REVIEW

Influenza vaccination in old age

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Abstract

Influenza is responsible for at least 3000–4000 deaths per year in the UK. During epidemics, death rates from pneumonia and influenza are much higher in elderly than younger people. With vaccination, the substantial medical and economic costs associated with influenza epidemics can be avoided. Countries with blanket vaccination have seen major reductions in morbidity and mortality. The vaccine is safe and effective in elderly people. Vaccination programmes for health-care workers who have contact with elderly people have also been shown to be effective in reducing deaths from influenza among this group.

Keywords: influenza prevention, influenza vaccination, old age

Introduction

During the past decade there has been growing recognition of the substantial medical and economic costs associated with influenza epidemics. Influenza causes a sharp increase in mortality and morbidity over a 6–8 week period each year, with at least 3000–4000 deaths in the UK. During epidemics, death rates from pneumonia and influenza are much higher in elderly people: Barker and Mullolay reported two deaths per 100 000 among healthy people under 65 compared with 797 per 100 000 in those over 65 with two or more high-risk conditions [1]. In major epidemics, over 20 000 excess deaths are recorded, as in 1989–90 in the UK [2]. Pandemics, by definition, cause very high morbidity and mortality; the 1918–19 pandemic is estimated to have caused about 40 million deaths world-wide.

The UK Department of Health recommends vaccination for those with chronic cardiac, respiratory or renal disease, immunosuppression due to disease or treatment, diabetes mellitus and those who are aged 65 years and over (revised in May 2000) or in long-stay residential care. The USA and 16 of the 25 European countries have also implemented blanket age-related vaccination of everyone over 65 irrespective of health status.

Virology of influenza

The three influenza virus types (A, B and C) are characterized essentially by differences in internal nucleoproteins. Influenza A viruses are further subtyped by differences in their surface glycoproteins, haemagglutinin (H) and neuraminidase (N), and the genes encoding them.

In the twentieth century, there were four pandemics caused by antigenic shift (a major change in H configuration with or without a concomitant change in N) producing a new subtype against which there is little circulating immunity. Pandemics are thought to originate in Southern China where ducks (the animal reservoir and breeding ground for new strains), pigs (thought to be the biological intermediate) and humans live in close proximity. Minor changes in viral antigenic configuration (known as ‘drift’) cause more circumscribed epidemics. The Hong Kong avian influenza virus [A/HK/156/97 (H5N1)] appears to be an example of a zoonotic infection with direct spread to humans.

Hospitalization of people over 65 occurs about 2 weeks after the peak in the general population, suggesting that children may be important disseminators of the virus [3]. Vaccinating children to reduce influenza in the community is currently under investigation [4].

Vaccination

Vaccine efficacy

New vaccine is needed each year because of viral antigenic drift. Based on global surveillance by the
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World Health Organisation, inactivated virus strains are used that are antigenically matched to the new strains expected to cause epidemics. Vaccination is recommended before the usual onset of influenza in the community (not generally earlier than mid-November in the UK).

Currently licensed vaccines consist of highly purified inactivated viruses in a trivalent preparation containing two type A strains and one type B. These cannot cause influenza and are safe but highly immunogenic, inducing immunity in 60–90% of children and adults. Immunogenicity is generally lower in elderly people but increasing the vaccine dose does not reliably improve the antibody response [5–7].

Pre-vaccination titres and the number of previous vaccinations have been identified as factors which markedly influence post-vaccination titres [8]. One or more vaccinations over the previous 4 years confers greater reduction in mortality (75%) than first-time immunization (9%) [9].

New vaccines

Live-attenuated vaccines are of potential interest in younger subjects, as better immunity is often produced. However in elderly people, local IgA and systemic IgG anti-haemagglutinin responses are low and relatively short-lived following live-attenuated compared with inactivated vaccine [10]. Limited studies in elderly people suggest possible benefit from a combination of inactivated and live attenuated vaccines [11]. Intranasal live vaccines have the advantages of eliciting a mucosal immune response, ease of administration and acceptability.

Adverse effects of the influenza vaccine

Inactivated influenza vaccine is generally well tolerated, but because egg is the medium for viral culture, this vaccine is contraindicated in people with egg allergy. The commonest side-effect in people over 60 is an acute local reaction, which occurs in about 1 in 3 subjects [12]. Under 1% have a mild systemic reaction consisting of fever with or without a flu-like illness. Guillain–Barré syndrome occurs in about 1 case per million [13].

