF59 (an oil-in-water emulsion containing squalene, polysorbate 80, and sorbitan trioleate) and immunopotentiating reconstituted influenza virosomes (IRIVs). The MF59-adjuvanted influenza vaccine (Fluad; Chiron Vaccines, Emeryville [CA], US) is more immunogenic than non-adjuvanted vaccines with a higher post-vaccination geometric mean titre of haemagglutinin antibody, though the overall seroconversion rate is similar.[9,10] Fluad, however, has a significantly higher reactogenicity than other vaccines in terms of local symptoms.

The IRIVs utilise a liposomal carrier system consisting of spherical, unilamellar vesicles, with an average diameter of about 150 nm.[11] The virosomes are produced by detergent solubilisation of whole virions, followed by purification and mixture with phospholipids (lecithin and a small proportion of viral phospholipids). About 70% of the virosome is made up of phosphatidylcholine, while the rest is derived from the original viral envelopes which carry the antigenic surface proteins HA and NA. The virosomes enter antigen-presenting cells in a way similar to natural infection by influenza viruses: HA-mediated endocytosis, conformational change of HA in endosomes, fusion of the virosome membrane with the endosomal membrane, and presentation of antigens to major histocompatibility complex (MHC) class I and II molecules. This more natural means of antigen presentation and concomitant activation of MHC class I and II pathways accounts for the excellent immunogenicity of the vaccine. The vaccine (Inflexal V; Berna Biotech, Bern, Switzerland) is free from preservatives and detergents and has a lower level of ovalbumin than conventional vaccines (Table 2[11-14]). The virosome subunit vaccine is as immunogenic as conventional vaccines but with a substantially lower incidence of local adverse events.[15]

Chemical contents and impurities

Different preparations of vaccines show remarkable variations in their chemical composition (Table 2). The subunit vaccines generally have a lower total protein content than split-virion vaccines. However, this lower protein content does not always equate with higher purity, as some subunit formulations have a substantially higher egg protein content than comparators. The amount of non-viral components (eg endotoxin, ovalbumin) in the vaccine may be related to the adverse reaction profiles. In this regard, the IRIV vaccine has the lowest non-viral component content.

Other vaccine excipients

Aminoglycosides, formalin or β-propiolactone may be present in vaccines but are generally reduced to trace quantities or below detection limits. Thimerosal (a mercurial compound) is commonly used as an antimicrobial and preservative in many vaccines, especially in multi-dose vials (often at a concentration of 25 μg per 0.5 mL dose). It may be present in trace amounts in some preparations.

Schedule and route of administration

The usual vaccination regimen is one yearly dose to be given at least 1 to 2 months prior to the expected onset of the influenza season. Two doses are given 1 month apart for children under 9 years if they have not been vaccinated previously. The recommended route of administration for inactivated vaccines is intramuscular injection, usually in the deltoid for adults. FluMist is administered as a nasal spray. Prior to the licensing of FluMist, another nasally administered trivalent inactivated vaccine consisting of virosomes (Nasalflu; Berna Biotech, Bern, Switzerland) had been marketed in Switzerland since 2000.[16] This vaccine was withdrawn from the market in 2001 because of a possible association with facial paralysis.

Choosing individual preparations of influenza vaccine

All currently available vaccines have comparable efficacy and adverse reaction profiles when properly administered and if they match the circulating viral strains.[17] Therefore, if a specific preparation is to be chosen, other factors need to be taken into account. Cost is an important consideration, especially in bulk purchasing for large organisations or health authorities. For the individual, one needs to consider the presence of excipients to which they may be allergic, the chemical composition of individual preparations (especially the content of non-viral components and endotoxin, and the presence of preservatives), the relative frequency of adverse reactions, underlying medical conditions which preclude the use of live attenuated vaccines, and the preferred route of administration, if intranasal vaccines are available locally.

