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Influenza vaccination of health care workers (HCW) to reduce influenza-related outcomes in high risk patients: A Systematic review of clinical and cost-effectiveness

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Influenza vaccination of health care workers (HCW) to reduce influenza-related outcomes in high risk patients: A systematic review of clinical and cost-effectiveness

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS

Beverley Wake was the main reviewer.*

Rachel Jordan – Assisted in project management and design of protocol. Co-reviewer of trials and other studies. Co-wrote text. Assisted in economic analysis.

Jeremy Hawker – Helped design protocol. Read and commented on text. Expert advice.

Elizabeth Boxall – Carried out a 'pilot study' on this topic as part of a systematic review course and shared the results and experiences with the current reviewers. Is also a public health virologist with expertise in the area of vaccination.

Anne Fry-Smith – undertook all biobliographic database searches and commented on the protocol.

Yen-Fu Chen – assisted in project management, collected information on previous economic evaluations and modelling and commented on report draft.

Pelham Barton – constructed the spreadsheet model for the economic analysis and commented on the draft report.

Esther Albon – undertook the analysis and text of vaccine questionnaire studies.

Amanda Burls – Senior Lead/overall project management. Helped design protocol Reviewed trials. Read and commented on final draft.

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Dr Jed Rowe, Consultant Geriatrician, Selly Oak Hospital; *Expert advice*

*DEDICATION

We dedicate this report to Beverley Wake who tragically died in a car crash in December 2003.

This work was supported by a grant from the European Scientific Working Group on Influenza (ESWI) and forms part of a larger project; **'*The effectiveness and cost-effectiveness of vaccinating low-risk groups against influenza in order to reduce transmission to high-risk groups: A systematic review*'**

I had a birdy,
his name was Enza
I opened the window
and in flew enza.

Chidren's rhyme circa 1918.

West Midlands Regional Evaluation Panel

Recommendation

The vaccination of healthcare workers against influenza is

Strongly Supported

Uptake among healthcare workers is presently extremely low despite the availability of the influenza vaccine. The evidence suggests that the vaccine is effective in reducing both patient mortality and influenza in vaccine recipients. It poses negligible adverse effects and is likely to be either highly cost effective or cost saving.

Anticipated expiry date

- This report was completed in November 2004
- The searches were completed in January 2003 and updated in June 2004
- There is currently one ongoing cluster RCT run by the UCL Centre for Infectious Disease Epidemiology. Staff in 24 nursing homes are being vaccinated against influenza and staff in 24 homes are not. The outcomes include surveillance for ILI, GP consultations, hospitalisations and deaths among residents, and also staff sickness absence. This trial finishes in winter 2004-05 and will add substantially to the data on effectiveness of preventing patient mortality and staff absenteeism and will be more relevant for the current climate of nursing home care.

GLOSSARY/ABBREVIATIONS AND ACRONYMS

Term/abbreviation/ acronym	Definition
Barthel Index	An index of the activities of daily living, can be used to give a score (originally out of 100 but now modified to 20) of the ability of an individual to carry out routine daily activities such as feeding and dressing oneself.
Bias (systematic error)	A tendency to produce results that depart systematically form the 'true' results. Unbiased results are internally valid.
Compensation absenteeism	Workers report they are absent from work with influenza, but in fact they take sick leave every year using influenza as an excuse.
Cost-benefit ratio	The return on investment for every unit of currency spent.
External validity	Also known as generalisability or applicability. The extent to which the effects observed in a study are applicable outside the study (in routine practice).
HCW	Health Care Workers (including hospital staff, institutional care staff and community health staff) includes all staff in a health care setting who may have significant patient contact i.e. doctors, nurses, housekeeping staff, auxillary staff etc. but excluding social workers.
Internal validity	The degree to which the results of a study are likely to approximate to the 'truth'. It is a prerequisite for external validity.
Methodological Quality	The degree to which a study employs measures to minimize biases, focusing on internal validity. A set of parameters in the design and conduct of a study that reflects the validity of the outcome, related to the external and internal validity and the statistical model used.
NH	Nursing home
PHCT	Primary health care teams
RCT	Randomised controlled trial
ILI	Influenza-like Illness
Vaccine (protective) efficacy	1- (rate in vaccine group/rate in control group)*100%

SUMMARY

- Introduction

Influenza causes significant morbidity and mortality in the elderly and chronically ill and is responsible for a high burden on healthcare resources. Vaccination of healthcare workers (HCW), for which there are variable policies (and variable uptake) throughout Europe, may reduce transmission of influenza to 'high-risk' patients and result in lower associated mortality and morbidity and a cost-saving for the health provider programmes. This review aims to investigate this possibility by systematically reviewing the evidence of the clinical and cost-effectiveness of vaccinating healthcare workers.

- Methods

Systematic inclusive searches were undertaken in several medical bibliographic electronic databases using predetermined search strategies. In addition relevant internet sites and citations were checked and clinical experts contacted. Pre-defined inclusion/exclusion criteria were applied to the output of all searches. Data extraction and quality assessment were carried out independently by two reviewers. Heterogeneity of included studies precluded meta-analysis so that synthesis of results was descriptive.

- Results

Two cluster randomised studies were found to measure the effects on high-risk patients of vaccination of health care workers, and 27 other studies were used to provide data on important contributory issues. From the two cluster RCTs, mortality in high risk patients was reported as significantly lower (13.6% v 22.4%-odds ratio 0.58 95% CI 0.4-0.84, p=0.014 and 10% v 17%, p=0.013) in hospitals where there was a policy of HCW vaccination compared to those where there was no such policy.

No cost-effectiveness studies examining the indirect costs were identified but the two most relevant studies considering direct costs only suggested that a cost saving would be likely.

This was confirmed in a simple economic model which indicated that the programme would be cost saving by approximately £12 per vaccinee under the base-case scenario.

- Discussion and Conclusion

Two clinical trials suggest that vaccination of HCW would be clinically effective in reducing mortality in high-risk groups. The policy is also likely to be cost-saving, or in the worst case highly cost-effective.

In order for a policy of vaccinating healthcare workers to be implemented effectively, it will be important to overturn the perceived barriers to vaccination, especially to convince healthcare workers

of the benefits to themselves and patients, and of the favourable adverse event profile. The vaccination will need to be delivered in a convenient way eg “mobile cart” and the whole programme more heavily promoted, implemented and monitored.

Evidence available to this review suggests that based on reasonable estimates of the key parameters a vaccination policy of HCW would be effective and probably cost-saving.

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1. AIM OF THE REVIEW

Aims and objectives

The aim of this study is to review systematically the evidence on the effectiveness of protecting people at high risk of significant morbidity and mortality (particularly the elderly), by vaccinating health care workers (HCWs) including hospital staff, institutional care staff and community health staff against influenza.

Introduction

Influenza causes significant morbidity and mortality, especially in the elderly and other high-risk groups (for example people with chronic medical conditions) [1]. Most European countries have well established programmes of vaccinating those groups of people at higher risk[2]. The evidence for vaccinating those at high risk is well known and covered by meta-analyses and systematic reviews for example of the elderly[3], healthy adults[4] and those with COPD[5]. However, elderly and frail people are less able to mount an immune response to the vaccine, and therefore, despite immunisation, are left vulnerable to infection[6;7]. An alternative approach is to vaccinate probable vectors, and therefore indirectly protect those at higher risk. Despite the recommendations by the World Health Organisation that healthcare workers and household contacts of high risk patients should be vaccinated[1], policy in Europe is variable and poorly implemented[2 8]. The evidence for the indirect protection approach has not been previously reviewed fully or systematically and the policy statements are not clearly based on this type of evidence.

The aim of this series of reports is to systematically review the evidence on the effectiveness and cost-effectiveness of protecting people at high risk by vaccinating those at low-risk. In this systematic review we evaluate the evidence of vaccinating **health care workers** (hospital staff, institutional care staff and community health staff) as an indirect means to protect patients against influenza.

2. BACKGROUND

2.1 Description of underlying problem

2.1.1 Nature of influenza[9]

Influenza (flu) is a common acute respiratory infection first shown to be caused by a virus in 1933. It causes outbreaks of varying severity almost every winter. Influenza virus is a member of the *Orthomyxoviridae* family of viruses of which there are three genera which cause human influenza: influenza virus types A, B and C. The most common symptoms are fever, myalgia, headache and cough although influenza viruses may also produce syndromes similar to other respiratory viruses such as common colds, pharyngitis, croup, tracheobronchitis, bronchiolitis and pneumonia.

The important features of influenza compared with other respiratory viruses are the epidemic nature of the disease and the mortality which is often attributable to its pulmonary complications.

Symptoms and complications[9]

During an influenza outbreak many people may have classic influenza (although others will have less severe disease), characterised by an abrupt onset of symptoms after an incubation period of 1-2 days. Although the median duration of acute illness (usually with fever) is three days, cough and malaise can persist for weeks. Secondary bacterial pneumonia is the most common complication and occurs mainly in the elderly and in those with chronic medical conditions[1]. Other complications include otitis media, pneumonia, exacerbations of chronic respiratory disease and bronchiolitis. Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye's syndrome, myositis, myocarditis and pericarditis. Since influenza itself (excepting pandemic strains) usually poses no great threat to the long-term health of previously healthy individuals, most of the mortality and serious morbidity associated with influenza infection occurs in those considered high risk (see Appendix 1 for WHO recommendations), including the elderly, those with serious medical conditions and the immunocompromised. However, the emergence of new strains (such as Fujian flu this season) often results in excess hospitalisation and deaths in children in those seasons, and vaccination policy in the US has recently changed to include healthy infants aged 6-23 months to reflect this. Deaths from influenza generally result from pneumonia and from exacerbations of cardiopulmonary conditions and other chronic diseases.

Transmission of influenza

The predominant method of transmission is via small-particle aerosols during sneezing, coughing and talking[9]. Influenza can also be transmitted by direct contact. The incubation period is 1-4 days with an average of 2 days and persons can be infectious starting from the day before symptoms begin to approximately 5 days after onset of illness. Children can be infectious for longer.[10]

Influenza virus

The influenza virus is an envelope virus covered with surface projections or spikes[9]. The surface spikes are glycoproteins that possess either haemagglutinin (H) or neuraminidase (N) activity. The nucleocapsid contains single stranded RNA which has a marked ability to mutate its external antigenic composition and so escape the hosts' immune defences, while retaining capacity for binding to and entering host cells. Antigenic variation involves mainly the two external glycoproteins (H and N).

Many strains of influenza therefore exist and are classified based on H and N typing (the antigens on the virus envelope). Additionally they are classified on the basis of antigenic type of nucleoprotein core (A, B or C), geographical location of first isolation, strain serial number and year of isolation. (eg A/Panama/2007/99). Pandemics (worldwide spread) are caused by antigenic shift (major change in H configuration with or without a concomitant change in N and perhaps viral alteration of tissue tropism) leading to the appearance of a new subtype against which there is little immunity in unexposed populations. Minor changes in viral antigenic configurations, known as drift, cause local or more circumscribed epidemics.[4] Three subtypes of influenza are currently in circulation; H1N1, H1N2 and H3N2.[11]

Diagnosis

The definitive diagnosis of influenza is made either on the basis of viral isolation or serology[1]. Virus is isolated from respiratory secretions such as nasal and throat swabs, nasal washes or sputum and grown on cultures. Most positive cultures can be detected within 3 days. Serologic tests are also available and are both sensitive and specific, but take longer as they compare sera during both the acute (within 5 days of onset) and convalescent phases (about 10-20 days). Fourfold or greater rises or falls in antibody titre (IgG) are diagnostic of infection.[9] There are also more rapid diagnostic tests (for viral antigens or nucleic acids) now available.

2.1.2 Epidemiology

Influenza A and influenza B can both cause severe epidemics although influenza B epidemics are usually mild. Epidemics usually occur every winter and last for 3-6 weeks in temperate climates. Major antigenic shifts have occurred at about 30 year intervals resulting in pandemics, the most severe of which was the 1918 pandemic. Influenza occurs in all age-groups but the attack rate is highest in children aged 5-9 years[1]. Influenza has been estimated to affect up to 20% of the population annually,[12] but is more commonly between 1% and 5%.[1] It can cause significant morbidity and mortality, especially among the elderly. Most people who die from influenza are over 75 years of age and have a chronic medical condition; although the very young are also vulnerable. In a non-epidemic year in the UK, influenza results in approximately 3000-4000 deaths in those aged over 65[13] and in an epidemic year (such as 1989/90) mortality can be as high as 30 000 deaths.[14] About half the deaths from influenza occur in people in residential care.

Influenza in care homes and other institutions

In practice, the evidence for this review is most likely to be from studies based in institutions such as nursing homes where the elderly residents are considered the high-risk group, and where nursing home staff may be important in introducing and propagating infection. Acute respiratory illnesses in nursing homes are very common[15], although often present in atypical ways. During influenza epidemics the attack rate can be as high as 60-75%.[16]

2.2 Economic Burden of Influenza

The economic burden of influenza is also significant resulting in costs to the individual, the health service and society. Each year up to 20% of the population may become ill with influenza[12] and there are on average over 400,000 general practitioner (GP) consultations annually in England and Wales attributable to influenza and influenza-like illness.[17] The excess of over 11,000 elderly respiratory hospital admissions (over 100,000 bed-days) in England during epidemics of influenza costs the UK health service over £22 million every winter.[18;19] In addition to the direct costs of medical care, indirect costs such as work or school absenteeism and loss of work productivity may be substantial and have been shown to be 5 to 10-fold higher than direct costs.[20] One study estimated that there were in excess of 6 million working days lost in the UK associated with certified influenza illness.[21] Other intangible costs include impaired performance and adverse effects on quality of life of patients and their families.

2.3 Treatment and prevention of influenza

Influenza vaccines are the primary preventive measure against influenza. However, two classes of antiviral agents have also been developed for the prevention and treatment of influenza. The M2 inhibitors, amantadine and rimantadine, are used in the prevention and treatment of influenza A, and the neuraminidase inhibitors, such as zanamavir and oseltamavir, have recently been licensed in some countries for the treatment and prevention of both influenza A and B.[1] These antiviral agents may be used as an adjunct to vaccination, particularly in public health situations such as outbreaks in institutions, but are not a substitute for vaccination.

2.4 Influenza vaccine[11]

The main purpose of influenza vaccination is to avoid severe influenza and its complications[1]. New influenza vaccine has to be produced for each year because of changes in prevalent strains. It normally contains three components; two subtypes of Influenza A and one subtype of influenza B which is decided by the WHO in February (for the Northern Hemisphere) each year.

At present in most countries the viruses for the vaccine are grown in embryonated hen's eggs, inactivated and purified. Inactivated vaccines are classified into 3 types:

- whole virus vaccines containing inactivated viruses
- split virus vaccines consisting of virus particles disrupted by detergents

- Subunit vaccines consisting of HA and NA components only. Some subunit vaccines have been combined with an adjuvant or delivery system.[1]

Influenza vaccine is generally administered by intramuscular injection into the upper arm; however current areas of development include an intranasal vaccine and also live-attenuated and cell culture vaccines.

