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Influenza Vaccinations
Who Needs Them and When?

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Abstract

Influenza vaccination programmes should aim at reducing the burden from influenza among those who need it most. The primary aim of this literature review is to identify who should receive priority in influenza vaccination programmes. Risk factors for severe post-influenza complications include immune-related factors, such as ageing or the presence of immune-suppression, respiratory tract disease, proneness to exacerbation of concomitant high-risk disease, potential adverse effects associated with long-term drug use or residence in closed communities with high transmission rate.

When given annually in autumn, inactivated trivalent influenza vaccines can reduce severe complications from influenza among persons aged 65 years or older by 30–60%. Among children aged less than 7 years, notably those with asthma, the occurrence of otitis media or acute respiratory disease is reduced by 20–75% with vaccination. In addition, vaccination of residents of long-term care facilities and their personnel leads to a 42% reduction in mortality among patients. However, uncertainty remains about whether influenza vaccination can reduce complications from influenza among the large group of older children and persons of working-age with high-risk disease.

To further increase the impact of prevention strategies, the development and application of clinical prediction rules to estimate absolute risks of post-influenza complications should be studied in relation to optimal vaccine delivery strategies. Furthermore, adequately powered studies should be conducted to demonstrate possible effectiveness of vaccination in reducing post-influenza complications among older children and working-age adults.

Uncomplicated influenza illness can be associated with severe respiratory symptoms and malaise, disrupt daily life for several days and lead to work loss. However, from a societal healthcare point of view, severe influenza-related morbidity and mortality have traditionally been the main focus of prevention.[1] The occurrence of post-influenza complications is common during influenza epidemics, notably of type-A(H3N2) influenza.[2] Influenza can cause direct and related complications, such as fatal and non-fatal primary viral or secondary bacterial pneumonia,[3] otitis media,[4] sinusitis,[4] exacerbations of chronic pulmonary disease,[5] congestive heart failure,[1,6] myocardial infarction[7,8] and events associated with diabetes mellitus.[9,10] Consequently, in temperate climate countries these complications are responsible for millions of primary care visits, hundreds of thou-

sands of hospitalisations and tens of thousands of deaths; hence, influenza continues to impose an enormous health economic burden on society.[11]

Prevention by vaccination should aim at reducing the burden of post-influenza complications among persons who need it most.[1] This report summarises the current scientific literature on prognostic factors and clinical benefits of influenza vaccination. It is well known that the attitude of the physician and patient towards these issues are important predictors of compliance with immunisation recommendations.[12] Using an extensive search of Medline, Embase and the Cochrane Collaboration in the period 1970–2001, we aim to give clear answers to the question: who should receive priority in influenza vaccination programmes and when vaccines should be administered? Moreover, gaps in scientific evidence on these issues are identified.

1. Clinical Prediction of Post-Influenza Complications

An individual's risk of developing post-influenza complications is determined by many factors simultaneously.[13] Among the general immune-related host factors, age most clearly is an important determinant of severe post-influenza complications.[14] Infants and preschool children at the one end and persons aged 65 years or older at the other end of the age spectrum clearly are at increased risk for post-influenza complications. This is at least partly attributable to a developing or impaired T- or B-cell response. In addition, the presence of immunosuppressive disease, such as HIV/AIDS, (haematological) cancer or renal disease, and the use of immunosuppressive drugs, for example in organ transplants or cancer, put patients at increased risk.[15,16] The most important organ-specific prognostic factor includes the presence of chronic disease of the respiratory tract, such as cystic fibrosis, asthma, chronic obstructive pulmonary disease (COPD) or lung cancer.[14,16,17] Respiratory viruses such as influenza can increase the airway responsiveness or inflammation, and alter neural control mechanisms and small airway geometry.[18] Hence, bacterial super-infection is common in these individuals, although most complications from influenza occur among patients of older age.[17,19] Another factor is proneness to exacerbation of underlying chronic metabolic or cardiovascular disease, mainly associated with ageing, including diabetes or renal disease and congestive heart failure or coronary heart disease.[14,20] Less common, the potential of severe adverse effects coinciding with long-term drug use is a prognostic factor. For example, children who are receiving long-term aspirin therapy are at increased risk for Reye's syndrome after influenza infection, although this is a very rare condition.[20] In addition, women who are in the second or third trimester of their pregnancy during the influenza period can be at increased risk for hospitalisation or death during influenza epidemics, although firm evidence to support this is lacking.[21]

Among the most important external factors, a high transmission or contact rate increases the chance of having an influenza infection. Day care centres for children,[22] schools,[23] hospitals[24] and long-term care facilities[25] are all closed communities in which, if influenza is introduced, the spread of the virus can be fast and complete. However, post-influenza complications are most common in healthcare facilities because their residents have other prognostic host factors.