Adverse reactions to vaccination

The most common adverse events to inactivated influenza vaccines are local inflammatory reactions such as pain, erythema, and induration. These occur

Table 1. Properties of some currently available influenza vaccines

Trade name	Manufacturer	Registration in Hong Kong[3]	List price* (HKD per 0.5 mL dose)[4]	Type of vaccine
Agrippal S1	Chiron	Yes	35	Subunit, inactivated
Fluad	Chiron	Yes	Not available	Subunit, inactivated
Fluarix	GlaxoSmithKline	Yes	148	Split-virion, inactivated
Fluvax	CSL	Yes	75	Split-virion, inactivated
Inflexal V	Berna Biotech	Yes	108	Virosome subunit, inactivated
Influvac	Solvay	Yes	70	Subunit, inactivated
Vaxigrip	Aventis Pasteur	Yes	58	Split-virion, inactivated
FluMist	MedImmune	No	Not available	Live attenuated

* Actual price may differ; information from Drug Education Resources Centre, Society of Hospital Pharmacists of Hong Kong
† Information from package insert of the vaccines and Drug Education Resources Centre, Society of Hospital Pharmacists of Hong Kong

Table 2. Comparison of the chemical composition of some influenza vaccines*

Trade name	Type of vaccine	Haemagglutinin protein content (μg per 0.5 mL dose)	Haemagglutinin titre	Neuraminidase activity (mU per 0.5 mL dose)
Agrippal S1	Subunit	58	1:6400	0.4
Begrivac	Split-virion	38	1:6400	0.5
Fluarix/Influsplit	Split-virion	56	1:6400	0.6
Fluvirin	Subunit	37	1:400	-
Inflexal V	Virosome subunit	-	-	-
Influvac	Subunit	33	1:12 800	1.5
Vaxigrip	Split-virion	45	1:12 800	0.5

* Data for vaccines other than Inflexal V are from Chaloupka et al[12]; data for Inflexal V are from Mischler and Metcalfe[11]
† Upper limits for inactivated split-virion and subunit vaccines for ovalbumin, <1 μg per human dose; bacterial endotoxin, <100 IU per human dose[13,14]; upper limit of ovalbumin for virosome vaccine (Inflexal V), <50 ng per human dose[14]

in up to 65% of recipients and are usually mild and self-limiting, lasting for 1 to 2 days. Systemic reactions including fever, myalgia, arthralgia, and headache may appear 6 to 12 hours after vaccination and last for 1 to 2 days. They occur at a frequency of 1% to 5%. Treatment is usually not necessary. Oral paracetamol may be used if symptoms are severe. Subunit vaccines (with the exception of the MF59-adjuvanted vaccine) have a significantly lower incidence of local and systemic reactions compared with split-virion and whole-virus vaccines.[17]

An unusual complication of inactivated influenza vaccination is the oculo-respiratory syndrome (ORS), first described in Canada in the 2000 to 2001 season, with 960 cases reported at that time.[18] Symptomatology of ORS includes respiratory symptoms (84%; cough, dyspnoea, chest tightness, wheezing, etc), ocular symptoms (55%; bilateral red eyes, discharge, itchiness, pain, blurred vision), oedema (33%; palpebral, mouth, lips, tongue, facial), and systemic upsets (fever, myalgia, headache, fatigue, chills, gastro-intestinal problems).[19] The syndrome lasted for 48 hours or less in 69% of cases, 3 to 7 days in 22%, over 1 week in 8%, and over 1 month in 3%.[19] Antihistamines were used by some patients for symptomatic control. The syndrome was associated with one particular preparation of split-virion vaccine (Fluviral S/F; Shire Biologics, Ville St Laurent, Quebec, Canada) which accounted for 96% of cases. Electron microscopy of Fluviral S/F showed that 13% to 33% of the virions were unsplit, compared with a figure of 2% for contemporary vaccines.[20] The unsplit virions formed large aggregates, believed to be the cause of the syndrome. Recurrence of ORS on subsequent influenza vaccination can occur but symptoms of recurrence noted have been mild and did not preclude further influenza vaccination.[20] It seems that