Effectiveness of vaccination

Clinical effectiveness

Protection against influenza requires adequate antibody titres against the haemagglutinin antigen (serum titres > 1:40) and higher titres may be required in elderly people [14]. On the other hand, after vaccination, elderly people develop relatively low levels of both IgG and IgA antibodies, delayed peak antibody titres and shorter maintenance of titres [5, 6]. The strength of evidence for these findings is limited, however, by small sample size and confounding factors such as previous vaccination status and exclusion of immunosuppressed subjects from studies [15].

In healthy working adults in North America, vaccination was associated with fewer episodes of upper respiratory illness, days of sick leave and visits to their family doctor [16, 17]. In elderly people, immunization was cost-effective and associated with reduced rates of hospital admission and influenza-related deaths [16]. People over 65 living in the community were assessed for vaccination rates and the occurrence of influenza and its complications in three successive seasons from 1990 to 1993 [17]. Each cohort included over 25000 individuals and immunization rates were 45–58%. Vaccination was associated with fewer hospitalizations for influenza, pneumonia and cardiac failure during 1991–2 and reduced mortality for all causes in all three seasons.

Case–control studies have also shown that vaccination of elderly people in long-term care in North America is associated with decreased risk of pneumonia and death [18]. A randomized double-blind placebo-controlled trial assessed the efficacy of influenza vaccine in over 1800 elderly people in the community in 1991/2 [19]. The incidence of serological influenza was halved in those vaccinated, showing the efficacy of influenza vaccine in healthy elderly subjects as well as those with previous disease. This confirmed the findings of three earlier studies which demonstrated the efficacy of influenza vaccine in non-institutionalized elderly people [20–22].

An effective immune response can be mounted within 10 days of vaccination in those at high risk. Most develop protective antibody levels against influenza A and a substantially raised titre against influenza B [23]. This means that vaccination is still worthwhile even after an epidemic is established, but should not discourage established vaccination programmes at the beginning of winter.

Cost-effectiveness

Vaccination costs much less than all other preventative and therapeutic interventions for influenza. In one study, taking into account reductions in hospitalization for cardiac failure and all respiratory conditions, direct savings averaged $117 per person with cumulative savings of nearly $5 million [16]. US studies show that universal vaccination of elderly people saves money [24].

Medicare, the United States health insurance programme for people over 65, began to cover the cost of influenza vaccine in 1993 after a large-scale demonstration of its cost-effectiveness [25].

Adequate cost-effectiveness analyses have not been carried out in the UK. However, one study showed a reduction in nosocomial infections, which could represent an important cost saving in reduced
patient bed days (although a reduction in staff absences was not demonstrated) [26].

**Vaccination of health-care workers**

Vaccination of health-care workers is an additional strategy for reducing nosocomial transmission to patients. Serological studies show that clinical and subclinical infections may occur in up to 23% of health-care workers during influenza outbreaks. Staff have occasionally been identified as index cases in nursing-home outbreaks [27]. Outside the UK, many countries have a policy of staff vaccination, but there has been little investigation of the efficacy and benefits.

Most observational studies and a placebo-controlled trial have shown no reduction in illness or absenteeism among vaccinated health-care workers, possibly because of small numbers. In 12 long-term care facilities in Glasgow, a reduction in resident deaths from 17 to 10% was associated with vaccination of health-care workers [28]. However, there was no direct evidence that this was due to prevention of influenza.

A randomized, prospective, double-blind, controlled trial over 3 years showed serological evidence of vaccine efficacy to be 88% for influenza A and 89% for influenza B in young healthy health-care workers. However, there was no significant reduction in days of reported febrile respiratory illness or days of absence [29]. A recent study showed that vaccination of health-care workers conferred a marked reduction in mortality among patients, but virological surveillance revealed no associated decrease in non-fatal influenza [30]. Larger studies of health-care workers have demonstrated important reductions in illness, the costs of medical care, loss of earnings and work absence associated with influenza vaccination [17, 31].

Fear of injection side-effects and misconceptions about the vaccine largely account for the low uptake of vaccination among health-care workers [32].