The estimates of vaccine efficacy vary considerably[1] according to:

- Antigenic match between vaccine composition and circulating strain
- Age and clinical category of the vaccine recipients
- Diagnostic end-point criteria of the trial
- Accuracy of the diagnosis.

It has been found that the vaccine prevents influenza in 70-90% of healthy persons aged <65 years[10] where there is a good match between vaccine and circulating strain. The match prediction is improving and in most years now there is a good match. However, the protection afforded by vaccination in the elderly and those with chronic medical conditions is frequently compromised, with a protective efficacy of 50-70% in the institutionalised elderly.[3] This is likely due to impaired immune function through inability to develop adequate protective circulating antibody concentrations following vaccination.[6;7]

Influenza cannot be distinguished from other respiratory viruses by clinical definition, therefore any trials which use a clinical definition (eg influenza-like illness) as an endpoint without culture or serological confirmation will be likely to dilute the effect of the vaccination. This is most likely when the incidence of influenza is low, when the definition of illness is broad and when the outcome of the trial extends outside the epidemic period.[4] In particular, among high-risk groups, influenza often presents atypically. On the other hand, serological measures tend to overestimate the protective effect as they tend to miss cases of influenza among vaccinated subjects (this is because their antibody rise may not be evident).

2.5 Current Practice in Europe

The World Health Organisation issued their latest position paper on influenza vaccines in 2002.[1] Vaccine is recommended for all countries where epidemic surveillance is well established and where reduction of influenza and its complications is a public health priority. The recommendations are intended to reduce incidence of severe illness and premature death in some high risk groups:

- Residents of institutions for the elderly or disabled
- All individuals >6mths of age with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies
- Elderly individuals above nationally-defined age-limit
- Other groups defined on the basis of national data

- Health care workers in contact with high-risk persons
- Household contacts of high-risk persons

In Europe, policies vary widely (table 1).[2] In 2000, most countries had a policy of vaccinating all elderly people over the age of 65 years, and also high risk people over the age of 6 months with cardiovascular, respiratory or renal conditions, diabetes mellitus, or conditions associated with immunocompromise. Only Belgium and Switzerland vaccinated pregnant women. 13 out of 17 countries vaccinated nursing home residents, and 12/17 health care personnel. Only 7 countries had a policy of vaccinating household contacts of high-risk patients. (Note that some of these policies may have changed in the intervening years).

Table 1 Influenza vaccination recommendations in countries in Western Europe in 2000[2]

Countries	**Age (year)**	**High-risk condition, ≥ 6 months**								**Other target groups**		
		Cardiovascular	Respiratory	Diabetes mellitus	Renal	Immunology	HIV	Children on long term aspirin	Pregnancy	Nursing home residents	Healthcare personnel	Household contacts
Austria	60	YES	YES	YES	YES	YES	-	-	-	YES	YES	YES
Belgium	65	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Denmark	65	YES	YES	YES	YES	YES	YES	-	-	YES	-	-
Finland	65	YES	YES	YES	YES	YES		YES	-	-	-	-
France	65	YES	YES	YES	YES	YES	YES	YES	-	YES	YES	-
Germany	60	YES	YES	YES	YES	YES	YES	-	-	YES	YES	-
Greece	65	YES	YES	YES	YES	YES	YES	-	-	-	YES	YES
Iceland	65	YES	YES	-	-	YES		-	-	YES	YES	-
Ireland	65	YES	YES	YES	YES	YES	YES	YES	-	YES	YES	YES
Italy	65	YES	YES	YES	YES	YES	YES	YES	-	YES	YES	YES
Netherlands	65	YES	YES	YES	YES	YES	YES	YES	-	YES	-	-
Norway	65	YES	YES	-	-	YES	-	-	-	YES	YES	-
Portugal	65	YES	YES	YES	YES	YES	-	-	-	-	-	-
Spain	65	YES	YES	YES	YES	YES	YES	YES	-	YES	YES	YES
Sweden	65	YES	YES	YES	-	YES	-	-	-	-	-	-
Switzerland	65	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
UK	65	YES	YES	YES	YES	YES	YES	-	-	YES	YES	-

2.6 Vaccine uptake rates

Vaccine uptake rates vary across the different risk groups and across different European countries. A questionnaire survey by influenza experts in 27 different European countries for the year 2000[8] showed that of the 18 countries who monitor vaccination uptake rates, most were able to provide data about the elderly, but few data were available for other risk groups. Uptake in the elderly ranged from 15% in Romania to 81% in the Netherlands. In the UK it reached 69% in winter 2002-3 (figures from Department of Health). For healthcare workers the uptake rate ranged from 15% in Scotland to 25% in Romania, and for children (universal vaccination in 4 countries) it ranged from 1% in Italy to 8% in Germany.

2.7 Vaccinating healthcare workers

Despite the recommendation by the WHO, endorsed by many individual European countries, uptake in healthcare workers remains low. There is a potential not only for avoiding illness and absenteeism in the recipients of the vaccine, but also to reduce the transmission of influenza to high-risk groups in whom direct protection from influenza vaccine is less effective. The purpose of this review is to evaluate the costs and benefits of protecting high-risk persons from influenza by immunising healthcare workers in contact with them. The review will also include information on the relative merits of different vaccination programmes to increase uptake.

2.8 Description of reviewed intervention

The intervention to be reviewed is an annual influenza vaccination program for health care workers to prevent transmission of influenza to high-risk patient groups. The vaccine would usually consist of three strains of influenza (two type A and one type B) representing the influenza viruses likely to circulate in the upcoming winter, and be given a few weeks prior to the influenza season.

This review seeks to answer the following questions to present a comprehensive view on the merits of vaccinating healthcare workers:

1. Does vaccinating healthcare workers protect the high risk group?
2. Is vaccination of the healthcare workers protective to the recipients?
3. Are there any appreciable adverse events associated with vaccination?
4. Will healthcare workers agree to have the vaccination ?
5. What is the best method to achieve optimal uptake rate?
6. Is vaccination of the healthcare workers cost-effective?

Potential trial design issues

There are several issues about influenza vaccine trial designs which need to be noted in advance of carrying out this review. Trials of vaccine efficacy in individuals are affected by:

- Presence/absence/relative size of the epidemic
- Timing of the epidemic
- Vaccine match
- Outcome measure (ie clinical vs serological/culture-confirmed influenza)

In addition, trials of vaccination programmes implemented at the level of the organisation (such as vaccinating the healthcare workers of an organisation) have these problems, but also problems of the **"cluster design".** [22] Individuals **within** a cluster (eg nursing home) are likely to be more similar than those **between** clusters. When calculating sample sizes and analysing the trial, the variation both within and between clusters should be taken into consideration. This usually has the effect of increasing the uncertainty around the final estimates of efficacy. It is not appropriate to present the effectiveness of the vaccine in terms of actual numbers in each arm, rather the effect of the cluster design should be considered. This can be carried out in three main ways:

1. Use of cluster means/proportions
2. Adjusted individual level analysis
3. Hierarchical regression analysis

and should be clearly presented.

2.9 Summary

Influenza has serious implications on morbidity and mortality of high-risk patients in Europe. It is also associated with placing a high economic and resource burden on healthcare providers. If effective, immunisation of healthcare workers will not only offer benefit to the recipient of the vaccine[4] but also have an effect on morbidity and mortality by indirectly protecting high-risk patient groups and help reduce the pressures placed on healthcare services in terms of cost and resources, particularly during influenza epidemics.

3. CLINICAL EFFECTIVENESS

3.1 Methods for Reviewing Effectiveness

3.1.1 Search for evidence of clinical effectiveness

The following were searched to identify primary studies on the clinical effectiveness of vaccinating health care workers in order to reduce transmission to high risk patient groups:

- Electronic databases – Cochrane library, Medline (1966-January 2003 , Embase (1980-January 2003), Cinahl (1982-December 2002), NHSEED, HEED, DARE. (See appendix 2 for search strategy)
- Specific internet sites such as PHLS, CDC Atlanta.
- Internet Search Engines – including Lycos, Copernic and Yahoo.
- Citation lists
- Contacting clinical experts
- Registers of trials found on the internet.

Note: In June 2004 the Medline and Embase searches were updated to ensure no further important trials were missed. The only studies to be revealed were 12 surveys of the reasons for non-uptake of the vaccine in HCW which provided similar results to the questionnaires discussed in this review.

3.1.2 Inclusion and Exclusion criteria

The main question of the review is whether the vaccination of health care workers reduces morbidity and mortality associated with influenza in high-risk patient groups. Since vaccination policies are likely to be implemented at the level of the healthcare centre (or at community area level) rather than the individual, the unit of interest should not be the individual health care worker but larger units such as hospitals or nursing homes.

- **Population** : A population of health care workers within a health care setting such as a hospital or nursing home or community in contact with high-risk patients (but excluding social workers).
- **Intervention** : Influenza vaccination programme i.e. a policy of offering vaccination to healthcare workers
- **Comparator** : No influenza vaccination programme (i.e. HCW may still be vaccinated of own accord), this may be a placebo programme.
- **Outcomes** : The primary outcomes considered were outcomes in **high risk patients**:

- mortality ,
- clinical influenza or influenza-like illness
- serologically confirmed influenza rates.

Secondary outcomes to be considered encompassed those **affecting the vaccinated population** such as adverse events, acceptability, uptake rates, absenteeism and influenza rates.

- **Study Design**: Any interventional study design was accepted, however the ideal was considered to be a cluster-randomised controlled trial (RCT). Other types of study were also included e.g. randomised trials, before-after studies.

3.1.3 Data extraction and quality assessment strategy

Two researchers (BW and RJ) independently extracted the effectiveness and quality assessment data from all included studies, using predefined criteria. Discrepancies were recorded and resolved by discussion. The quality of the included studies was assessed using a pre-formed assessment forms developed from previous systematic reviews or established checklists.

3.1.4 Synthesis of results

The main method of synthesis was qualitative; few studies were found and the strengths and weaknesses of each study were compared to allow useful estimates of effect to be obtained.

3.2 Characteristics and Quality of Evidence

3.2.1 Output of searches

Table 2 Output of effectiveness searches

Study types	Number of studies
Cluster RCTs with outcomes in high-risk patients	2
Cluster RCTs assessing promotion of vaccine uptake in HCW	1
RCTs assessing effectiveness and adverse events of vaccinating HCW	6
Other intervention study assessing uptake rates and outcome in HCW	6
Observational studies assessing uptake rates and attitudes to vaccination (12 were questionnaires and 2 were of other designs)	14

The clinical effectiveness searches identified 493 references. 28 studies[23-50] were included as relevant to the review question (one study was both an observational and an interventional study) , of which 15 were interventional studies and 14 were observational studies. Of the 14 observational studies, 12 were surveys/questionnaires and 2[31;32] were of other designs.

The breakdown of quality issues is given in a series of tables in the appendix, with studies categorised according to study design. **The details of each of these studies will be discussed in the appropriate sections below.**

3.3 Results for Effectiveness

3.3.1 Effects of the HCW vaccination programme on high risk patients

There were only two studies of the vaccination of HCW with patient outcomes – these were both cluster RCTs.[23;24] Potter 1997[24] was a pilot study for Carman 2000.[23] Different patients were used for each trial. The trials took place in long-term care geriatric hospitals with the main outcomes pertinent to this review being patient all-cause mortality and HCW vaccination uptake rates.

Detailed characteristics can be found in appendix 6, table 6.1.

Quality and characteristics of the two trials

In general, the quality of the two trials was reasonable (table 3). They used an appropriate cluster design although both studies had a relatively small number of clusters (6 clusters and 10 clusters in each arm in the pilot and main trial respectively). The limitation of both studies was in the reporting, which did not always allow for a clear description of the analysis and procedures. In particular, it was very difficult to decide whether the analyses had indeed been correctly carried out with full adjustment for the cluster design although it seems plausible.

In the pilot study[24] 12 hospitals were stratified by policy of vaccination of patients and then randomised all HCW to be offered vaccination or not. No further details were given about the randomisation process.

In the main trial[23] 20 hospitals (clusters) were randomly allocated to either a vaccination programme for all HCW or no programme. Randomisation was balanced and stratified for policy of vaccination of patients and size of hospital. Hospitals were paired according to these criteria and one chosen using a random number table to be in the intervention group. This resulted in two trial arms of 10 clusters each.

Only the Carman trial reported the sample size calculation (which did take into consideration the cluster design). Despite attempts to stratify the randomisation process, the baseline characteristics were not balanced for important potential confounders, although this was addressed in the analysis.

Table 3 Quality of cluster RCTs

Trial Criteria	Potter 1997	Carman 2000
Was the study randomised appropriately?	Yes (although no details given of process)	Yes
Was the control arm appropriate?	Yes	Yes
Where cluster numbers were small, did researchers attempt to balance trial arms for baseline characteristics relevant to the outcome?	Yes (but stratified for patient vaccination policy only)	Yes (but stratified for patient vaccination policy and hospital size only)
Was the response rate given for each arm?	Yes	Yes
Were appropriate methods used to determine sample size i.e. intra-class correlation coefficient?	None given	Yes (based on previous study)
Was an appropriate analysis carried out*?	It does not appear that the confidence intervals for the OR allowed for the cluster design	Probably
Where the same individuals were studied repeatedly at follow-up, were attrition rates given?	Not stated	Only applicable for routine screening. (all patients gave at least 3 nose/throat swabs every 2 weeks)
Was the balance of baseline characteristics and potential confounders between arms given?	Yes	Yes but differences in Barthel score and patient vaccination rates between trial arms apparent at analysis
Where differences existed, were regression methods for clustered data used to allow for confounding at both the individual and cluster level?	No	Yes

* Cluster level analysis should use the cluster means, proportions or log odds and apply standard parametric or non-parametric statistical methods. If individual level data is used i.e. individual patient outcomes, then the design effect must be incorporated into the analysis i.e. estimating the intra-class correlation coefficient.
For dichotomous outcomes a random effects meta-analysis can be used by pooling the cluster specific outcomes, however these should be weighted where clusters differ in size.

Results of the two trials

A summary of all the results from these studies can be found in appendix 7, table 7.1. Below gives details of mortality, as analysed using cluster analysis.

Table 4 Mortality in high risk patients

	Potter 1997[24] (pilot study for Carman)	**Carman 2000[23]**
Epidemic [HPA website][11]	1994-5 Week 01 to week 11 Peak week 6 158 per 100,000	1996-7 Week 49 to week 9 Peak week1 220 per 100,000
Vaccine match	Shandong/9/93 H3N2 Reasonable match	Wuhan//359/95 H3N2 Good match
Cluster numbers	12	20 (10 in each arm)
HCW number	1078 identified in intervention group and 653 (61%) agreed to participate and receive vaccination	1217 offered vaccination but number in control group not given
Patient outcomes	All cause mortality Deaths with pneumonia Influenza-like illness rates	All cause mortality Virological screening
Patient number	1059 (490 intervention, 569 control)	1437 (749 intervention, 688 control)
Balance of Baseline Characteristics	No significant differences between trial arms for size, age, sex, Barthel score.	Hospital size, patient age, sex not statistically different between arms. **Barthel score** (median 5 (range 3-7.5) intervention group vs. median 3 (range 1-5) control group) and **Patient vaccination rate** (mean 48 (range 0-94) in inter-vention group vs. mean 33 (range 0-70) control group) different. Analysis corrected for this.