Growth substrate	Adjuvant	Recommended route of administration	Thimerosal†	Other excipients listed (other than buffers and salts)†
Eggs	Nil	Intramuscular	0.5 μg/dose	Not listed
Eggs	MF59	Intramuscular	Not listed	Formaldehyde, cetyltrimethyl-ammonium bromide, sucrose, kanamycin, neomycin
Eggs	Nil	Intramuscular	Residual amount	Formaldehyde, gentamicin, Tween 80, octoxynol 9, sucrose, sodium deoxycholate
Eggs	Nil	Intramuscular	Not listed	Neomycin, polymyxin, sucrose, sodium taurodeoxycholate
Eggs	Immunopotentiating reconstituted influenza virosomes	Intramuscular	Nil	Lecithin
Eggs	Nil	Intramuscular	Nil	Not listed
Eggs	Nil	Intramuscular	2 μg/dose	Triton X-100, sucrose, neomycin, formaldehyde (≤30 μg)
Eggs	Nil	Intranasal spray	Nil	Not listed

Neuraminidase/ nucleocapsid protein content (μg per 0.5 mL dose)	Matrix protein content (μg per 0.5 mL dose)	Viral protein per total vaccine protein (%)	Ovalbumin content† (ng per 0.5 mL dose)	Endotoxin content† (IU per 0.5 mL dose)
-	-	81	35	<0.5
18	1	80	11	1.0
27	6	89	10	<0.5
4	-	88	10	4.6
-	-	-	1.85	0.55
-	-	61	325	0.9
22	7	80	11	64.0

complications compatible with ORS may have occurred in Europe and the United States in the 1990s.[21]

Guillain-Barré syndrome (GBS) is one of the more serious, though rare, potential adverse reactions following influenza vaccination. The association was first noted in 1976 to 1977, with a relative risk ranging from 3.96 to 7.75 for the 6-week period following vaccination.[22] The relative risk ranged from 0.6 to 1.5 in the seasons from 1978 to 1979 and 1993 to 1994.[23,24] The incidence of post-influenza vaccination GBS appeared to have a decreasing trend in the United States from 1993-1994 (1.7 per million vaccinations) to 2002-2003 (0.4 per million vaccinations).[25] Autoimmune damage induced by endotoxin or other cellular components of bacteria (eg *Salmonella* and *Campylobacter* which also have a zoonotic reservoir in poultry) and egg proteins have been postulated to contribute to the development of GBS.

Intranasal administration of influenza vaccines is generally well-tolerated. FluMist has been associated with an increased risk of asthma in young children aged 18 to 35 months.[26] Other studies in older children with stable moderate-to-severe asthma have not shown significant worsening of asthma, however.[27] Use of CAIV-T in patients with asthma should be avoided for the time being. Musculoskeletal pain, lymphadenopathy, otitis media with effusion, rhinorrhoea, and nasal congestion have occurred following the use of FluMist.

Efficacy of vaccination

Outcome measures used in different vaccine efficacy studies have varied widely. Parameters measured have included serological- or culture-confirmed cases of influenza, influenza-like illness, influenza-related hospitalisations, complications, or deaths. In general,

Table 3. Summary of meta-analyses and reviews on influenza vaccine efficacy studies