To increase the impact of influenza prevention programmes both clinical priority setting and optimal vaccine delivery strategies need to be balanced.[26] A clinical prediction rule estimating an individuals absolute risk of developing post-influenza complications based on a patient profile can be used to set priorities for preventive and therapeutic measures, including vaccination and disease monitoring. In our opinion, these rules are also especially useful in case of influenza pandemics or vaccine shortage.[1] Clinical prediction rules have already been developed for patients with pneumonia.[27,28] However, these rules can not merely be applied to predict post-influenza complications, partly because the endpoints studied were not confined to influenza epidemics and some predictors,

particularly laboratory tests, can not easily be assessed. A milestone influenza study by Barker and Mullooly[14] showed a clear difference in absolute influenza-related mortality rates between patients with or without high-risk disease of several age groups. In that study, patients aged between 45 and 64 years with two or more high-risk diseases (377 deaths per 10 000) and elderly (≥65 years) with one or more high-risk diseases (157 and 615 deaths per 10 000, respectively) were at increased risk compared with individuals without such disease (<10 deaths per 10 000). To our knowledge, no published study addressed the question of how to distinguish low- from high-risk individuals with regard to the development of the full range of post-influenza complications given their individual patient profile.

Although prediction rules might enable further refining of the target population, a prerequisite is that clinical information is available to apply the rule and set up an efficient vaccine delivery strategy. Importantly, refining the target group might negatively influence compliance to vaccination recommendations. Honkanen et al., for example, observed higher vaccination rates among elderly in an age-based strategy compared with a risk-based strategy, although their study was not adequately designed.[29] Therefore, more research is needed to study the relationship between the use of prediction rules, compliance to vaccination and impact of the prevention strategy.

2. Influenza Prevention

So far, the main direct option for reducing post-influenza complications is immunoprophylaxis with conventional trivalent inactivated (i.e. killed-virus) vaccine.[30] Most of these vaccines are currently sub-unit or split vaccines. Since during influenza seasons both A- and B-type strains circulate, the WHO each year recommends trivalent vaccines based on worldwide surveillance of prevalent strains. Other options include immunoprophylaxis with intra-nasally administered cold-adapted live-attenuated influenza virus vaccines,[31] and use of antiviral drugs such as amantadine and rimantadine, or zanamivir and oseltamivir. The first two antiviral drugs are effective against influenza A only.[32] Treatment with zanamivir[33,34] or oseltamivir[35] reduce the course of influenza infection by 1–1.5 days. Preventive use of these latter neuraminidase inhibitors reduce the occurrence of influenza illness by 30–89%,[36-38] similar to the effects of the conventional influenza vaccination in healthy individuals.[39] However, antiviral drugs can cause considerable adverse effects and are costly. Importantly, as of yet it is not known whether these drugs prevent complications from influenza.

2.1 Influenza Vaccine Efficacy and Effectiveness

In general, epidemiological studies on the impact of vaccines distinguish two measures: vaccine efficacy and vaccine effectiveness. Vaccine efficacy is commonly calculated from pre-marketing, randomised, double-blind, placebo-controlled, clinical trials. The most frequently used clinical endpoints in these trials are post-vaccination protective antibody titres as a measure of indirect protection or influenza infection rates as a measure of direct protection. Study populations include healthy individuals and sometimes patients of a selected low-risk category. In these influenza vaccine trials, more than 70% of vaccinated children and young adults developed protective antibody titres against influenza with strains similar to vaccine components.[39-41] Some studies suggest that elderly persons[42] and patients with certain chronic diseases[43,44] may develop lower titres. Only one randomised placebo-controlled trial has been conducted to establish clinical direct effects of vaccination among healthy elderly people.[45] In this Dutch study by Govaert et al. the vaccine appeared to reduce the incidence of serologically confirmed influenza by 50%.