Mortality	Cluster analysis by hospital site showed a reduction in mortality, analysed by t-test p=0.013 (reduction from 17% to 10%) **(OR = 0.56 for "non-cluster" analysis)**	Uncorrected : 102/749 (13.6%)intervention, 154/688 (22.4%) control. Odds ratio **0.58 95% CI 0.4,0.84** p=0.014. All corrected rates significant except when corrected for Barthel score, age, sex and vaccination profile together: **OR 0.61 (0.36, 1.04)** (borderline p=0.092). Samples for virological screening with PCR at death showed 0% in intervention arm compared to 20% in control arm had influenza.

Both trials showed a potentially clinically significant reduction in mortality when a staff vaccination programme was introduced. In the pilot trial[24], a reduction from 17% to 10% was reported with a p values taking into account the cluster design of 0.013. The odds ratio was reported as 0.56 (95% CI 0.4, 0.8) but this did not appear to take account of the clustered design, and therefore the confidence intervals are too narrow.

In the main trial[23] uncorrected mortality was reported as 13.6% compared to 22.4% in control arm (odds ratio 0.58 95% confidence intervals 0.40-0.84) with a p-value of 0.014. The difference remained statistically significant when the analysis was adjusted for possible confounding factors except when all studied confounding factors were adjusted together i.e. Barthel score, age, sex and vaccination of patients (OR=0.61 (0.36, 1.04)) where the results were of borderline significance.

There is however some difficulty in interpreting the results of this study. The reporting of the cluster analyses was not clear and needs some assumptions to take the data as reported. In general, it is unlikely that the point estimate of effectiveness would be altered substantially whether the clusters design had been accounted for or not, but taking into account the effect of the cluster design tends to increase the uncertainty about the estimates.

In this paper, the hospitals were paired before randomisation. The authors used a Mann Whitney U test to compare the two arms, which would have taken into consideration the cluster design and therefore the p values would reflect a correct approach. It was not however clear how the authors calculated the odds ratios and confidence intervals. We cannot replicate the analysis without the cluster-level data (because of the paired nature of the data). However, repeating the analysis not accounting for either the paired design or cluster design produced an OR=0.55 (95%CI 0.42, 0.72) p<0.0001, where the confidence intervals are substantially narrower than the reported confidence interval in the paper and the p values considerably smaller than in the paper. This leads us to conclude that it is entirely plausible that the odds ratios and confidence intervals reported in the paper probably do take account of the cluster design, and that the reduction in mortality is statistically significant.

In the main Carman trial, samples for virological screening with PCR at death showed 0% in intervention arm compared to 20% in control arm had influenza (although small numbers). This lends weight to the theory that the reduction in all-cause mortality was influenza-related.

Both trials also reported that **patient** vaccination policy was not significantly associated with an increase in patient mortality despite that in the pilot study[24] patient vaccination rates differed from < 1% to 89%. Here the Barthel score (p=0.004) and age (p=0.03) were significantly associated with patient mortality but unlike Carman[23] no adjusted results were given. These data were not a randomised comparison.

3.3.2 Other high risk patient outcomes

Other patient outcomes studied in the two cluster RCT's included:

(1) In the main study, prospective virological screening (every 2 weeks) in a random sample of 50% of the high-risk patients.[23] Overall, 5% of the intervention group and 7% of the control group were PCR-positive for influenza (not significantly different, although small numbers).
(2) In the pilot study, rates of lower respiratory tract infection (LRTI) and influenza-like illness (ILI) were also compared.[24] The odds ratios for effect of HCW vaccination on LRTI was given as 0.69 (0.4,1.19) and on ILI was given as 0.57 (0.34, 0.94). However this is unlikely to be a cluster analysis and therefore the reported confidence intervals are probably too narrow.

More details can be found in table 7.1 in appendix 7.

3.3.3 Ongoing trials

There is currently one ongoing cluster RCT run by the UCL Centre for Infectious Disease Epidemiology (Richard Harling, Personal Communication). The trial is in progress over two winters, 2003-04 and 2004-05. Staff in 24 nursing homes are being vaccinated against influenza and staff in 24 homes are not. The outcomes include surveillance for ILI, GP consultations, hospitalisations and deaths among residents, and also staff sickness absence.

Effects of vaccination on HCW

3.3.4 Vaccine uptake rates in HCW

Vaccine uptake rates by HCW are an important factor when considering the introduction of a vaccination programme. The programme may be clinically and cost effective in theory, however if HCW are still not being vaccinated then the effectiveness may be severely hampered. 22 studies were identified, from Europe, North America and Australia[23-25;27-36;38-40;43-47;50] (see table 5 overleaf for results and appendix 9 for quality assessment). There were 3 reports of trials of a specific vaccine programme with a control arm, and 4 before/after studies with an "internal" inbuilt control. The remainder were surveys or evaluations of a vaccine programme with no control comparison.

Vaccine uptake where there was no specific campaign (this included the control arm of 2 of the controlled trials) was usually in the range of 5-15%, but ranged up to 48% in one hospital[38]. Where there was a vaccination campaign, uptake ranged from 14.5%[30] to 81% (in staff with patient contact)[28]. Of the seven studies with controls[23;28;30;34;35;45;46] the % improvement with a campaign varied between a 5%[30] increase to a 45% increase[23] . This wide range may be due to differences in setting i.e. teaching hospital or nursing home, different countries and different methods of data collection, but must also be due to the varying programmes delivered. If the data are to be taken at face value, then the most effective programme would seem to be a mobile clinic (in Australia) which achieved 49% uptake in all staff (a 41% increase pre-intervention) and 81% in staff in contact with patients[28]. A similar mobile vaccination cart in the USA achieved 61% uptake in a survey[40].

The intervention arms of two cluster RCTs[23;24] achieved a 50% and 61% uptake rate respectively without a mobile cart. It would however be unusual to achieve similar results in normal practice

Table 5 Vaccine uptake rates and promotional campaigns

Study	Setting	Study design	Study details (n)	Details of vaccine campaign	Uptake Rates
Randomised/external comparison					
Dey, 2001[30]	UK Primary health care teams and nursing homes All HCW	Cluster RCT	Large cluster trial but underpowered	Letter +/- Public health nurse visit & promotion	14.5% vs 9.1% in control 5.4% increase
Carman, 2000[23]	UK Long-term geriatric hospital All HCW Data for nurses only	Cluster RCT	Vacc programme vs no programme (n=1217)	Letters and interviews and local vaccination	50% vs 5% in control 45% increase
Tannenbaum,1993[45]	Canada 2 nursing homes All HCW	Before/after study with control arm	Vacc programme vs no programme (n=268)	Information sessions, posters, memos and vaccination clinics.	16% before 26% after in intervention 17% before 10% after in control Effect-Adjusted odds ratio: 2.8 (1.4-5.8)
Before/after study – internal comparator					
Cooper, 1990[28]	Australia 347-bed hospital All staff	Before/after study	(n=880)	Mobile clinic 'needles on wheels'	8% before 49% after intervention (41% increase) in all staff (81% after intervention in staff with patient contact)
Harbath, 1998[34]	Switzerland 1500 bed University hospital (Primary & tertiary care) All HCW	Before/after study	Large, good quality study (n=5514)	Whole hospital: Adverts, newsletter personal letters 3 Targeted depts: educational conference, visit by special health nurse	26% (vs 10% in previous year) 16% increase (3 targeted depts changed from 13% to 37%)
Thomas, 1993[46]	USA 300-bed nursing home All staff	Before/after study	N=195	Educational intervention & 'Staff vaccination fair' with vaccine offered	8-46% (to 54% following year) 46% increase (49% of nurses vaccinated)
Heimburger, 1995[35]	USA Chronic care psychiatric facility All staff	Before/after study 17% increase	N = 1293 Poorly reported study	In-service meetings, video tapes and pamphlets	16% before extended programme and 33% after (following year)
One arm –no comparator					
Potter[24]	UK Long-term geriatric hospital All HCW	Cluster RCT Uptake in intervention arm only	Vacc programme vs no programme (n=1078)	Not described	61% in intervention arm

Study	Setting	Study design	Study details (n)	Details of vaccine campaign	Uptake Rates
Al Mazrou, 1991[25]	Canada Tertiary care childrens' hospital All staff	RCT (uptake given for both arms together)	Split virion vs whole virion vaccine (n = 2200)	Recruitment letters, information meetings and posters	25% (64% were first-time vaccines)
Christian, 1991[27]	USA Acute care hospital All staff	Survey	(n=407)	'Vaccine offered'	Year 1: 5% Year 2: 6%
Raszka, 1996[29]	USA Paediatric Health care providers during outbreak Mainly physicians	Survey following campaign	Small survey, subjects from list in large city (n=117)	Unknown	68%
Doebbeling, 1997[31]	USA 900-bed hospital All staff	Survey following campaign	Year 1: n=7320 Year 2: n = 8632	Written invitation, flyers, letters to department heads, signs posted in facility. Vaccine offered free.	Year1 :32% Year 2: 31%
Elorza Ricart, 2002[32]	Spain Tertiary hospital	Survey following campaign	Poorly reported small survey N = 593 N=670	Workplace vaccinations with a leaflet	13% in 2000/1 and 15% in 2001/2
Ganguly, 1990[33]	USA Veterans hospital Nurses & physicians	Survey	Small survey N = 62	Government recommendations only	19%
Manuel, 2002[36]	Canada 2x230-bed long-term care facilities All staff	Survey following campaign	N=401 Low response to survey (58%)	Educational sessions with PH nurse, free vaccination, prize incentive	40%
Murray, 2001[38]	Australia Tertiary Adult hospital All HCW	Survey	N=269	None	48% (self-reported)
Nafziger, 1994[39]	USA 2 hospitals	Survey following campaign	Physicians only	Posters, newsletter, emails, memos and reminders	51%
Nichol, 1997[40]	USA 400-bed teaching hospital	Survey following campaign	Low response to survey (38%)	Walk-in clinics + mobile vaccination cart, information meetings	61%
Schiefele, 1990[43]	Canada Setting not stated All HCW	Evaluation of programme		Notices. memos and meetings	58%
Stephenson, 2002[44]	UK 3 acute hospitals Staff in direct contact with patients	Survey following DH recommendations	N=597	Posters, mailshots, walk-in and appointment based clinics.	14%
Watanakunakorn, 1993[47]	USA 650-bed community teaching hospital All staff	Evaluation of programme	N = 3501	Free vaccination offered to all personnel	30%
Yassi, 1994[50]	Canada 1100-bed acute care hospital HCW in contact with high risk patients (Not physicians)	Survey	N = 494 Low response to survey (55%)	None	14%

3.3.5 Reasons for non-vaccination

Reasons for HCW not being vaccinated were addressed in 10 studies[27;29;33-35;39;40;44;46;47]. The information was collected in the form of questionnaires and the main reasons for non-vaccination are shown in table 6.

Survey methods have not always been clearly reported but included asking the HCW to document their own reasons or asking the employee to complete tick boxes for a suggested list of reasons. Questionnaires were only shown in 2 of the 10 papers[27;47].

The studies shown overleaf cannot easily be compared across studies. General conclusions are that the most common reasons relate to a fear of side effects (up to 51% fear general side effects) including that the vaccination would cause influenza (up to 45%), a dislike of injections (up to 27%) and general avoidance of medications/immunisations (up to 47%). A belief in being able to fight off infection or that they are at low risk of infection also appears to have been important (up to 32%). Being unaware that the vaccination was necessary or available (up to 53%) or simply forgetting (up to 45%) and a lack of time were also common barriers to vaccine uptake. In up to 22% of HCW there was a doubt about the efficacy of the vaccine.

Other reported reasons for non-uptake included allergy to the vaccine components, pregnancy, breast-feeding or other contraindication, a belief in homeopathy, not being at high risk or no contact with high risk patients, cost or being unaware that the vaccine was free, and not knowing how or where to receive the vaccination.

In general, many HCW seemed either unaware or unconvinced of the benefits for patients or themselves of their vaccination.

Nichol[40] also reports factors influencing the decision to receive vaccine ranked as ‘very important’ by *vaccine recipients*. Not wanting to get sick accounted for 83% of respondents, with convenience accounting for 68%, protecting patients 62%, and the fact that the vaccine was free accounted for 58%. National recommendations and physician’s recommendation were considered ‘very important’ by only 25% and 8% of responders respectively. Thomas[46] reported that the “majority of those receiving the vaccine did so to prevent personal infection with influenza (82%) and to protect the residents from possible influenza (67%)”.

Table 6 Common reasons for non-uptake of influenza vaccine in unvaccinated HCW following active vaccination campaigns or annual programmes

Study	Population	Response rate to survey	Fear of Adverse Reaction				Perceptions and beliefs about influenza and immunization				Accessibility			[g]Summary of main reasons
			General side effects	Causes flu/ ILI	Previous reaction	Dislike injections/ Pain & discomfort	Doubt efficacy	Low risk contracting flu/ Never had flu	Avoidance of medication/ Dislike immunization	Don't mind flu, or consider serious/ Disagree with recommendations	Inconvenience	Unaware needed/ No recommendation/ Not offered/ Unaware available	Forgot/ Lack of time	
[a]Christian[27] (USA), 1991	*n*= 240 all staff at 1 hospital, 82% had patient contact (91% unvacc)	63%	37%	45%	20%	15%	22%	29%	47%	24%	19%	25%		Avoid medications (47%), causes flu (45%)
[b]DeAngelis[29] (USA), 1996	*n*= 117 paediatric medical health care providers in El Paso (32% unvacc)	99%	6%			20%	11%					3%	60%	Forgot/ Lack of time (60%)
[c]Ganguly[33] (USA), 1990	*n*= 62 staff at 1 hospital, 81% medical staff / other staff 19% (81% unvacc)	100%	11%		15%	6%	6%					5%	6%	"Didn't want it" (47%)
Harbath[34] (Switzerland), 1998	[h]*n*= 797 all staff at 3 Depts with high risk pts in 1 hospital ([e]63% unvacc)	73%	9%		3%	8%	19%	[f]23%/ 18%	12%	16%	14%		9%	Belief in own host defence (32%), low risk of contracting flu (23%)
Heimburger[35] (USA), 1995	*n*= 922 [d]HCW in 1 chronic care psychiatric facility, 47% HCW/ 53% non-med jobs (84% unvacc)	71%	35%		24%	18%	9%	18%	33%		6%		5%	Fear of side effects (35%), avoid medications (33%)
Nafziger[39] (USA), 1994	*n*= 78 medical residents at 2 hospitals (49% unvacc)	73%	8%			13%	3%						[f]45%/ 42%	Forgot (45%), lack of time (42%)

Study	Population	Response rate to survey	Fear of Adverse Reaction				Perceptions and beliefs about influenza and immunization				Accessibility			Summary of main reasons
			General side effects	Causes flu/ ILI	Previous reaction	Dislike injections/ Pain & discomfort	Doubt efficacy	Low risk contracting flu/ Never had flu	Avoidance of medication/ Dislike immunization	Don't mind flu, or consider serious/ Disagree with recommendations	Inconvenience	Unaware needed/ No recommendation/ Not offered/ Unaware available	Forgot/ Lack of time	
Nichol[40] (USA), 1997	*n*= 392 physicians and nurses only at 1 hospital (61% unvacc)	38%	36%			5%				10%	10%		5%	Fear of side effects (36%)
Stephenson[44] (UK), 2002	*n*= 597 [d]HCW across 3 hospitals (86% unvacc)	99%	29%	21%			14%			4%	16%	53%		Not offered or did not know available (53%), did not want immunization (38%)
Thomas[46] (USA), 1993	*n*= 173 all staff at 1 life-care hospital (54% unvacc)	89%	51%			16%	12%							Fear of side effects (51%)
Watanakunakorn[47] (USA), 1993	*n*= 1203 all staff at 1 hospital, 67% had pt contact (61% unvacc)	34%	37%		19%	27%	14%	5%				10%	[f]5%/ 10%	Fear of side effects (37%), dislike injections (27%)

[a]no details of campaign or annual programme given but survey conducted in Mar/ Apr.