Population	No. of clinical trials reviewed; years conducted	Outcomes: efficacy (95% confidence interval)	Other findings (95% confidence interval)
Healthy children, aged ≤18 years[28]	13; 1985-2001	Culture-confirmed influenza: 74% (57-84%) Serologically confirmed influenza: 59% (43-71%) ILI*: 33% (29-36%)	No difference in efficacy between inactivated vs live attenuated vaccines: Culture-confirmed influenza: 65% (45-77%) vs 80% (53-91%) Serologically confirmed influenza: 63% (43-76%) vs 54% (20-74%) ILI: 33% (22-42%) vs 34% (31-38%)
Healthy adults[29]	39; 1966-1995	Inactivated vaccines ILI: 24% (15-32%) Serologically confirmed influenza: 68% (49-79%) Live attenuated vaccines ILI: 13% (5-20%) Serologically confirmed influenza: 48% (24-64%)	-
Elderly, aged ≥65 years; mean or median age, ≥80 years[30]. All studies except one involved institutionalised elderly patients	20; 1968-1989	ILI: 56% (39-68%) Pneumonia: 53% (35-66%) Hospitalisation: 48% (28-65%) Death: 68% (56-76%)	No significant difference in efficacy when the epidemic strain was a drift variant from the vaccine strain
Elderly, aged ≥65 years, living in the community[31]	15; 1965-1996	ILI: 35% (19-47%) Hospitalisation: 33% (27-38%) Death: 47% (25-62%)	-

* ILI influenza-like illness

higher vaccine efficacy has been seen when more specific outcomes (eg laboratory-confirmed cases of influenza) are measured. Vaccine efficacy, as determined by several large meta-analyses, is summarised in Table 3.[28-31] The level of protection achieved is also higher when the vaccine strains match the prevailing epidemic strains of viruses.[29]

At 7 days' post-vaccination, 59% to 100% of recipients have been shown to have developed protective levels of antibody, with the antibody titre peaking between day 14 and 21.[32] At 280 days' post-vaccination, 71% to 100% of recipients still had protective antibody titres. Levels of antibody and duration of protection wane with time at variable rates. In otherwise healthy young adults, protection lasts for more than 1 year, with a 68% to 75% reduction in laboratory-confirmed influenza infection observed 1 year after vaccination.

Influenza vaccination: controversies and policies

Could vaccines be administered by other routes?

The subcutaneous route may be more reactogenic and less immunogenic than the intramuscular route but current evidence is inconclusive.[33] Patients receiving anticoagulant therapy had been given intramuscular vaccination without an increased incidence of haemorrhagic complications.[34] The intradermal route was recently re-examined as an alternative in two studies which employed different vaccine preparations.[35,36] Kenney et al[35] used one fifth of the dose (0.1 mL) of a standard inactivated vaccine (Fluvirin; Evans Vaccines, Liverpool, UK) in a population aged 19 to 41 years. Belshe et al[36] used a specially prepared formulation which contained 40% of the usual intramuscular dose in 0.1 mL volume. This study population included subjects of over 60 years of age. In both studies, immunogenicity was similar for both intramuscular and intradermal routes, but local reactions were significantly more common after intradermal injection. The intradermal route has been shown to be a viable and valuable alternative to other parenteral (mainly intramuscular) routes of vaccination, most notably in the case of rabies vaccines,[37] in which substantial cost-saving can be achieved in resource-limited situations without compromising vaccine efficacy. Intradermal injection, however, requires a higher level of technical compe-

tence for administration than the intramuscular route. If the efficacy of intradermal vaccination is confirmed by future studies, its dose-sparing property could be a major benefit, especially in pandemic situations or at times of vaccine shortage.

Are booster doses of value in the elderly?

Elderly people (≥65 years) are commonly believed to respond less well to influenza vaccination than younger adults. However, a poorer antibody response in the elderly has not been universally observed.[38] An extensive review of studies has failed to show a significant inferiority of immune response among the elderly following influenza vaccination, but a tendency to better response in the younger population was observed.[39] The use of a booster dose or a double-dose of vaccine has been trialled in the elderly. The effectiveness of these approaches was again conflicting, with variable degrees of augmentation of the immune response being observed.[40-43] It is difficult to recommend such approaches in general because it is impossible to predict who may benefit from a booster. In addition, a routine booster dose would entail a substantial increase in the demand for vaccines.

Does vaccination work in immunocompromised individuals?

