Influenza vaccines in adults

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Available influenza vaccines contain inactivated viruses, either whole or in parts, and are administered parenterally or intranasally. Their composition varies yearly because of viral antigenic shifts and drifts. Vaccines with a composition matching yearly World Health Organization recommendations are 72% [95% confidence interval (CI) = 54–83%] efficacious (prevention of influenza cases caused by influenza viruses A and B). Their effectiveness [capacity to prevent clinical influenza, or influenza-like illness (ILI)] is lower, at 37% (95% CI = 18–52%). A decision to vaccinate an adult population has to take into account the efficacy of the vaccines and their effectiveness (the likely proportion of ILI caused by influenza A and B viruses, amenable to prevention by vaccination), as well as costs and likely compliance. As the yearly levels of circulating A and B viruses are difficult to predict during the decision time for a vaccination campaign, there is a considerable element of uncertainty regarding the likely effectiveness of ‘this year’s’ vaccine.

Key words: Burden of influenza; Cochrane reviews; decision making; effectiveness and efficacy; healthy adults; influenza vaccines; prevention.

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Introduction

Vaccines against influenza A and B viruses have been available since the late 1940s and today are considered the mainstay of influenza prevention worldwide. The development of influenza vaccines was spurred by extensive trials by the US military during World War II. One of the first lessons learnt in these early trials was that vaccine performance depended on the closeness of the match between haemagglutinin (HA) and neuraminidase (NA) antigens of the current strain and those of the vaccine being tested [1].

Types of vaccine

Current influenza vaccines are of three types:

- Whole virion vaccines, consisting of complete inactivated viruses. These are not infectious but retain their strain-specific antigenic properties, thus enabling our bodies to build strain-specific immunity.
- Subunit virion vaccines, which are made of surface H and N antigens only.
- Split virion vaccines, in which the viral structure is broken up by a disrupting agent. These vaccines contain both surface and internal viral antigens.

Immunization is usually through a single i.m. or deep s.c. shot for adults and the elderly, or two shots with a 4- to 6-week interval in not previously immunized children aged <12 years. Inactivated and live attenuated vaccines for intranasal aerosol administration have also been developed. The first aerosol live cold-adapted vaccine (Flumist®; Aviron, USA) has completed phase 3 trials in healthy children and healthy adults, but has not yet been registered in the USA [2]. Cold adaptation limits the capacity of the seed virus destined for the vaccine to grow in tissues with temperatures >32–33°C. Thus, vaccine viruses grow in the nasal mucosa, stimulating local and systemic immunity, but cannot infect the lower airways or other parts of the human body. Genetic reassortment allows the insertion of HA and NA genes of the annual World Health Organization (WHO) recommended strain. Intranasal cold-adapted live attenuated vaccines may in the future provide a simple and effective route
to the immunization of whole populations by the minimization of local reactions to the vaccine (such as tenderness at the site of injection). These affect compliance, especially in the paediatric age groups, which plays an important part in viral transmission. However, the licensing and availability of attenuated vaccines will have to be subordinated to their safety assessment, as concerns over their potential interaction with wild-type non-human strains and their antigenic purity have not been fully assessed yet [2]. Readers can access http://www.fda.gov or http://www.aviron.com for the latest news on the development of Flumist.

The procurement cycle

Influenza vaccines are produced by a variety of public and private manufacturers worldwide, but periodic antigenic drifts and shifts pose problems for vaccine production and procurement, as a new vaccine closely matching the circulating antigenic configuration must be produced and procured for the beginning of each new influenza ‘season’. To achieve a close match between vaccine and circulating viruses, the WHO has established a worldwide surveillance system allowing identification and isolation of viral strains circulating in the different parts of the globe. Sentinel practices recover viral particles from the naso-pharynx of patients with influenza-like symptoms, and these samples are sent to the 110 laboratories of the national influenza centres in 79 countries. When new strains are detected, the samples are sent to one of the four WHO reference centres (London, Atlanta, Tokyo and Melbourne) for antigenic analysis. Information on the circulating strain is then sent to the WHO, who in February of each year recommends, through a committee, the strains to be included in the vaccine for the forthcoming ‘season’. Surveillance and early identification thus play a central part in the composition of the vaccine [1,3]. Production of a new vaccine takes 6–8 months.