[b]questionnaire carried out in person or by phone across several institutions with varying policies on influenza vaccination.

[c]reported a random survey that did not appear to be associated with any programme.

[d]HCW includes all employees having regular direct patient contact (medical and non-medical).

[e]63% represents total number of unvaccinated employees in the high risk Departments and is not a % of those surveyed.

[f]where 2 numbers are given, both reasons listed in the sub-heading were measured separately.

[g]main reasons are those listed by the highest percentage of respondents within each study. “Didn’t want it” and “belief in own host defence” were only listed as reasons by Ganguly and Harbath respectively and were therefore not included in the main table.

[h]unclear whether responses have been given by all staff or unvaccinated group only.

3.3.6 Influenza, Influenza-like illness and absenteeism in HCW

Four trials[41;42;48;49] studied rates of influenza (or ILL) and absenteeism in HCW. Three were randomised trials[42;48;49] and the fourth a non-randomised controlled trial[41] (table 7)(see appendix for details of quality and characteristics).

Of these trials, two[41;49] found a statistically significant difference between rates of serologically confirmed influenza[49] or rates of febrile illness[41] in vaccinated versus unvaccinated HCWs. The remaining trials[42;48] did not find a statistically significant difference, however one of the trials[48] had a poor match between the vaccine strains and the circulating strains whilst the other trial noted that there was a low incidence of influenza during the weeks of the trial due to the fact that the temporal distribution of influenza A and B was very wide.

The most useful trial, Wilde[49], indicated that influenza vaccine could have a protective efficacy (95% CI) of about 88% (47%, 97%) for Influenza A(H3N2) and 89% (14%, 99%) for Influenza B.

The same four trials measured absenteeism from influenza in the influenza season following vaccination. Where absenteeism due to influenza was not available, total absenteeism or absenteeism due to febrile illness etc was given. The results from these studies are provided in table 7.
Two[41;42] of the studies, which were considered to be poorer quality trials although they were relatively large trials, did find a statistically significant difference in the rate of absenteeism between the vaccine and control arms of the trials in favour of vaccination. For the randomised trial[42], this was a mean of 1.0 days lost in the vaccine group compared with 1.4 days lost in the control group (p=0.02).

The other two better quality trials[48;49] found no significant differences between absenteeism in the vaccine and placebo control arms.

Comparison with all healthy workers
It is not clear whether illness and particularly absenteeism effects of influenza in HCW would be any different from that in other healthy workers, although healthcare workers might be more likely to continue to work when ill, thus exposing their patients to influenza. A very good quality systematic review and meta-analysis of trials[4] assessed the effectiveness of influenza vaccine in all healthy adults. They found that for inactivated vaccines, the protective efficacy for clinical case definitions of influenza was around 30% (which increased to 37% if the vaccine was a complete match); and for serologically confirmed influenza was 65% (95%CI 44%, 79%)(6 trials) (which increased if the vaccine was a complete match to 72% (54%, 83%, 7 trials).

3 trials measured absenteeism – one of the trials from our study of HCW was also included in this.[48] Vaccination saved on average around 0.4 working days (on the margins of significance), but caution should be used on interpreting these results as the data were skewed.

Table 7 Influenza, ILI and absenteeism in HCW

Study	Brief description	Influenza/ILI Rates	Vaccine efficacy. **%** (95% CI) (serologically confirmed influenza)	Absenteeism	Vaccine match/epidemic
Wilde[49] 1992 US	**RCT** Vaccine v placebo 3 years 361 person- winters. **Good quality trial**	OVERALL Serologically confirmed: Influenza A : **1.1% vaccine v 8.9% control** (p=0.001)* Influenza B: **0.6% vaccine v 5% control** (p=0.02)* YEAR 2: **0% vaccine v 7.1% control** cases of flu A	**88%** (47%, 97%) for Influenza A(H3N2) **89%** (14%, 99%) for Influenza B.	Mean absence (all illness) (days) +/- SD **0.1 days +/- 0.35 (vaccinated) v 0.21 days +/- 0.75 (control).** **"Not statistically different" (no p value given)**	Year: 1- Partial 2- Good 3- Partial Epidemic each year.
Saxen[42] 1999 Finland	**RCT** Vaccine (216) v placebo (211). **Poorer quality relatively large trial**	1.8 episodes respiratory infection per person (vaccine) v 2 episodes (placebo) **Not statistically different (no p value given)**	N/A	Mean absence (days) due to respiratory infection **1.0 day (vaccinated) v 1.4 days (unvaccinated) p=0.02***	Good match Low incidence of flu.
Weingarten[48] 1988 US	**RCT** Vaccine (91) v placebo (88) Follow-up completed for 99% patients. **Good quality small trial**	No significant differences between trial arms for rates of clinical influenza (23% vaccinated vs 22% control), duration of flu or fever and severity of flu. (p=0.95)	N/A	Mean absence (all illness) (hours) (+/- SD) **7.6 hours +/- 12.1 (vaccinated) v 8.2 hours +/- 18.3 (control). (p=0.91)** % employees absent **42.9% (vaccine) v 43.2%** **No statistically significant differences (p=0.97)**	Poor match. Epidemic present
Nishi[41] 2001 Japan	***Non-randomised controlled trial*** *Comparative trial of vaccine (132) v placebo (595). Relatively large trial Adequate quality*	*Febrile illness* 10 v 20 events per 100 persons, rates severe febrile illness* 6 v 14 events per 100 persons Rates febrile upper resp. tract illness* 4 v 12 events per 100 persons. All higher in unvaccinated arm.*	*N/A*	*2.3 days per 100 persons (vaccinated) v 10.7 days (non-vaccinated) **	No information on match (in Japanese) Epidemic present

* Statistically significant differences (p<0.05)

3.3.7 Adverse events in HCW

Six[25;26;37;43;48;49] studies reported adverse events from influenza vaccination injections in health care workers. Five of the studies[25;26;37;48;49] were part of randomised trials but only two[48;49] allowed a comparison between vaccine and placebo. These two trials were of good quality (for full details see appendix).

The results are given in table 8. There was some heterogeneity between the values of adverse events in the vaccine arms for example sore arm ranged from 18% to 73% while erythema at the site ranged from 11% to 54%. Values for other adverse events were closer, such as fever (5-13%), headache (8-20%), nausea (5-10%) and tiredness (10-20%). In the one trial[48] which clearly compared influenza vaccine to a saline placebo the only significant side-effects were sore arm and redness at the injection site.

The review of healthy adults[4] found that local tenderness and soreness was twice as common in the vaccine groups compared with the placebo groups (RR = 2.1 (1.4, 3.4)). There was also an increase in erythema although this was not significant. 30% of the vaccinated group reported possible systemic side effects; which was 26% (0, 59%) more than the placebo group. However, many of these could have been ILI.

Table 8 Side-effects of influenza vaccine

Study	Design	Most commonly reported side-effects						Notes
		Headache	Fever	Sore arm	Erythema	Nausea	Tiredness	
Weingarten[48]	RCT Vaccine vs placebo	$	$	*51 v 7%	*11 v 0%	$	$	Follow-up for 60% patients Good quality small trial. **Values for vaccine vs placebo control N=179**
Wilde[49]	RCT Vaccine vs placebo	Serum sickness, cellultis and lymphangitis in 3 controls. "Other than mild pain or swelling at injection site, the rest of the subjects reported no significant adverse effects"						Not clear what "significant"means. Probably not a comparison between vaccinated and placebo. N = 156
Al Mazrou[25]	*RCT SVV vs WVV*	*11%*	*9%*	*35%*	*18%*	*5%*	*18%*	*93% response rate to survey Very good quality fairly small trial.* ***Values for split-virus only***
Aoki[26]	*RCT vaccine vs vaccine + analgesic*	*18%*	*5%*	*61%*	*NS*	*10%*	*NS*	*Good quality small trial* ***Values for vaccine only***
Mostow[37]	*RCT SVV vs WVV*	*20%*	*10%*	*73%*	*54%*	*8%*	*20%*	*76% response rate to survey Poor quality large trial* ***Values for split-virus only***
Scheifele[43]	*Uncontrolled safety study*	*8%*	*13%*	*18%*	*16%*	*10%*	*10%*	*90% survey response rate Adequate quality large trial.* ***Values for vaccine only***

* denotes statistically significant difference from placebo p<0.05

$ denotes no statistically significant differences with saline placebo

NS Not studied

SVV split virus vaccine

WVV whole inactivated virus vaccine

4. COST EFFECTIVENESS

4.1 Methods for Reviewing Cost-Effectiveness

4.1.1 Searches for evidence

Searches were undertaken to identify any published economic analyses (generally cost-effectiveness or cost-utility) of vaccination programmes of HCW. Included studies were then systematically reviewed for internal and external validity. In the absence of suitable analytical studies costs associated with a vaccination programme in HCW were to be extracted from any published source; this information could then be integrated with information gained in the clinical effectiveness review to perform a cost-consequence analysis.

The following were searched to identify economic analyses on vaccinating health care workers in order to reduce transmission to high risk patient groups:

- Electronic databases – Cochrane library, Medline (1993-April 2003), Embase (1993-April 2003), Cinahl (1993-April 2003), NHSEED, HEED, DARE. (See appendix 4 for search strategy)
- Specific internet sites such as PHLS, CDC Atlanta.
- Internet Search Engines – including Lycos, Copernic and Yahoo.
- Citation lists
- Contacting clinical experts
- Registers of trials available on the internet.

4.1.2 Inclusion and Exclusion criteria

Preliminary scoping searches indicated that there were unlikely to be many papers published specific to the topic of this review. The search strategy was very broad in order to capture anything which might be relevant to the review or contain cost information which could be used or adapted (see appendix 3 for search strategy). Cost data in papers published more than a decade ago were considered inappropriate to the current economic context.

- **Population** : A population of health care workers within a health care setting such as a hospital or nursing home (excluding social workers)

- **Intervention** : Influenza vaccination programme i.e. a policy of offering vaccination. For cost-effectiveness this was vital, however in order to provide costs a paper looking at any related costs to vaccination programmes was acceptable.

- **Comparator** : No influenza vaccination programme (i.e. HCW may still be vaccinated of own accord), this may be a placebo programme. Again this was the ideal.

- **Outcomes** : The primary outcome considered was
  Cost-effectiveness or cost-utility, although basic information on costs was acceptable. Costs would be related to all aspects of the vaccination programme including all those outcomes studies in the clinical effectiveness section.

- **Study Design**: Any study design was accepted and assessed for quality.

4.1.3 Data extraction and quality assessment strategy

Two researchers (BW and RJ) independently extracted the cost-effectiveness and quality assessment data from all included studies, using predefined criteria. Any discrepancies were recorded and resolved by discussion. The quality of the included studies was assessed using a pre-formed assessment forms developed from previous systematic reviews or established checklists.

4.1.4 Synthesis of results

Useful information from any relevant studies are tabulated and the information used to inform the discussion and conclusions of this review.

4.2 Characteristics and Quality of Evidence

4.2.1 Output of searches and characteristics of studies

18 economic studies published within the last decade were identified[51-68]. No studies examined the cost-effectiveness of vaccinating HCW against influenza with outcomes relating to high-risk patients, although there were 2 studies in HCW or care workers (one study each from Finland and the Netherlands) which assessed the value of the vaccine in the recipients. 4 others examined the cost-effectiveness of vaccinating the elderly or other high-risk groups and 12 calculated the cost effectiveness in healthy workers other than HCW (see appendix 10 for brief details of each study).

Two of the studies recently published describing the cost-effectiveness of influenza vaccination in the recipients are provided as examples below (one study in HCW in the Netherlands[52] and one in healthy workers in the UK[51]) to provide some basic information for the discussion and conclusion. Further details of the characteristics of these studies and in particular the model are given in table 9

Table 9 Characteristics of economic analyses

	Das Gupta 2002[51]	**Parlevliet 2002[52]**
Country	UK	Netherlands
Study type	Cost-benefit	Cost-benefit
Type of analysis/model used	Decision tree model comparing vaccination programme to no vaccination programme	Retrospective cost-benefit model(basic input/throughput/ output model)
Population	1000 Healthy working adults in UK business	6251 HCW in Amsterdam University academic medical centre
Perspective	Employer	Employer
Costs/benefits: Vaccine Vaccine clinic Time to vaccinate Side-effects Absenteeism/productivity Campaign promotion High-risk groups Costs to population	 Yes Yes Yes No Yes No No No	 Yes Yes Yes No Yes No(not directly) No No
Other elements considered: Compliance rate Vaccine/strain match Vaccine effectiveness Epidemic/incidence	 Yes No Yes Yes	 Yes No Yes Yes
Source of costs/benefits	From literature search of published studies and NHS databases	Partly based on real costs and other inputs from the organisation and partly from literature searches
Year of costs	2000	2000
Currency	£ UK	Euros
Discounting?	No – unlikely to be relevant as costs/benefits immediate	No – unlikely to be relevant as costs/benefits immediate
Sensitivity analysis?	Yes	Yes
Elements considered in sensitivity analysis: Compliance rate Vaccine/strain match Vaccine effectiveness Epidemic/incidence Others	 No No Yes Yes Vaccine costs, average daily wage, absenteeism, length of time absent, reduced productivity after returning	 Yes No Yes Yes (univariate and multivariate analysis) effect of 'compensation absenteeism'

4.2.2 Quality of included studies

Table 10 gives details of quality concerns for the 2 cost studies based on criteria from a paper by Drummond[69] in the BMJ.