The overall protective clinical effect on reducing post-influenza complications in routine medical practice is defined as vaccine effectiveness.[2,6,19] Influenza vaccine effectiveness is the result of both the vaccine's direct effect, which

refers to the ability of the vaccine to protect the individual against complications, and the indirect effect, which refers to reduction of the spread of influenza in the population. This latter effect is one of the reasons to vaccinate individuals in closed communities such as nursing homes,[25] healthcare institutions[24] and day-care for children.[22] A key element is the compliance with vaccination recommendations. To maximise a programme's effectiveness in terms of absolute reduction of influenza-related morbidity and mortality in the target population, compliance with the preventive measure should be optimal. Essential elements to increase uptake with the vaccine are the physician and patients beliefs towards risks of influenza and benefits of the vaccine.[12] Vaccine effectiveness can be estimated using post-marketing observational study designs including cohort and case-control studies incorporating clinical endpoints relevant to the individual patient. In general, vaccine effectiveness in percent is given by 1–relative risk reduction × 100 in clinical trials and cohort studies or 1–odds ratio × 100 in case-control studies.[46] However, potential 'confounding by indication', that is, the natural presence of differences in risk between the vaccinated and unvaccinated groups, should be sufficiently controlled for in these studies.[46]

In contrast to the scarcity of large, randomised, placebo-controlled trials with clinically relevant endpoints such as post-influenza complications, there are many published non-experimental studies on influenza vaccine effectiveness. Gross et al. have summarised the results of 20 cohort studies carried out among the elderly.[47] The pooled estimates of vaccine effectiveness were 56% (95% CI 39–68%) for preventing respiratory illness, 53% (95% CI 35–66%) for preventing pneumonia, 50% (95% CI 28–65%) for preventing hospitalisation and 68% (95% CI 56–76%) for preventing death. However, all except one included study consisted of institutionalised patients. One of the key studies on the vaccine's effectiveness on severe endpoints among non-institutionalised seniors was a serial prospective cohort study by Nichol and colleagues.[6] In this study, more than 25 000 elderly were followed up using medical databases during three consecutive influenza periods. The overall vaccine effectiveness in reducing the incidence rates of death or hospitalisation for pneumonia or influenza appeared to be between 48 and 57%, respectively. In a case-control study, Fedson and colleagues observed reductions in hospitalisations for pneumonia or influenza and death of approximately 30% among adults of whom more than 70% were elderly.[48] Furthermore, Ahmed and colleagues estimated a 42% reduction in mortality from all causes in a case-control study among individuals aged 16 years or older, mostly elderly.[49] Most subsequent studies among the elderly confirmed the vaccine's effectiveness in reducing serious complications, such as need for hospitalisation for influenza or pneumonia, or death, with estimates varying from 30 to 60%.[2,50,51] Importantly, the vaccine's effectiveness in reducing these severe complications among non-institutionalised, community-dwelling seniors is not substantially modified by the presence of underlying disease.[2,52] Even among patients with HIV and elderly with immune-suppression, the vaccine yields substantial benefit.[53] In addition, several studies in countries with different healthcare systems indicate acceptable cost-effectiveness of immunising elderly persons aged 65 years or over against influenza.[6,19,54,55]

Only few studies were carried out among children with chronic, high-risk disease, and they were small and often only covered one influenza season. In studies including infants and children aged under 7 years, the vaccine reduced the occurrence of episodes of otitis media by 40%[56,57] and the number of febrile influenza episodes among young asthmatics by 49%.[58] In a two-season, retrospective cohort study, Smits et al. showed that on average the occurrence of acute respiratory disease during an influenza epidemic among children with asthma aged under 7 years was reduced by 55%.[59] This confirmed earlier evidence by Bell et al. who observed a 66% reduction in hospitalisation rates

among vaccinated compared with unvaccinated young patients with asthma.[60]

From a primary care-based study, we know that approximately 40% of the total population recommended for vaccination according to the Dutch immunisation guidelines is of working-age.[26] Among healthy adults inactivated *parenteral* influenza vaccine reduces the occurrence of clinical influenza cases, which is an endpoint that is not the main focus of prevention in many countries.[61] However, reductions were small ranging between 13 and 24%, and time off work was reduced by only 0.4 days.[61] Among the large group of patients with high-risk disease under 65 years of age, most with asthma or COPD, such data are absent and, in the few available clinical studies, reductions in post-influenza complications, such as asthma exacerbations, by vaccination have not so far been demonstrated.[62]