Rationale for vaccination

Although many countries have policies for yearly vaccination of at-risk groups and the elderly, with the aim of diminishing morbidity and mortality, vaccination of a workforce is left to the discretion of the employer, so uptake is variable. The strongest rationale for use of influenza vaccines in an adult working population is the prevention of economic losses through sickness absence in different workplaces (e.g. homes, factories, barracks, health services) [3]. When considering the effects of influenza vaccines, we must distinguish between their efficacy, i.e. their impact on real influenza, and their effectiveness, i.e. their impact on influenza-like illnesses (ILI). Efficacy is tested in the rarified environment of highly controlled clinical experiments, but ILIs present to clinicians all the year round, following seasonal patterns similar to real influenza, from which they are indistinguishable. As only a variable proportion of ILIs are caused by influenza A and B viruses, and there are no licensed vaccines against the other ILI causal agents (such as respiratory syncytial virus, rhinoviruses and adenoviruses), ILIs are not completely amenable to prevention by vaccination. Thus, the effectiveness of influenza vaccines is usually lower than their efficacy [1,3].

Efficacy and effectiveness of vaccines not matching the WHO recommended strain antigenically

Demicheli et al. [1] carried out a Cochrane review of clinical trials of influenza vaccines in healthy adults. Within their review, the authors meta-analysed trials assessing the effect of different types of vaccines with different types of case definitions and endpoints. Live aerosol vaccines were not effective in preventing cases of clinically defined influenza (which can be considered similar to ILI). A combined analysis of data from the two existing trials estimated the vaccine effectiveness to be 2% [95% confidence interval (CI) = –5 to 8%]. However, data from two studies showed that aerosol live vaccines had high efficacy, reducing the number of serologically confirmed cases of influenza by 79% (95% CI = 44–92%).

Inactivated vaccines offer significant protection. A meta-analysis of 10 trials of parenteral vaccines showed a reduction of the number of cases by 29% (95% CI = 12–42%), regardless of case definition. Aerosol vaccines had greater effectiveness (31%, 95% CI = 5–51%). Estimation of effectiveness as risk differences suggests that 5% (95% CI = 2–8%) and 9% (95% CI = 3–16%) fewer participants who received inactivated parenteral vaccine and inactivated aerosol vaccine, respectively, experienced ILIs.

The efficacy of inactivated parenteral vaccines was 65% (95% CI = 44–79%).

The meta-analysis of three parenteral inactivated vaccine trials evaluating time off work estimated that vaccination saved on average ~0.4 working days. This result was not statistically significant. There was little difference in complication rates between vaccinated and unvaccinated groups.

Efficacy and effectiveness estimated from trials of vaccines with at least one strain matching the WHO recommendations antigenically

The combined effectiveness (against ILI) estimate from
placebo-controlled trials of live aerosol, inactivated parenteral and inactivated aerosol vaccines was 24% (95% CI = 14–33%). Live aerosols had a vaccine effectiveness of 13% (95% CI = 5–20%), inactivated parenteral vaccine had an effectiveness of 24% (95% CI = 15–32%) and inactivated aerosols had a vaccine effectiveness of 40% (95% CI = 13–59%). There was significant heterogeneity in the meta-analysis, probably caused by different populations with different exposure and risk profiles.

Individual study results were more consistent when expressed as risk differences. Overall, the percentage of participants experiencing ILI decreased by 5% (95% CI = 3–7%), using data from the placebo-controlled trials. The reductions were 3, 5 and 9% for the live aerosol, inactivated parenteral and inactivated aerosol vaccines, respectively.

The vaccine efficacy was estimated to be 48% (95% CI = 24–64%) for live aerosol vaccines and 68% (95% CI = 49–79%) for inactivated parenteral vaccines [1].

Efficacy and effectiveness estimated from trials of vaccines wholly matching WHO recommendations antigenically

Not surprisingly, these showed the highest estimates of vaccine efficacy and effectiveness [1]. Overall, vaccine effectiveness based on results of placebo-controlled trials was 37% (95% CI = 18–52%). The estimate declined to 31% when the non-placebo-controlled trials were included. Expressing the effectiveness as a risk difference, on average 7% (95% CI = 4–10%) fewer participants who received matched vaccine suffered ILIs compared with placebo recipients. The efficacy was also greater than in any other analysis, at 72% (95% CI = 54–83%).

None of the live aerosol vaccines used in the trials included in the Cochrane review matched circulating strains.

Use of all types of vaccines reduced time off work by less than half a day per influenza or ILI episode.