Table 10 Elements of study quality

Das Gupta 2002[51]	Parlevliet 2002[52]
Study was carried out in the UK in 2000 therefore recent but did not focus on health care workers	Study carried out in The Netherlands on health care workers but included no costings for effects on high-risk patients
Done from employers perspective only i.e. societal perspective is preferred or NHS perspective would have been more acceptable	Done from employers perspective only i.e. societal perspective is preferred or NHS perspective would have been more acceptable
All cost and effectiveness inputs gained from literature searches	Many of the costs used were 'real' costs gathered retrospectively although some costs and effectiveness inputs were gained from literature searches
A basic model was developed and then a sensitivity analysis of several important issues carried out	A Baseline scenario featuring the most likely estimates was used and then three other scenarios also used (vaccination promotion in the workplace and an efficient promotion scenario and high influenza incidence due to resistant strain scenario) A sensitivity analysis on several important issues also carried out.
The study did not investigate the effect of the circulating virus not matching the vaccine strain	The study did not investigate the effect of the circulating virus not matching the vaccine strain
Values of elements and unit costs are given as well as overall costs and benefits.	Values of elements and unit costs are given as well as overall costs and benefits.

4.2.3 Results

The results of the study of healthy working adults in the UK showed[51], using a base case scenario (see table 11), that there was a net benefit for the vaccination programme when the incidence of influenza was 2%, 6% and 10% (a legitimate range of values based on previous year's incidence). The cost-benefit ratios (determined as ratio of benefits:costs ie costs averted) for these scenarios are 1.03, 3.09 and 5.15 respectively.

A sensitivity analysis was carried out in this study altering such parameters as incidence, vaccine efficacy, costs of programme, number of days of work amongst others. The conclusion was that the vaccination programme resulted in a cost-saving even at an incidence of 2% providing; efficacy is at least 65%, costs of implementing programme no more than £6.20 per vaccination, average wage at least £80 per day, employees took on average more than 4.8 days off work if they had influenza and had on average at least 0.5 days of reduced productivity when they returned to work.

The second study[52] used in this review is a study of health care workers in a medical facility in Amsterdam. The baseline scenario, which used the most likely estimate of each parameter showed a net benefit for the vaccination programme of EUR 125 per vaccination. Since the costs of promoting the campaign were not included in this estimate there would be a net benefit providing the promotional campaign cost less than EUR 117,000.

Three other scenarios were also used, two were vaccine promotion scenarios with clinics held in the workplace and an assumed higher compliance and one scenario was a resistant strain scenario with increased incidence, reduced vaccine effectiveness and increased absenteeism.
The vaccine promotion scenarios showed a net benefit of EUR 122 per vaccination while the resistant strain scenario showed a net benefit of EUR 194 per vaccination.
A sensitivity analysis was carried out, showing that vaccine acceptance had the greatest effect on net benefits. However only the most pessimistic multivariate analysis varying several parameters including influenza incidence, vaccine acceptance, vaccine cost and lost time per vaccination resulted in a net cost for the vaccination programme.

Table 11 Values of costs and benefits used in studies

	Das Gupta 2002[51]	**Parlevliet 2002[52]**
Vaccination cost per vaccination	£5.97 (base case)	EUR 10.32 (baseline) EUR 17.47 (workplace promotion scenario) EUR 9.53 (efficient promotion scenario)
Work time lost per vaccination	15-20 mins (assumed to have negligible costs associated with them)	20 mins (baseline) 10 mins(workplace promotion scenario) 25 mins (efficient promotion scenario)
Clinic cost	£10.71 per vaccination (sensitivity analysis)	EUR 15.88 (full doctors consultation)-not in baseline scenario
Cost of promotional campaign	Not costed	Not costed directly
Side-effects	Not costed as assumed to be negligible	Not costed as assumed to be negligible
Compliance rate	Base case looked at effects of 25%, 50%, 75% and 100% compliance	15% (baseline) 60% (promotion scenario)
Vaccine efficacy	68% (95% CI 49-79%)	80% 65% (high flu scenario)
Influenza incidence	2, 6 and 10%	0.19 cases per person per year 0.23 cases per person per year (high flu scenario)
Average flu days absent	5	8 11.8 (high flu scenario)
Other	Productivity reduced by 60% for one day in 85% employees returning to work	

Table 12 Summary of results from studies

Das Gupta 2002	Parlevliet 2002
Includes estimates of vaccination, vaccination duration, influenza incidence, absent days due to flu, uptake rates, average salary costs of absent days, vaccine effectiveness	Includes estimates of vaccination, vaccination duration, influenza incidence, absent days due to flu, uptake rates, average salary costs of absent days, vaccine effectiveness
Expected cost of lost productivity in absence of the vaccination programme when incidence of influenza was 2, 6 and 10% was £9, £27, and £45 per person respectively. **Base case scenario showed a net benefit for the programme when the incidence of influenza was 2%, 6% and 10%. Cost-benefit ratio (costs averted) was 1.03, 3.09 and 5.15 respectively.** i.e. there was a net benefit even when the incidence is as low as 2%	**Baseline Scenario (most realistic) showed net benefit of EUR 125 per vaccination** i.e. vaccine is beneficial in this setting if less than EUR 117,000 spent on vaccine campaign
	Vaccination promotion efficient planning Scenario (high compliance) showed net benefit of EUR 122 per vaccination
	Resistant strain scenario showed net benefit of EUR 194 per vaccination.
Sensitivity analysis showed that vaccination would be cost saving even at an incidence of 2% providing; efficacy is at least 65%, costs of implementing programme no more than £6.20, average wage at least £80 per day, employees took more than 4.8 days off work with flu and there was at least 0.5 days of reduced productivity when they returned to work.	Sensitivity analysis showed that compliance had the greatest effect on net benefits and only the most pessimistic multivariate analysis showed any net costs for the vaccination programme
	Also studied 'compensation absenteeism' which when set at 50% of absences resulted in a small net cost

5. ECONOMIC MODEL

5.1 Introduction

This analysis follows on from our systematic review of the effectiveness of vaccinating healthcare workers in order to protect high-risk patients from influenza. Only two randomised controlled trials have been published which address the effects on patient mortality of this type of vaccination programme[23;24], and we found no studies which evaluate the cost-effectiveness of such a programme.

In order to allow policy-makers to decide on whether the benefits of this type of vaccination programme on the health of the population justify the costs, some estimate of cost-effectiveness is necessary. Given the limited data, it is not possible to provide an exact answer, but we can make good use of the information available to construct an economic model which can provide a potential range of cost-effectiveness and can be modified for different scenarios.

We have used the main randomised-controlled trial [Carman][23] as the basis for our economic model, as described below, and UK costs in the base-case.

5.2 What is cost-effectiveness analysis?

Cost-effectiveness analysis involves comparing two (or more) courses of action in terms of their costs and effects. Effects must be aggregated into a single scale. In the case of influenza, since mortality in this group of patients is so high (22% over the 6 winter months in the control group of the Carman trial) the most appropriate measure of effectiveness is life-years gained by an intervention. Thus to assess the cost-effectiveness of a vaccination programme, it is necessary to estimate the difference in relevant costs with and without the programme, and compare that to the life-years gained by the programme. Assuming that the life-years gained are positive, there are two cases to consider.

(1) If the total relevant costs with the programme are **less** than they would be without the programme, then the programme is **cost-saving** as well as beneficial. In such cases, the programme is unconditionally worthwhile and should be implemented.

(2) If the total relevant costs with the programme are **greater** than they would be without, then it is necessary to establish whether the programme represents **good value for money**. Decisions of the NICE appraisals committee suggest that at present in the UK a programme is good value for money if the additional cost is less than £30,000 per life-year gained[70].

5.3 Methods to estimate the costs and benefits of a programme

The most direct way to estimate costs and benefits of a programme is a randomised controlled trial in a setting which sufficiently represents the population to which the programme would be applied, and with sufficient follow-up to determine all long-term outcomes. Since in practice such trials are rarely, if ever, available, it is necessary to combine information from a variety of sources in the form of an economic model.

In our case, there is a trial available[23] which was carried out in long-term geriatric hospitals across west and central Scotland. The trial reports short-term mortality: this can be converted into life-years gained by multiplying the number of survivors by the life expectancy of such people.

We have constructed a "spreadsheet" model which completes a cost-effectiveness analysis based on the Carman trial. The spreadsheet can be adapted to other settings. However, key inputs include the rate of uptake of vaccination among health care workers (with and without the programme) and the difference in short-term mortality due to the programme.†

To estimate the mortality gain from a programme of vaccination in a setting substantially different from that studied by Carman and colleagues would require a full transmission dynamic model. Such a model would normally require detailed data inputs about the various factors affecting transmission of influenza and since much of the information is not available it is beyond the scope of the present project.

5.4 Detailed description of the model

The first part of the spreadsheet relates to the basic setting. This gives the number of patients, the number of healthcare workers per patient and the breakdown of these into doctors, nurses and others.

The second part relates to costs. These consist of the cost of the promotional campaign, cost of the vaccine (including administration time for both giver and recipient), and an allowance for absenteeism. From these, the additional cost of the promotional campaign can be estimated.

The last part relates to effects. The difference in mortality is multiplied by the number of patients and by the life expectancy per patient to give the estimated life-years gained from the programme.

† An electronic version of this economic model is on the floppy disk inside the back cover of this publication.

Comparing the additional costs with the life years gained produces an Incremental Cost-Effectiveness Ratio (ICER) to compare against a threshold.

5.5 Source of parameter estimates

Table 13 Estimates (and their source) used in the base-case scenario

Parameter	Estimate		Source	Comment
Patients and staff				
Number of patients	1437		Carman[23]	
Staff:patient ratio	1.62		Carman[23]	
Number of staff	2335		Carman[23]	
Nursing/care staff hours per patient per week	35.4h		Wood 1993[71]	Approx 1.0 fte per patient per week
Average fte per nursing staff	0.75		Community Care Stats 2001[72]	Generates nursing staff per patient ratio of 1.3
Doctors (5%)			Estimate	Carman ratio 1.6 minus 1.3 = 18% for doctors and others. Remaining 82% split between nurses and auxiliaries where nurses = 38% and auxiliaries = 62% (From Community Care statistics 2001)
Qualified nurses (32%)			Community Care Stats 2001[72]	
Auxiliaries (51%)			Community Care Stats 2001[72]	
Others (13%)			Estimate	
Staff vaccine uptake				
With campaign	51%		Carman[23]	
Without campaign	5%		Carman[23]	
Absenteeism (h per person)				
Vaccinated	7 h		Demichelli[4], Wilde[49]	
Not vaccinated	10 h			
Costs	**Unit cost**	**Total cost**		
Vaccine promotion campaign	£0.70 per recipient		Estimated	Admin time, stationary, postage for letter
Vaccine	£6.59		BNF[73]	
Vaccine delivery recipient	30 minutes			
Doctors	£24 ph			Senior House Officer
Nurses	£17 ph		Netten & Curtis (April 2004)[74]	Staff nurse 24h ward
Others	£12 ph			Healthcare assistant
Vaccine delivery staff (nurse)	£17 ph			5 minutes
Absenteeism costs (locum multiplier)	1.0			
Effects				
Mortality in patients (vacc, control)	13.6%, 22.4%		Carman[23]	
OR reported	0.58 (0.40, 0.84)		Carman[23]	
Discount rates	3.5%		NICE appraisals guidance[75]	
Life expectancy				
% males	30%		Carman[23]	
Age distribution (m)(f)	M F			
Under 60	3% 1%		SHRUGS 1999[76]	(Rounding errors in males)
60-74	28% 11%			
75-84	40% 36%			
85+	26% 52%			
SMR (nursing homes)	600%		Raines 2002[77]	

Discounted life expectancy taking SMR into account (m)(f)(yrs)					
Under 60	9.10	10.96			Calculated from Interim life table 2001-03 E&W[78;79]
60-74	4.63	6.02			
75-84	2.09	2.69			
85+	1.49	1.83			
Overall	**2.75 yrs**				

The majority of the estimates are obtained directly from the published Carman data, and a relate to a scenario where:

- The staff ratios are 1.6 per patient
- The staff vaccination uptake rates are 51% with a campaign
- The vaccine match was good
- There was a community epidemic of influenza A which peaked in the first 2 weeks of January
- The setting is long-term geriatric care hospitals
- The age distribution is as above
- The size of the hospital is mean of 72 patients (range 44 – 109)
- The uptake of vaccination in patients is 41% (range 0 – 94%)
- The dependency (median Barthel score) is high (approx 4 on the modified 20pt Barthel index)

We used the Carman paper for parameters which would affect effectiveness of vaccine, and information relating to present day values for parameters affecting costs (eg costs of vaccine, campaign, staff delivery time, staff ratios, staff absenteeism costs).

Life expectancy in geriatric medical wards would be markedly reduced compared with the general elderly population in England and Wales as the patients are very frail in comparison and likely to have a worse prognosis. Raines et al[77] used routinely collected data to investigate the SMR of people admitted to nursing homes between 1993 and 1997 in Wakefield (compared with the 1995 E&W population 65+. SMR for the first year for all admissions from hospital was 606% (536, 676) and from community was 546% (458, 635) (a non-significant difference).

For the base case we assumed that locum costs would be the same as standard employment costs. We include in the model a multiplier to allow for increased costs.

5.6 Discounting

It is standard practice to discount costs and benefits that both accrue in the future to their present net value. Both future costs and benefits are discounted at 3.5% (consistent with the most recent UK guidelines on the topic[75].

5.7 Results

Our base-case analysis, including the costs of replacing staff arising from staff absenteeism, shows this programme to be cost-saving by approximately £28,000 for the 1437 patients (table 14). This would equate to a saving of about £1400 for a 72-bed hospital.

5.8 Ignoring absenteeism

We have assumed that NHS staff absent due to sickness would be replaced and have costed this at the normal cost of employment. We tested an alternative costing perspective excluding the cost of absenteeism (table 15). From this perspective the cost-effectiveness becomes £51 per life-year saved.

5.9 Worst case scenario

In a worst case scenario where the costs of the vaccination increases, where vaccination has no effect on staff absenteeism, where the life expectancy in general is lower and where the vaccine has lower efficacy (table 15), the cost-effectiveness becomes £405 per life-year saved.

5.10 No protective effect on mortality

There is some confusion over the extent of the mortality reduction as reported in the paper by Carman, where it was not fully clear whether the 95% confidence intervals of 0.4 to 0.8 around the OR of 0.6 were correct. The extent of mortality reduction has been explored in the sensitivity analyses. It is conceivable that there is no protection of the elderly. If this is the case, then there would be no benefit to the programme in terms of patient-gain. If the programme is cost-saving from the perspective of absenteeism avoided, then the relative value of mortality reduction has no effect.