Individuals with chronic medical conditions may respond less favourably to influenza vaccination. Patients on haemodialysis, for example, were shown to develop a lower post-vaccination antibody titre than healthy controls, but still had a 23% to 44% response rate and a 46% to 87% protection rate after vaccination.[44] A booster dose 8 weeks later was shown to increase the response and protection rates slightly but is not generally recommended. Patients with diabetes likewise have a lower response rate but similar post-vaccination protection rates when compared with healthy controls.[45]

In HIV-infected individuals, the CD4 count generally correlates with the response to the vaccine; patients with CD4 counts of less than 100×10^6 /L were shown to have severely impaired antibody responses which were not improved by booster doses.[46] For transplant recipients, lower seroconversion and protection rates are commonly observed.[47] In bone marrow transplant recipients, vaccine responsiveness is usually restored at 2 years post-transplant, unless there is concomitant graft-versus-host disease. Among solid organ transplant recipients, recipients of a renal transplant (43-58%) appeared to have a higher seroconversion rate compared with recipients of heart (21-53%), lung (0-13%) or liver transplants (15-31%).[48]

The safety of CAIV-T in pregnant women and in immunocompromised individuals requires further study, although it has been given to apparently healthy HIV-infected patients without significant adverse effects.[49] The latest guideline from the United States Centers for Disease Control and Prevention (CDC) recommends against the use of CAIV-T in a number of patient groups including patients with asthma, reactive airway diseases, other chronic pulmonary and cardiovascular diseases, underlying medical conditions such as diabetes mellitus, renal dysfunction, or haemoglobinopathies, and individuals with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies. Additional groups are children or adolescents receiving aspirin or other salicylates (Reye's syndrome is associated with wild-type influenza infection), individuals with a history of GBS, and pregnant women.[50]

Does thimerosal in vaccines pose any health risk?

The use of thimerosal has raised safety concerns, especially in relation to use in children and infants. There is currently no evidence for a causal relationship between exposure to thimerosal in vaccines and adverse health effects, with the exception of the rare occurrence of hypersensitivity reactions.[51] Nevertheless, there have been moves towards the use of 'preservative-free' (<1 μg thimerosal per 0.5 mL dose) influenza vaccines in some countries.[50]

Can patients with egg allergy be vaccinated?

The main absolute contra-indication is an anaphylactic reaction towards the vaccine. Anaphylactic reactions towards aminoglycosides, latex, and thimerosal are theoretical risks but these have not been reported in association with influenza vaccines. Thimerosal allergy may present as delayed-type or immediate (IgE-mediated) hypersensitivity reactions, with the former being more common.[52] Patch tests and intradermal tests to thimerosal could be performed but these are considered to be poor predictors of the likelihood of reaction to thimerosal-containing vaccine.[52]

The egg protein content of available influenza vaccines has been reported to vary from 0.02 to 42 μg/mL.[53,54] Egg-derived vaccines, such as the measles-mumps-rubella vaccine, have been given to children with severe egg allergy without adverse reactions.[55] Influenza vaccines could also be administered to these children safely, including some with anaphylactic reactions to eggs.[53] A skin patch test to egg and skin testing of influenza vaccine could be performed. Those found to have a positive skin test towards the influenza vaccine could then

either opt for chemoprophylaxis (if necessary), to receive the usual regimen for influenza vaccination under specialist supervision, or to undergo a desensitisation protocol.[54] Cell culture–derived vaccine will be an alternative in the future.