Adverse effects

Local tenderness and soreness were more than twice as common among parenteral vaccine recipients than those in the placebo group (relative risk = 2.1, 95% CI = 1.4–3.4). There were also increases in erythema (non-significant), but not induration or arm stiffness. The combined local effects endpoint was significantly higher for those receiving the vaccine (relative risk = 2.6, 95% CI = 1.6–4.2), with 69% reporting some effect.

None of the systemic effects was individually more common in parenteral vaccine recipients than in placebo recipients. However, the combined endpoint was increased, and nearly statistically significant, with 26% more vaccine recipients reporting some side-effect than placebo recipients (95% CI = 0–59%). Overall, 30% of those receiving the vaccine reported possible systemic effects, although many of these equally could be attributed to ILIs.

None of the trials of inactivated aerosol vaccines reported adverse effects that could be included in the Cochrane review.

Significantly more recipients of aerosol live vaccines experienced sore throats after vaccine administration than after placebo administration (relative risk = 2.5, 95% CI = 1.5–4.2), but the overall number of local adverse effects was not significantly different between the vaccine and placebo groups. There was also no significant increase in systemic side-effects, but rates of fever and myalgia were higher in vaccine than placebo groups. Overall, 26% of vaccine recipients reported a combined endpoint for local reactions, whilst only 8% reported the combined endpoint for systemic effects [1].

Disease burden and the decision to vaccinate

The decision to vaccinate a workforce is not straightforward, and several factors need to be taken into consideration.

First, the yearly burden of ILIs is a serious problem, as shown in a study of 141 293 subjects in England and Wales for the period 1991–1996. Meier et al. [4] estimated that 56 985 out of 78 394 (72%) study subjects who contracted ILI at least once were aged 15–64 years. The higher incidence of ILI in this age group was also associated with the greatest use of any medication (56.6%), but had the lowest incidence of complications. An estimate of incidence of working days lost (WDL) from another study [5] in the adult age group is summarized in Table 1. The data are compared in a vaccinated and an unvaccinated cohort, and the difference is statistically significant, indicating a protective effect of influenza vaccines against ILI. Overall, the preventive effect of influenza vaccines on WDL appears to be in the region of half a day per person, although this estimate is based on clinical trials of vaccines matching the recommended composition partially or not at all [1].

<table>
<thead>
<tr>
<th>Age group</th>
<th>Vaccination status</th>
<th>Size</th>
<th>WDL</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Vaccinated</td>
<td>2905</td>
<td>1116</td>
<td>38 417</td>
</tr>
<tr>
<td>Adults</td>
<td>Unvaccinated</td>
<td>3437</td>
<td>1603</td>
<td>46 640</td>
</tr>
</tbody>
</table>

Rate = rate of WDL due to ILI per 100 000 population.
The second factor is the aim of the vaccination programme and the likely acceptable level of effectiveness, not efficacy, of the vaccine. This is because the proportion of ILIs caused by influenza A and B viruses (hence preventable) can only be known retrospectively, and the decision to vaccinate must be taken before the October–March influenza ‘season’ [3]. Some help can come from the monitoring of the WHO influenza website (http://oms2.b3e.jussieu.fr/flunet/nav_news.htm), which can give advance warning of an epidemic. As a general rule, the greater the circulation of influenza A and B, the greater the effectiveness of the vaccine will be. It is worth noting that the recent track record of matching the vaccine antigens to circulating strains is very good.

The third factor is the likely cost of the vaccination campaign and the economic repercussions on an unvaccinated workforce. Unfortunately, published economic evaluations of influenza vaccination are not of great help, owing to the variability of assumptions of the likely incidence and effectiveness of the vaccines underlying the models [6].

The fourth factor is the likely compliance of the workforce with an immunization campaign. There is a growing body of evidence showing that doubts about the vaccines’ effectiveness and the relatively high incidence of local adverse events may be vital factors in determining uptake [3,7]. In addition, people’s attitudes to influenza vaccination may vary according to the seasonal exposure risk, with ‘off-season’ aversion to local adverse effects and ‘seasonal’ willingness to trade off induration and pain at the injection site for protection [3]. Physician and nurse involvement is also known to be an effective intervention in increasing uptake [7].

**Conclusions**

In healthy adults, influenza vaccines matching the WHO recommended composition are safe and ~70% efficacious. Their effectiveness is lower (~35%). The decision to undertake an immunization campaign is complex, and needs to take into account characteristics of the vaccines, costs and consequences, and likely compliance of the target population.

Unfortunately, yearly exposure to influenza A and B viruses can only be judged a posteriori. Thus, expenditure of resources on vaccination of healthy adults remains somewhat of a gamble.

**References**