Table 14 Base-case calculation

Basic setting				
Number of patients	1437			
		numbers		
Total ratio HCW/patients	1.62	2335		
Estimated staff per patient	0.08	117	doctors	
	0.52	747	nurses	
	1.02	1471	others	
	High uptake	Low uptake		
Uptake rate	0.51	0.05	from Carman	
Costs				
Vaccine promotion campaign	1634			
Vaccine	7847	769		
Vaccine delivery - recipient time (doctors)	714	70		
Vaccine delivery - recipient time (nurses)	3239	318		
Vaccine delivery - recipient time (others)	4501	441		
Vaccine delivery - staff time	1687	165		
Influenza in HCW -absenteeism	280826	326580		
Total costs	**300449**	**328344**		**Cost Saving of 27895**
Effects				
Mortality in patients	0.136	0.224	0.088	Mortality reduction from high uptake
Odds	0.157	0.289	**348**	**Life-years gained from high uptake**
Odds ratio		0.545		
Life year calculations				
Life expectancy	2.75			

Cost calculations

Time per vaccination	30	mins	(recipient time)	Given to all staff
	5	mins	(staff time)	Given by nurses

Hours absenteeism

vaccinated	7	7
not vaccinated	10	10
overall	8.47	9.85

locum time (hours)	989	1150	doctors
	6328	7360	nurses
	12459	14489	others

locum cost (£)	23732	27598	doctors
	107584	125112	nurses
	149510	173870	others

Cost of workers' time		locum		
doctors	24	24	£/hour	Netten and Curtis
nurses	17	17	£/hour	(accessed 20 Oct 2004)
others	12	12	£/hour	

Unit cost of vaccine	6.59	
Promotion cost per worker	0.7	(estimate including admin time, stationery and postage)

Locum cost multiplier 1.00

Table 15 Base case and worst case scenarios

Parameter	Base-case	No absenteeism base-case	Worst case
Cost of promotion per recipient	£0.70	£0.70	£2
Cost of vaccine per recipient	£6.59	£6.59	£10
Absenteeism reduced per person	3 hours	N/A	0 hours
Cost multiplier for locum absenteeism	1	N/A	
Life expectancy	2.75 yrs	2.75 yrs	1.5 yrs
Mortality reduction	8.8%	8.8%	4%
Nurse time to vaccinate	5 mins	5 mins	10 mins
Staff uptake rate	51%	51%	70%
Discounting	3.5%	3.5%	3.5%
Additional cost	Saving of £28,000	£18,000	£35,000
Life years saved	350	350	86
	Cost saving (approx £12 per vaccinee)	£51 per life year saved	£405 per life year saved

5.11 Alternative settings

In the UK, this type of setting, geriatric long-stay medical wards has been almost totally superseded by smaller nursing homes (and other residential homes for the less dependent). Across Europe the care for older people will also vary. This simple spreadsheet can be used to model different scenarios in terms of setting and also costs. The effectiveness of the vaccine may vary according to:

- Vaccine match
- Presence/extent of epidemic
- Uptake of vaccination in staff
- Uptake of vaccination in patients
- Dependency/frailty of patients
- Age

Policy makers in Europe can use this electronic template with their own specific parameters to assess cost-effectiveness in relation to their location.

5.12 Conclusions

Our base-case estimate shows the programme to be cost-saving. The main driver of this is the effect of absenteeism, as reflected in the worst-case scenario. Even in the worst case scenario the cost-

effectiveness of the programme is only £405 per life year saved and represents excellent value for money.

Although these were calculated for a particular setting, the results are so far from any recognised threshold that it is reasonable to suppose that vaccination of health care workers to prevent transmission to elderly patients would be cost effective in any setting.

Healthcare decision makers could insert their parameters into this simple model to produce estimates for their own setting.

Note that this model depends on an estimate of mortality benefits. This would have to be derived from an exterior source such as trial evidence or a full transmission dynamic model. Such information is not yet available. However, there are ongoing trials which may answer these questions.

6. DISCUSSION

Clinical effectiveness :

Effects on high risk patients: Mortality

Two cluster randomised controlled trials[23;24] were included to answer the main question on mortality in high-risk groups. The main trial[23] reported an odds ratio of 0.58 (0.4-0.84) in favour of a reduction in mortality where a HCW vaccination programme existed (p=0.014), while the smaller trial also showed a statistically significant reduction in mortality (p=0.013). [24]

Unfortunately, although the trials were generally of good quality, the methods of analysis were not clearly described. In the pilot trial, it did not appear that the clustered nature of the data had been taken into account properly in the reporting of the odds ratio and confidence interval. This would tend to affect the degree of certainty around the estimates rather than have a substantial effect on the point estimate as a cluster design tends to increase uncertainty. In the main trial, our calculations suggest that although not totally clear, it is plausible from the width of the confidence intervals and p values reported that the analyses allowed for the cluster design.

Although mortality in patients is the most important outcome, the success of a vaccination programme is clearly dependent on several factors.

Vaccine Uptake in HCW

Vaccine uptake in the two included studies[24] on mortality was 50%[23] and 61%[24]. Other studies on vaccine uptake were included in the review in order to determine if these uptake rates were realistic outside of a cluster RCT. Twenty other studies[25;27-36;38-40;43-47;50] were found for this outcome. Seven of these studies had values of uptake with and without a vaccination programme with/without a promotional campaign, all of which showed an improvement in uptake with a vaccination campaign.

The most effective of these appeared to be where a 'mobile clinic' system was used[28] i.e. a public health nurse took a vaccination cart to each ward. This resulted in vaccination taking less time and being very successful (uptake of 81% in its 2nd year). Most of the other campaigns were promotional campaigns giving information about vaccination and promoting clinics offering free vaccination. Vaccination rates where a campaign existed ranged from 15%[30] to 81%[28] and clearly there is a high degree of heterogeneity between not only the campaigns but also the setting and the HCW involved. 8/17 studies with campaigns achieved an uptake of 50% or more. Since studies in the UK where no campaign existed[23;30] have shown low uptake 5% and 9%, it is clear that a well-thought out, successful campaign is necessary if a vaccination programme is to be successful in terms of patient outcomes. A personal letter and information leaflet could be included in payslips, for example, as is the case in some primary care trusts in the UK.

Reasons for non-vaccination

In studies where HCW were asked for their reasons for non-vaccination, the main reason stated was lack of knowledge that it was necessary/advantageous to patients (and themselves) to be vaccinated. In 3/10 of the surveys this was cited as a reason for non-vaccination in over 50% of survey respondents. This further substantiates the need for a successful promotional campaign, not only for convenience of vaccination but also for information. More knowledge of the vaccination is needed for other reasons also, e.g. fear of side-effects was also one of the main reasons for non-vaccination in 8/10 studies.

Side-effects

Side-effects in HCW is also a key issue, not only might it affect uptake rates but might also have an impact on absenteeism following vaccination. Side-effects were studied in 6 studies used for the clinical effectiveness portion of the review. There was some heterogeneity in the reported frequency of side-effects amongst vaccines; experience of sore arm ranged from 18-73%, although values for systemic side-effects were less variable e.g. fever 5-13%. In the one trial[48] which clearly compared vaccine to saline placebo, the only side-effects occurring at significantly increased frequency in the intervention arm were sore arm and redness at the injection site.

A promotional campaign may therefore be used not only to inform staff of the need for vaccination but also allay fears about side-effects.

Rates of influenza

The positive benefits for HCW should also be promoted i.e. protection from influenza. 4 trials[41;42;48;49] studied rates of influenza/ILL in HCW. The best quality RCT [49]showed statistically significant higher rates of influenza/ILL in unvaccinated HCW compared to vaccinated HCW, giving a protective efficacy of 88% (47%, 97%) for Influenza A(H3N2), while the other two[42;48] failed to show a significant difference (although one trial was poor quality with low influenza incidence[42] whilst the other[48] had a poor vaccine match to the circulating strain). The meta-analysis in healthy workers conducted by Demicheli found a best estimate of protective efficacy where the vaccine was a complete match, of 72% (95% CI 54%, 83%). In recent years scientists have become better at predicting vaccine composition and the vaccines are now likely to be a good match to the circulating strain of influenza.

Absenteeism

The Health Service may also directly benefit from HCW vaccination not only from a decrease in spending on morbidity from influenza in high-risk groups but also from reduced absenteeism in HCW. The two best quality RCTs[48;49] showed no statistically significant difference. In the remaining poorer quality RCT[42] a statistically significant reduction in absenteeism of 0.4 days was seen with HCW

vaccination, which agrees with the meta-analysis of healthy adult workers.[4] Effect on absenteeism was further investigated in the included cost-benefit studies.

Cost-benefit review

Results from the two cost-benefit studies[51;52] used in this review show, in most likely scenarios, that implementation of a vaccination programme would represent a cost-saving for the employer. Since these studies only take into account costs from an employers point of view it seems likely that vaccination would result in even higher benefits when assuming a societal or even healthcare provider perspective. For example there would be fewer GP visits, fewer over the counter medications, fewer hospitalisations due to complications. This is assuming that there would be no other costs associated with vaccination for the healthcare provider or society. It seems likely that in terms of outcomes in health care workers i.e mostly absenteeism, a vaccination programme would be cost-saving.

Following on from this argument, if it is cost-saving when considering only health care worker outcomes, the cost-saving is likely to be greater when considering costs averted due to reduced transmission to high-risk groups.

Economic model

We were able to perform only a simple economic model based on the main published RCT. Without cluster-level data, we can only draw conclusions in that setting and its associated parameters. However, despite this, our model clearly shows that under the base-case scenario the programme would be cost-saving (in our scenario by approximately £12 per vaccinee). Under less favourable conditions (for example when there is no saving from absenteeism avoided), the programme would still be highly cost-effective. This simple model will be useful for decision-makers, who can apply their own parameters. When the UCL trial reports in a couple of years, firmer estimates of cost-effectiveness can be derived for the UK nursing home setting.

Limitations of the review and recommendations for further work

Overall there is generally a limited quantity of data directly addressing the effectiveness and cost-effectiveness of vaccinating low risk personnel to indirectly protect those at high risk. However, it seems plausible to draw out conclusions on the current state of the evidence.

There are only two studies addressing the effect on patients (the data is really limited to patient mortality), but although there are some concerns about the analysis of both of these studies there probably is a significant protective effect. The large cluster randomised trial underway in UK nursing homes should go some way to resolving this situation, but will not be reporting for a couple of years.

The effectiveness of the vaccine in the healthcare workers themselves also has limited data, but is likely to be of similar effectiveness to other healthy adults. The information on absenteeism is very sparse and cannot necessarily be assumed to be the same as other adults.

The studies addressing the reasons why healthcare workers declined to have an influenza vaccination are very variable in design and quality, but there are overall themes consistent across the studies which are likely to reflect the true situation. Effective methods to improve uptake were also studied in a range of settings and were again of variable design and quality. However, taking a pragmatic view, it would seem that a convenient mobile system plus clear education to overcome misconceptions would be an effective approach, perhaps with a personal letter and clear education message inserted into payslips. Particular attention should be paid to those who have never had the vaccine, as they are less likely to receive it again in subsequent years.[40]

There was no published economic data which incorporated the indirect effects of protecting patients. Extrapolation from the two good quality economic studies would suggest that incorporating the effect on patients would also be cost-saving or highly cost-effective. This was confirmed in our economic model which indicated that the policy would be cost-saving in the base-case scenario, or extremely cost-effective under the worst case scenario. Despite the model being based on only one trial, it is unlikely that the current values for the key parameters will be hugely different, but the current UCL RCT (yet to be reported) is an important trial which will further solidify the parameters for the UK setting.

7. CONCLUSION

- From the evidence available to this review the following conclusions were drawn:-

- Two reasonable quality trials carried out in the UK were available to assess the clinical effectiveness of vaccinating healthcare workers to protect patients. Both reported a statistically significant difference in mortality in the intervention group (vaccination policy) compared to the control group (no vaccination policy) in favour of vaccination.

- No cost-effectiveness studies were available to directly answer the question of this review, although two partially relevant cost-benefit studies were included. Both showed a net-benefit associated with a vaccination policy but were only concerned with outcomes in healthy working adults (HCW in one study) and were from an employers perspective only.

- The studies indicated that if benefit in high-risk groups were taken into account it is likely that a vaccination campaign would prove more cost-effective or could well also be cost-saving.

- Our simple economic model, based on the data from the main Carman RCT, suggest that the vaccination of HCW is indeed cost-saving (under the base-case scenario) or highly cost-effective (under the worst-case scenario).

- If an intervention is found to be cost-saving to the health provider, it should be properly implemented immediately. If there is a net cost, then a judgement is needed as to whether the vaccination programme would meet the criteria for implementation.

- If the vaccination of healthcare workers is to be implemented effectively, then the misconceptions about the influenza vaccine need to be addressed and the vaccine to be delivered in a setting convenient to the workers, probably by some sort of mobile clinic. To facilitate this, an education campaign would seem mandatory. Workers could be sent a personal letter with clear information leaflet with their monthly payslips for example.

Despite the limited evidence available at this time, this review suggests that based on reasonable estimates of the key parameters a vaccination policy of HCW is likely to be both clinically effective and probably cost saving.

8. APPENDICES

Appendix 1: Definition of high-risk groups

A. The WHO recommendations[1]:

- Residents of institutions for the elderly or disabled
- Elderly non-institutionalised individuals suffering from chronic heart/lung diseases, metabolic/renal disease, immunodeficiencies
- >6 months of age with any of the above conditions
- Elderly individuals above a nationally defined age limit irrespective of medical risk status
- Other groups defined on the basis of national data
- Health care workers in contact with high-risk persons
- Household contacts of high-risk persons

B. National (UK) policy for influenza immunization (2003/2004):

(a) People of all ages in the following risk groups:-

- **Chronic respiratory disease including asthma**

This includes chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, asthma requiring continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission.

- **Chronic heart disease**

This includes chronic ischaemic heart disease, congenital heart disease and hypertensive heart disease requiring regular medication and follow-up (but excluding uncomplicated controlled hypertension), and chronic heart failure.

- **Chronic renal disease**

Including nephritic syndrome, chronic renal failure, renal transplantation.

- **Diabetes**

Diabetes Mellitus requiring insulin or oral hypoglycaemic drugs.

- **Immunosuppression**

Due to disease or treatment, including systemic steroids equivalent to 20mg prednisolone daily for more than 2 weeks. However, please note that some immunocompromised patients may have a suboptimal immunological response to vaccine.

(b) All people aged 65 years and over and those living in long-stay residential and nursing homes or other long-stay facilities.

(c) All healthcare workers involved in the delivery of care and/or support to patients.