**Uptake of vaccination**

Annual administration makes compliance a burden for patient and doctor. General practice policies and immunization rates vary widely. When influenza vaccination was surveyed in primary care in central southern England in 1998, national guidelines advised immunization only for people with specified high-risk medical conditions or living in care homes. At this time, 11.5% of a population of 2 million had been immunized, including 64% of those over 75 years [33]. Questionnaires from 47 of 60 nursing or residential homes in Carmarthenshire, UK, showed 81% of 1399 residents had received influenza vaccine in the winter of 1998/9. The vaccine was offered to 99% of residents and the commonest reason for non-vaccination was resident refusal [34].

There is considerable variability in policies for promoting influenza vaccination in long-stay facilities in England and Wales. In a study from Nottingham, 52% of residential and nursing homes operated a policy for influenza vaccination, but only 12% had a written policy and none set targets for vaccine uptake [35]. In South Wales, only 48% of patients aged >65 and hospitalized during December 1998 and January 1999 in a district general hospital received vaccination, but this was an improvement on previous figures [36]. Reasons given by those not vaccinated were lack of information from the general practitioner (26%), concern over safety (21%), perceived good health (16%) and doubt about vaccine efficacy (11%). In the USA, immunization may have attained the goal set by the Public Health Service for the year 2000 in certain groups (including 60% of those aged 65 years and over) [37].

Recommendations for improving uptake of influenza vaccination in elderly patients in hospital include inquiry about previous vaccination in routine history taking, targeting high-risk patients while they are in hospital and mentioning the need for vaccination in discharge summaries or clinic letters [38].

In the community, strategies to increase uptake include agreed written general practice policies, reminder letters to patients at high risk and in care homes, follow-up reminders to non-responders, regular vaccination sessions, home vaccination for immobile patients, reminders on repeat prescriptions and reminders for the doctor on daily appointment lists [39–41]. Sending a postal reminder about vaccination to healthy elderly people can produce high compliance [42, 43]. Most people would accept vaccine if offered and recommended by their doctors, but improvements in targeting and education are needed to achieve optimal coverage.

**Alternatives to vaccination**

The adamantanes (amantadine, rimantadine) have been approved for influenza A in some countries for decades, but are not widely used, primarily because of concerns about side-effects and development of viral resistance. They reduce viral shedding by inhibiting replication of influenza A and shorten the duration of symptoms if started within 48 h of the onset of influenza. Resistant viruses have been isolated from patients treated with either amantadine or rimantadine, and there is cross-resistance with these drugs [44]. However, the frequency of transmission of resistant viruses and their impact on efforts to control influenza are unknown. Rimantadine, which is not licensed in the UK, has similar efficacy but a better safety profile than amantadine. Amantadine is excreted renally and can cause neurological side-effects (including convulsions and hallucinations), particularly when renal function is impaired.

Zanamivir (Relenza) is the first specific inhibitor of influenza neuraminidase to be marketed. In cell culture,
it inhibits the growth of influenza A and B viruses. It is safe and effective in preventing influenza in healthy adults but there is no evidence that it prevents serious complications or reduces mortality in high-risk patients in ‘field conditions’ [45]. Currently there are studies in primary care to clarify the benefits, costs and unwanted outcomes.

Aims for the future include evaluation of the cost-effectiveness and equitable use of antiviral compounds and vaccines. Increased uptake in high-risk target groups is needed, as well as improved vaccine formulations. Better prevention will require identification of viruses with epidemic or pandemic potential by techniques such as molecular archaeology, the use of modelling techniques to examine spread, and increased animal and human surveillance.

Many high-risk elderly patients remain unvaccinated [36], and the immediate challenge is to improve the education of health-care professionals and the general public alike that the vaccine is safe, cheap and effective in order to improve uptake. Careful review of available data suggests that the benefits to healthy over-65s make vaccination a worthwhile intervention for them as well as for the previously recommended risk groups. National Health Service policy in the UK now sets a target of 70% uptake in people over 65 years old, with the aim of a minimum 60% uptake from 2000.

**Key points**

- Influenza vaccine is safe and effective in elderly people. It is also cheap.
- In countries with blanket vaccination, there have been major reductions in morbidity and mortality.
- Vaccination is still worthwhile after an epidemic is established, as an effective vaccine response can be mounted within 10 days.
- The risks of influenza and its complications are underestimated and improved education of healthcare professionals and the general public is required.
- The substantial medical and economic costs associated with influenza epidemics are potentially avoidable.

**References**

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