2.2 Adverse Effects of Influenza Vaccination

The literature on the potential adverse effects of the influenza vaccine is vast. Local reactions such as soreness at the site of injection usually lasting about 2 days occur in approximately 10–64% of patients.[20] Severe systemic reactions may occur in patients who are hypersensitive to egg allergens, although in practice it is very rare. A recent trial by the American Lung Association Asthma Clinical Research Centers showed that inactivated influenza vaccine can be safely administered to adults and children with asthma, including those with severe asthma.[63] Although an association with Guillain-Barré syndrome has been put forward,[20] this risk, if present, is as low as one in a million. In summary, the conventional influenza vaccine may be considered 'safe', even in combination with routine child vaccinations or pneumococcal vaccines.[64]

2.3 When Should Influenza Vaccines Be Administered?

Influenza vaccination should be given annually in autumn (fall) since protection lasts between 4 and 6 months.[65] It has been suggested that vaccination in previous years reduces vaccine efficacy in the long-term. Beyer et al. performed a meta-analysis to determine whether the protection of influenza vaccine decreases when vaccination is repeated annually.[66] Ten trials with 5 117 observations could be subjected to meta-analysis. The pooled protection-rate difference was close to zero (1.1%; 95% CI –0.2–2.4%), thus detecting no difference between single or multiple vaccination. Hence, the data convincingly showed no evidence for a decreasing protection with annually repeated influenza vaccination. This was confirmed by a case-control study among the vaccine target group by Ahmed and colleagues who observed a higher reduction in mortality among those who were immunised in the previous year as compared to first vaccinations.[49] Therefore, influenza vaccination should be administered annually in populations at risk.

2.4 Recommendations for Influenza Vaccination

In most guidelines on influenza vaccination, individuals with at least one of the prognostic factors are recommended to receive the yearly conventional influenza vaccine in autumn (see table I).[67] In vaccination programmes both an age-based strategy in which all elderly, including in the US those 50 years or older, and a disease-based strategy, including all younger persons with one or more of the other host prognostic factors, have been implemented.[67] In addition, some countries include residents, personnel of health institutions and household members of at risk persons in their guidelines.[67] Given the available evidence, individuals over 65 years of age, including those in nursing homes, and preschool children with high-risk disease can benefit from vaccination and they should be strongly recommended for vaccination. Furthermore, in pandemic planning, it is essential to reach high inter-pandemic influenza vaccination rates among these individuals. Since the few data on the clinical effectiveness of influenza vaccination among adults of working age with high-risk disease do not indicate substantial benefit, we

Table I. Recommended groups for influenza vaccination[a]

Individuals at risk
All individuals who are 65 years of age or older[b]
Individuals of all ages with physician-diagnosed chronic respiratory disease (asthma, COPD, lung cancer, cystic fibrosis)[b]
Individuals of all ages with physician-diagnosed chronic metabolic disease (including diabetes mellitus), cardiovascular or renal disease, haemoglobinopathy, dementia or malnutrition[b]
Individuals of all ages who are immunocompromised (use of immunosuppressive medications, cancer or HIV/AIDS)[b]
Children under 18 years of age who receive long-term aspirin therapy[c]
Women in their second or third trimester of pregnancy during the winter[c]
Individuals transmitting influenza to high-risk individuals
Healthcare personnel of healthcare institutions, notably nursing homes and long-term care facilities[c]
Household members of high-risk individuals[c]

a On the basis of current recommendations of the US Advisory Committee on Immunisation Practices.[20]

b Most Western countries recommend these groups for vaccination.

c Only some Western countries recommend these groups for vaccination.

COPD = chronic obstructive pulmonary disease.

would not give high priority to this large group of individuals.

3. Conclusion

Inactivated, trivalent influenza vaccines can considerably reduce post-influenza complications among the elderly when given annually in autumn and vaccination programmes targeting these individuals are cost-effective. Among pre-school children, both healthy and those with asthma, the occurrence of otitis media or acute respiratory disease is reduced by vaccination. Presently, although healthy individuals of working-age might benefit from vaccination, there appears to be a lack of evidence for clinical benefit of vaccination among a large group of individuals of working age who are at high-risk, most with asthma or COPD.

The usefulness of further refining of the target population by application of clinical prediction rules in relation to optimal vaccine delivery strategies should be the focus of future study. Furthermore, large enough studies, preferably experimental, should be set up to demonstrate clinical effectiveness and cost-effectiveness of influenza vaccination among individuals of working-age.

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