Appendix 2: Search strategies: clinical effectiveness

Database: Medline <1966 to Present>Search Strategy:

1 exp influenza/
2 (influenza or flu).tw.
3 or/1-2
4 exp health personnel/
5 health care worker$.tw.
6 health worker$.tw.
7 caregiver$.tw.
8 care giver$.tw.
9 exp physicians/
10 exp medical staff/
11 nurses/
12 care givers/
13 or/4-12
14 nursing homes/
15 homes for the aged/
16 or/14-15
17 vaccination/
18 influenza vaccine/
19 or/17-18
20 3 and 19 and 13
21 3 and 16 and 19 and 13
22 20 or 21

Database: EMBASE <1980 to Present>Search Strategy:

1 influenza/
2 (influenza or flu).tw.
3 exp health care personnel/
4 health care worker$.tw.
5 health worker$.tw.
6 caregiver$.tw.
7 care giver$.tw.
8 exp medical personnel/
9 nurse/
10 caregiver/
11 nursing home/
12 residential home.tw.
13 or/1-2
14 or/3-10
15 or/11-12
16 vaccination/
17 influenza vaccination/

18 or/16-17
19 13 and 14 and 18
20 13 and 14 and 15 and 18
21 19 or 20

Database: CINAHL <1982 to 1997>Search Strategy:

1 exp influenza/
2 (influenza or flu).tw.
3 or/1-2
4 exp health personnel/
5 health care worker$.tw.
6 health worker$.tw.
7 caregiver$.tw.
8 care giver$.tw.
9 exp physicians/
10 medical staff.tw.
11 exp nurses/
12 care givers/
13 or/4-12
14 nursing homes/
15 homes for the aged/
16 or/14-15
17 vaccination/
18 influenza vaccine/
19 or/17-18
20 3 and 19 and 13
21 3 and 16 and 19 and 13
22 or/20-21

Database : Cochrane Library

INFLUENZA
FLU
INFLUENZA*:ME
INFLUENZA-A-VIRUS-HUMAN:ME
INFLUENZA-B-VIRUS:ME
((((#1 or #2) or #3) or #4) or #5)
(HEALTH next WORKER*)
(HEALTH next (CARE next WORKER*))
HEALTH-PERSONNEL*:ME
CAREGIVER*
(CARE next GIVER*)
PHYSICIANS*:ME
MEDICAL-STAFF*:ME
NURSES*:ME
(((((((#7 or #8) or #9) or #10) or #11) or #12) or #13) or #14)

INFLUENZA
INFLUENZA-VACCINE*:ME
VACCINATION*:ME
VACCINAT*
((#17 or #18) or #19)
((#6 and #15) and #20)

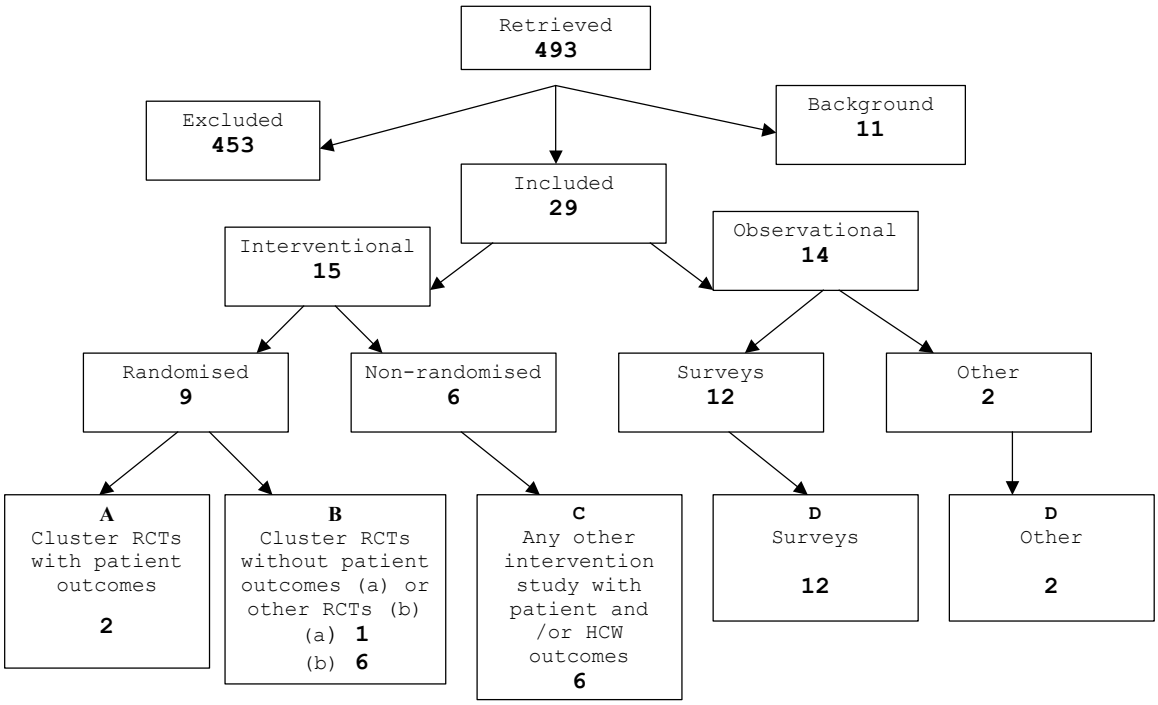
Appendix 3: Search strategies-cost-effectiveness

influenza.mp. [mp=ti, ab, rw, sh]
flu.mp. [mp=ti, ab, rw, sh]
1 or 2
economics/
exp "costs and cost analysis"/
exp "fees and charges"/
(cost or costs or costed or costly or costing).tw.
(economic$ or price$ or pricing).tw.
5 or 6 or 7 or 8
3 and 9
limit 10 to human
limit 11 to yr=1993-2003

Search strategy adapted from York CRD report (ref) and adapted to be deliberately inclusive.

Appendix 4: Search Output Flow Diagram

Flow diagram of search output for clinical effectiveness



Appendix 5: Barthel Index[80]

Activity	**Score** **(100 pt scale)**	**Score** **(20 pt scale)**
Feeding 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	0 5 10	0 1 2
Bathing 0 = dependent 5 = independent (or in shower)	0 5	0 1
Grooming 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	0 5	0 1
Dressing 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	0 5 10	0 1 2
Bowels 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	0 5 10	0 1 2
Bladder 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	0 5 10	0 1 2
Toilet Use 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	0 5 10	0 1 2
Transfers (bed to chair and back) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	0 5 10 15	0 1 2 3
Mobility (on level surfaces) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	0 5 10 15	0 1 2 3
Stairs 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	0 5 10	0 1 2
TOTAL	**0 -100**	**0 - 20**

Appendix 6: Tabulation of Extracted Data on Study Results

Table 6.1 Characteristics of studies with patient outcomes.

	Carman 2000	**Potter 1997**
Country	Scotland	Scotland
Trial dates	1996-7	1994-5
Trial design	'Parallel group design with cluster randomisation' Cluster randomised control trial of vaccination programme	Cluster randomised control trial of vaccination programme
Number of clusters	20	12
Type of clusters/unit of randomisation	UK NHS medical long-term-care geriatric hospitals	Geriatric medical long-term-care hospitals in Glasgow
Number of trial arms	2 (10 clusters each)	4 (2 where patients were routinely offered vaccine already – i.e. not part of the trial to vaccinate patients)
Intervention	Vaccination routinely offered by letter and interview by trained study nurses	Vaccination routinely offered
Control	Vaccination not routinely offered	Vaccination not routinely offered
Vaccine match	Good match to circulating strain	
Number HCW	1217 offered vaccination but number in control group not given	1078 identified in intervention group and 653 (61%) agreed to participate and receive vaccination
Number patients	1437 (749 in intervention clusters, 688 in control clusters)	1059
Trial arms	Health care workers offered vaccination (intervention) or not offered vaccination (control).	Health care workers offered vaccination (intervention) or not offered vaccination (control).
Randomisation procedure	Random allocation, clusters balanced and stratified for policy of vaccination of patients and size. Cluster paired by these characteristics and one chosen from each pair by random number tables for intervention.	Hospital sites stratified by unit policy for vaccination and then randomised to receive intervention or control.
Health care workers involved	Nurses, doctors, therapists, porters and ancillary staff.	Nurses, doctors, therapists, porters and ancillary staff
Patient outcomes and method of collection	Mortality 18/11/96-31/3/97 Prospective virological monitoring (nose and throat swabs) during winter epidemic on random sample (50%) of patients	Mortality (10/94 – 03/95) Influenza-like infection rates Lower respiratory tract infection
HCW outcomes and method of collection	Response rate in sub-group by questionnaire	Overall participation rate
Power calculations	Based on previous study. For patient mortality : with 1600 patients in 20 hospitals – 80% power to detect 5% decrease in mortality	None given
Analysis	It is stated that analysis by cluster was done for mortality, however it is not known if the other outcomes were correctly analysed	It is stated that analysis by cluster was done for mortality, however it is not known if the other outcomes were correctly analysed

Relevant definitions	None	Influenza-like illness defined as temp ≥ 37 + one or more of ; cough, coryza, sore throat, malaise, headache, muscle pains. Lower respiratory infection defined as pulmonary cackles, wheeze or tachypnea + temp ≥ 37 or wbc > 10 x 10^9/L. Or identified with positive sputum culture.

Table 6.2: Characteristics of Dey 2001 (cluster RCT of HCW vaccination uptake).

	Dey 2001
Country	England
Trial dates	1999-2000
Trial design	Cluster randomised control trial of promoting vaccine uptake
Number of clusters	96
Type of clusters/unit of randomisation	Primary Health Care Teams (PHCT) and nursing homes (NH)
Number of trial arms	2 (control-32 PHCT, 17 NH and intervention 30 PHCT, 17 NH)
Intervention	Vaccine offered by letter and then visit by public health nurse to promote uptake
Control	Vaccine offered by letter only
Number HCW	2984 (1759 in control, 1225 in intervention)
Number patients	Not relevant
Trial arms	HCW offered vaccine with letter (control) or offer letter and follow-up visit with public health nurse (intervention)
Randomisation procedure	Worksites were stratified into PHCT and NH and then randomised within strata to intervention or control
Health care workers involved	Nurses, doctors and admin/ancillary staff
Patient outcomes and method of collection	None
HCW outcomes and method of collection	Vaccine uptake rates
Power calculations	The study has 80% power to detect a difference of at least 20% between control and intervention groups
Analysis	'The rate of uptake of vaccination was compared between study groups using a chi^2 statistic adjusted for the cluster randomised design'
Relevant definitions	None

Table 6.3: Characteristics of RCTs wth HCW outcomes.

	Al Mazrou 1991	**Aoki 1993**	**Mostow 1977**	**Saxen 1999**	**Weingarten 1988**	**Wilde 1999**
Country	Canada	Canada	USA	USA	USA	USA
Trial dates	1989-90	1990-1	Not stated	1996-7	1985-6	1992-5
Study period	48 hours	6 months	3 days	5 months	2 months	3 consec. seasons
Trial design	Recipient-blinded randomised trial to compare 2 vaccines	Double-blind placebo-RCT to evaluate effects acetaminophen	Double-blind RCT determine impact flu programme	Double-blind placebo-controlled RCT for vaccine effect in HCW	Double-blind placebo-RCT vaccine effect HCW	Double-blind placebo-RCT vaccine effect HCW
Trial arms	2	3	2	2	2	2 per season
Intervention	Split-virion (SVV) vs trivalent inactivated whole-virion (WVV)	Acetaminophen 325 or 650mg followed by vaccine	Split-virus vaccine vs whole-virus vaccine	Influenza vaccine	Influenza vaccine	Influenza vaccine
Control	No control	Placebo followed by vaccine	No control	Saline placebo	Saline vaccine	**1992-3** Meningo-coccal**1993-4:** Pneumococcal **1994-5:**Saline
Number HCW	358	262	4100	547	181	**92-3**:102**93-4**:103 **94-5**:156
No. per trial arms	187 in SVV 171 in WVV	88 placebo, 87 325mg, 78 650mg	Split-virus 1571 Whole-virus 1565	216 intervention 211 control	91 intervention 88 placebo (2 excluded)	92-3: 52 vs 50 93-4: 51 vs 52 94-5: 78 vs 78
HCW involved	All HCW	All HCW	All HCW	All HCW	All HCW	Physicians, nurses and respiratory therapists
Outcomes	For 48 hrs-record analgesia taken, symptoms and work loss.	Adverse events	Adverse events, absenteeism by questionnaire	Adverse events and sick absence survey and follow-up diary	Adverse reactions Clinical influenza Sick absence Costs	Flu-serol. confirm, days febrile respiratory illness, work loss
Analysis	One-sided Fisher's exact test used as expected a difference only in direction of fewer adverse events with SVV	Chi^2 to compare proportions, ANOVA to compare means and Kruskal-Wallis to compare medians. Logisitc regression to adjust for effects of confounders	Not given	Student's t-test or Wilcoxon two sample test. Side effects compared using Mantel-Haenzel chi^2.	Discrete data-chi^2, normal continuous data-t-test, skewed continuous-Mann Whitney-U	361 person-winters. ITT basis. 2-sided Wilcoxon rank sum test for cont. variables. Nominal- chi^2 or Fishers exact. Mantel-Haenszel estimates of rate ratios used to compare groups.
Relevance to review	**Details adverse events of vaccination in HCW**	**Gives details of adverse events associated with vaccine but without a control**	**Details adverse events and absenteeism but without control**	**Details of adverse events and absenteeism due to immunisation and influenza with a placebo control**	**Does vaccination reduce absence and flu in HCW and details adverse events compared to placebo?**	**Details adverse events and absenteeism and uptake rates (ITT analysis carried out)**

Table 6.4: Characteristics of other intervention studies of uptake rates and outcomes in HCW.

	Cooper 1990	**Harbath 1998**	**Nishi**	**Schiefele 1990**	**Tannenbaum 1993**	**Thomas 1993**
Country	Australia	Switzerland	Japan	Canada	Canada	USA
Dates	2000	1996	1999-2000	1988	Autumn 1989	1990-1
Trial design	Before-after	Before-after	Controlled trial	Feasability/safety	Controlled trial	Before-after
Arms	1	2	2	1	2	1
Intervention	Mobile immunisation programme	Geriatric, paeds and obs depts received control + edu. conf. and special health nurse visit with vaccine	Influenza vaccine	Voluntary vaccination programme with promotion	Information sessions and memos, vaccine clinics	Educational intervention followed by vaccination fair
Control	Retrospective comparison	(Rest hospital) newsletters, reminders, posters, letters	No influenza vaccine	None	No intervention programme	Retrospective comparison
Number HCW	880	5432 before 5514 after	727	Approx. 500	268	195
Setting	n/a	1500 bed university hospital	Central hospital	Not stated	135 bed nursing home	300 nursing home
Contact high-risk patients?	Unknown	Yes (intervention group)	Unknown	Unknown	Yes	Yes
Numbers per trial arms	n/a	Before : 5432 (1076 inter, 4356 control) After: 5514 (1092 inter., 4422 control)	132 intervention 595 control	n/a	135 (133 staff at another home used as control)	Total 195 staff
HCW involved	All staff	All staff	All staff	All staff	All staff	All staff
HCW outcomes	Uptake rate Costs Attitudes from survey	Changes in uptake rate over 2 years	ILL Absenteeism Costs(work loss)	Uptake rate Adverse events	Uptake rate knowledge and beliefs about flu vaccination	Vaccination rate Attitudes
Analysis	None	Differences in Vacc. Rate - chi^2 binomial prop. Means-unpaired t-test. Sig. tests 2-tailed	Fisher's exact test	None	Logistic regression analysis	5-point Likert scale. Group means compared using t-test
Relevance to review	Uptake rates	Uptake rates Outcome of vaccination program	Details ILL and absenteeism in season following vaccination with placebo control	Uptake rates and adverse events	Uptake rates with and without vaccination promotion	Uptake rates and attitudes to vaccination

Table 6.5: Characteristics of observational studies assessing uptake rates and attitudes to vaccination.