General policies for influenza vaccination

Vaccination programmes usually attempt to achieve three objectives—individual protection (eg to prevent the disease and its complications in high-risk individuals), prevention of institutional outbreaks of the disease which may in turn affect high-risk patients and staff (eg immunisation of health care workers and residents of long-term care facilities), and reduction of the burden of disease in the community setting as a public health measure (eg vaccination of young children). These objectives are reflected in the target groups specified in various national guidelines. In most guidelines, the key target groups include:

(1) elderly people, usually defined as persons aged 65 years and above (in the United States in 2000, this age limit was reduced to above 50 years);
(2) residents of long-term care facilities;
(3) adults and children suffering from chronic diseases including respiratory, cardiovascular, metabolic, or renal diseases; haemoglobinopathy, or immunosuppression;
(4) children receiving long-term aspirin therapy (in order to minimise the risk of Reye's syndrome);
(5) pregnant women; and
(6) health care workers and workers in long-term care facilities.[50]

Vaccination of health care workers has been shown to be associated with a significant decrease in patient mortality.[56] Since 2004, young children aged 6 to 23 months have also been included as a target group for influenza vaccination by the CDC.[50]

Although influenza vaccination is effective in the prevention of infection, routine yearly vaccination of all otherwise healthy adults has not been deemed cost-effective.[57] In addition to the limitation in the supply of vaccines to achieve such a goal, studies have not been able to show benefits of such an approach in significantly reducing the spread of the disease, the economic loss (as measured by working days lost; only minimal reductions were demonstrated), and in reducing morbidity and hospitalisation (likely to be related to the lower complication rates in this population compared with the elderly). It was therefore suggested that the limited resources available should not be directed toward mass vaccination for public health reasons, although the vaccine may still be offered to individuals for individual protection.

Vaccination recommendations in Hong Kong

The target groups for influenza vaccination in Hong Kong presently include elderly people living in residential care homes, residents of institutions for the disabled, elderly people aged 65 years or above, those with underlying medical conditions (similar to CDC recommendations), health care workers, children aged 6 to 23 months, and poultry workers.[58]

Farmers and workers in the poultry industry represent a special target group in high-risk areas for avian influenza, including Hong Kong.[59] This issue was raised following the latest avian influenza epidemic in Southeast Asia that started in late 2004. Vaccination against human influenza, though not protective against avian strains of the virus, has the theoretical benefit of reducing the chance that these individuals will be co-infected with an avian and a human virus, thereby allowing genetic reassortment to occur.

Improving influenza vaccine coverage

Although influenza vaccination has proven clinical and epidemiological benefits, its uptake in the general population and among health care workers has generally been suboptimal. In the United States, the vaccination rate among health care workers was 10% in 1989, 34% in 1997, and 40% in 2003. The vaccination rate in other target groups is also below 50%.[60] Common reasons for non-uptake include concern about side-effects, doubts regarding the efficacy of the vaccine, perception of seriousness of influenza, the individual's health, and lack of information from general practitioners. An educational campaign alone does not improve vaccination uptake significantly.[60] Other measures, such as a 'mobile cart programme', using vaccine days in institutions, peer vaccination, and the use of gift incentives, have been used with some success.[60-62] A better understanding of the knowledge, attitudes, and behaviour of target groups, as well as novel approaches to programme delivery is necessary to improve vaccine uptake. In the community setting, the perceived ineffectiveness is best exemplified by reports of influenza outbreaks in residential homes for the elderly in Hong Kong during the last influenza season in 2004 to 2005, despite a territory-wide campaign by the Department of Health to vaccinate this target population. The degree of match between

vaccine strains of viruses and circulating strains could partly explain the occurrence of these outbreaks.

On a broader perspective, health-care policy makers need to develop locally relevant and practical vaccination policies. An example would be the vaccination of poultry workers in places where avian influenza is endemic. Health authorities should ensure that vaccine supplies are adequate for target populations, especially in unexpected situations where overall vaccine shortage is imminent.[63] The logistics of vaccinating target groups (in the community and health care institutions) should be well planned, taking into account contingency measures during pandemic situations. The government's preparedness plan for an influenza pandemic is a good example of this process in action.[64] Frontline doctors and health care workers should realise the importance of being vaccinated, not only for personal protection, but also for the protection of patients. In addition, those working in primary care could further promote vaccine uptake in the community by providing adequate information and provision of vaccination, especially to at-risk populations.

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