	Christian 1991	**Elorza Ricart 2002**	**DeAngelis 1996**	**Doebbelin g 1997**	**Ganguly 1990**	**Harbath 1998**	**Heimburger 1995**
Country	USA	Spain	USA	USA	USA	Switzerland	USA
Study design	Survey	Descriptive analysis	Survey	Multi logistic regression models	Survey	Survey	Survey
Setting	123-bed acute care hospital	Tertiary hospital	Paediatric health care providers (PHCP) in El Paso, Texas outbreak	900-bed hospital	Veterans hospital	Geriatrics, paediatrics & obstetrics depts. at 1500 bed university hospital in Geneva	Large chronic care psychiatric facility
Vaccination campaign	'Vaccine offered'	Workplace vaccination s with a leaflet	Unknown	Written invitation, flyers, letters to department heads, signs posted in facility.	None	Adverts, educational conference, visit by special health nurse	In service meetings, videotapes, pamphlets
Questionnaire details	Yes/No self-administ-ered 40 question survey	N/a	In person/ telephone. 4 questions	N/a	Randomly assigned	24 multiple-choice	Anonymously-administered

Table 6.5 continued.

	Manuel 2002	**Murray 2001**	**Nafziger 1994**	**Nichol 1997**	**Stephenso n 2002**	**Watana-kunakorn 1993**	**Yassi 1994**
Country	Canada	Australia	USA	USA	UK	USA	Canada
Study design	Survey	Survey	Survey	Survey	Survey	Survey	Survey
Setting	2, 230-bed long-term-care facilities	Tertiary adult hospital	891-bed university tertiary referral hospital & 278-bed veterans hospital	400-bed teaching hospital.	3 acute hospitals, total 2300 beds, 8500 employees	650-bed community teaching hospital	Health Sciences Centre, 1100-bed acute care teaching hospital
Vaccination campaign	Educational sessions with PH nurse, free vaccination, prize incentive	None	Posters, newsletter, emails, memos and reminders	Walk-in clinics + mobile vaccination cart, information meetings	Posters, mailshots, walk-in and appointmen t based clinics	Free vaccination offered to all personnel	None
Questionnaire details	58 item self-administ-ered	Pre-piloted telephone survey-single interviewer.	32 question survey given during clinics	35 item, self-administ-ered mailed survey	18-item survey hand delivered to ward staff	14 questions	Mailed to 948 targeted HCW

Appendix 7: Tabulation of Extracted Data on Study Results

Table 7.1: Results of studies with patient outcomes.

	Carman 2000	**Potter 1997**
Number of clusters	20 (10 in each arm)	12
Patient outcomes	All cause mortality and virological screening	All cause mortality. Deaths with pneumonia Influenza-like illness rates
Patient number	1437 (749 intervention, 688 in control arm)	1059 (490 intervention, 569 control)
Balance of Baseline Characteristics	Hospital size, patient age, sex not statistically different between arms. **Barthel score** (median 5 (range 3-7.5) intervention group vs. median 3 (range 1-5) control group) and **Patient vaccination rate** (mean 48 (range 0-94) in inter-vention group vs. mean 33 (range 0-70) control group) different. Analysis corrected for this.	No significant differences between trial arms for size, age, sex, Barthel score.
Mortality	Uncorrected : 102/749 (13.6%)intervention, 154/688 (22.4%) control. Odds ratio **0.58 95% CI 0.4,0.84** p=0.014. All corrected rates significant except when correct for Barthel score, age, sex and vaccination profile together **OR 0.61 (0.36, 1.04)** (borderline p=0.092). Samples for virological screening with PCR at death showed 20% compared to 0% in control arm had influenza.	Cluster analysis by hospital site showed a reduction in mortality, analysed by t-test p=0.013 (reduction from 17% to 10%) Cluster analysis showed no sig. diff between clusters where patients offered vaccine and those where they were not.
Rates of influenza/influenza-like illness	NOT MEASURED DIRECTLY Samples also taken from some patients (not part of screening programme) with symptoms. 15% in control and 10% in intervention PCR-positive for influenza.	Odds ratio 0.57 (0.34-0.94) effect of HCW vaccination NOT KNOWN IF CORRECTLY ANALYSED
Other patient outcomes	Routine Virological Screening 527/719 offered screening accepted.5% in intervention and 7% in control were PCR-positive for influenza.	Lower respiratory tract infection Odds ratio 0.69 (0.4-1.19) effect of HCW vaccination NOT KNOWN IF CORRECTLY ANALYSED
Other analysis	Patient mortality plotted against vaccination rate (in patients) showing no association.	None
Uptake Rate (vaccination in HCW)	620 (51%) of those offered were vaccinated. Questionnaires on nurses showed uptake rate of 50% in intervention group and 5% in control group. (Questionnaire return rates were 68% in intervention group and 49% in control group – nurses only studied)	653 (61%) agreed to participate and received vaccination

Table 7.2: Results of Dey 2001 (cluster RCT of HCW vaccination uptake).

	Dey 2001
Number of clusters	96
HCW outcomes	Uptake rate
HCW number	2984
Uptake Rate	OVERALL : 14.5% intervention group, 9.1% control group vaccinated 22% of HCW in intervention group (PHCT) were vaccinated while 21.% in control group (PHCT) vaccinated. **Not significant (p=0.91)** 10.2% of HCW in intervention group (NH) were vaccinated while 5.% in control group (NH) vaccinated. **Not significant (p=0.34)**

Table 7.3: Results of RCTs wth HCW outcomes.

	Al Mazrou 1991	**Aoki 1993**	**Mostow 1977**	**Saxen 1999**	**Weingarten 1988**	**Wilde 1999**
HCW number	558 (174 in SVV 159 in WVV)	262 (88 placebo, 87 325mg, 87 650mg)	Data available on 3146 of the 4100 took up vaccine	547 (216 vaccine, 211 placebo)	181-91 intervention 88 placebo (2 excluded)	264 (over 3 years)
Uptake Rate	25 (93% response rate for survey)	n/a	67% (77% response rate for survey).	100%	n/a	n/a
Rates of influenza/influenza-like illness	Not studied	Not studied	Not studied	1.8 episodes respiratory infection per person in vaccine group compared to 2 in placebo	No significant differences between trial arms for rates of flu, duration of flu or fever and severity of flu.	Infl. A& B Over 3 years:1%A, 0.6%B in vaccine vs 9% A and 5%B control (p=<0.05)
Adverse events	Total adverse events reported by 86% WVV and 78% SVV p=0.036 1% absenteeism in each trial arm following vaccination	Nausea10% vs 1% Sore arm 61% vs 44%. P<0.05	Stat.sig less for SVV than. No sig. diff. In absenteeism (3% for SVV and 9% for WVV)	20% in vaccine group vs 7% in placebo had local pain (p=0.01). Related to immunisation – not stat. sig.	Erythema 11% vs 0% p<0.05.Pain 51% vs 7% sig. i.e. p<0.01.	No significant side effects No absences due to vaccination
Absenteeism in following season	Not studied	Not studied	Not studied	Days lost at hospital due to respiratory infection 1.0 in vaccine vs 1.4 in placebo p=0.02	No statistically significant differences	Mean absence from work for vaccinated 0.1 days (SD 0.35) and for control group 0.21 days (SD 0.75) No significant differences
Other	93% response rate to questionnaire	None	76% response rate to questionnaire	No other statistically significant results	Costs	Vaccine response Overall response in 57% subjects for A(H3N2) and 40% for Infl.B
Follow-up	None	251 (96%) completed trial	None	78% completed 5 month follow-up	99% for influenza rates, 60% for adverse events	Not stated
Baseline characteristics	No stat. sig. differnces	Not described	Not described	Not described	Not described	No stat. sig. differnces

Table 7.4: Results of other intervention studies of uptake rates and outcomes in HCW.

	Cooper 1990	**Harbath 1998**	**Nishi**	**Schiefele 1990**	**Tannenbaum 1993**	**Thomas**
Uptake Rate	Before study 8% vaccinated In 2000 49% vaccinated After intervention 81%	Before : 9% vs 13% Overall– 10% After : 27% vs 37% Overall– 26% Greater increase interv. grp (p<0.001) Nurses least likely, physicians most likely to be vaccinated	Not studied	58%	Before : 16% vs17% After : 35% vs 13% Odds ratio=3.2 Adjust for age, sex, patient contact and FT/ PT status OR=2.8 (95% CI 1.4-5.8)	8% before 46% after 2nd interv year 54% 49% of nurses, 100% doctors, 85% admin
Adverse events	n/a	Not studied	Not studied	Surveys from 90%. None-10%, local only-41%, systemic-49%- fever 13%, nausea 10%, tiredness 10%, aches 15%, headache 8% Absenteeism due to side effects :16/288 (6%) 3 likely to be other infections	n/a	n/a
Absenteeism in following season	n/a	Not studied	Days missed due to illness higher in unvaccinated (2.3 v 10.7 dy per 100 persons) p<0.05	Not studied	n/a	n/a
Other	Good previous vaccination contributed to uptake. Frequently often incorrectly believed could develop flu from vaccine.	Response rate 73% Reasons for non-acceptance of vaccination were confidence to ward off flu (32%), supposed low-likelihood of getting flu 23% ,efficacy doubts 19%. Nurses most reluctant	ILL : Febrile illness 10 v 20 events per 100 persons, Severe febrile illness 6 v 13.6 events per 100 persons (p=0.013) (p=0.018), febrile upper resp. tract illness 4 v 12 events per 100 persons (p=0.005)	None	74% response rate (65% intervention , 82% control) Respondents more likely to receive shot (34% vs 11%) No stat sig diff on knowledge and beliefs about flu vaccination found between groups.	Reasons for vaccination: prevent flu 82% protect residents 67%. Reasons against; side effects 51%, fear needles 16%, efficacy fears 12%, egg allergy 7%Intervention Post-fair attitude positive for vacc. 4.2 vs 3 p<0.001
Follow-up	None	None	One seasons results	None after initial questionnaire	3 months- survey 74% response rate	Survey – 89% response rate
Baseline characteristics	None given	Overall only 14% physicians, 30% nurses, 10% auxillary, 3% housekeeping, 2% midwives, 4% physiotherapists, 36% other	None given	Vaccinees: Mean age 35.5 46% nurses, 10% lab staff, 9% doctors, 35% others. 15% previous vaccinees.	Mean age higher interv (43.8 vs 36.8) % nursing staff higher in control (12% vs 23%) Interv. more likely F/T 68 vs 47%	Not given

Table 7.5: Results of observational studies assessing uptake rates and attitudes to vaccination.

	Christian 1991	**Elorza Ricart 2002**	**DeAngelis 1996**	**Doebbeling 1997**	**Ganguly 1990**	**Harbath 1998**	**Heimburger 1995**
Number HCW	379	Approx. 4500 each year	119	1991:7320 1992:8632	62	1092	1293
Response rate	63%	Na	99%	na	100%	73%	71%
% vaccinated (respondents)	5%	2000-1 : 12.7% 2001-2 : 14.7%	68%	32%	12%	10% before 26% after intervention	1989-90 : 16% 1990-91: 33%
Vaccination campaign?	Not described	Yes	Unknown	Yes	No	Yes	For 1990-91 season only
Main reasons for non-vaccination	Avoid medication 47%, Get flu from vaccine 45%, side-effects 37%	na	60% forgot, 20% avoid shots, 11% thought not efficacious, 6% side-effects	Not studied	Fear of shots or side-effects 28%, 39% lack motivation	Can ward off flu 32%, unlikely to get flu 23%, 19% doubt efficacy vaccine	Side-effects 35%, avoid medication 33%, reaction in past 24%.
Attitudes to/Knowledge of vaccination	High % (45) believed you can get flu from vaccine	na	Not studied	Not studied	Not studied	Not studied	Not studied
Demographics-More likely to be vaccinated	Females	Females & younger HCW	Not studied	Females , physicians and older	More ($p<0.01$) nurses than others - side-effects outweighed benefits	Not studied	Older HCW, previous vaccinees and non-medical personnel
Respondents, non-respondents - differences	Not studied	na	Not studied	No significant differences	na	Not studied	Not studied

Table 7.5 continued

	Manuel 2002	**Murray 2001**	**Nafziger 1994**	**Nichol 1997**	**Stephenson 2002**	**Watana-kunakorn 1993**	**Yassi 1994**
Number HCW	401	308	108	1031	604	3501	948
Response rate	58%	87%	73%	38%	99%	34.3%	55%
% vaccinated (respondents)	39%	48%	51%	61%	14%	38%	14%
Vaccination campaign?	Yes	No	Yes	Yes	Yes	Yes	No
Main reasons for non-vaccination	Not studied	Not studied	Lack of time 42%, forgot 24%, dislike shots 13%, side-effects 8%	Side effects 31%, thought not in target group 8%	67% unaware , 29% did not want it, 26% side-effects, 24% doubt efficacy	Side-effects 37%, previous side-effects 19%, Dislike shots 18%, Doubt efficacy14	Not studied
Attitudes to/Knowledge of vaccination	72% hand-washing and 56% good diet & exercise better than vaccine to prevent flu.	Not studied	86% correctly identified those who should be vaccinated	Vaccine recipients better knowledge of need for vaccination	Previous vaccination, belief flu is serious assoc. with vaccination (controlling for other variables)	Not studied	56% knew flu could be life-threatening
Demographics-More likely to be vaccinated	Not studied	Not studied	–3rd year residents (Only physicians surveyed)	Older HCW, physicians and previous vaccinees	Physicians **least** likely	Not studied	Previous vaccines ($p=0.001$)
Respondents, non-respondents - differences	Not studied but 89% respondent female	No significant differences	Not studied	Not studied	Not studied	Not studied	No significant differences

Appendix 8: Relevance of all Studies used

Study	Group	Study Type	Relevance
Carman	A	Good quality Cluster RCT	Directly answers question :ideal study design with patient outcomes (mortality)
Potter	A	Adequate quality Cluster RCT	Directly answers question :ideal study design with patient outcomes (mortality)
Dey	B(a)	Adequate quality Cluster RCT	Ideal study design but no patient outcomes, vaccine uptake rates only
Al Mazrou	B(b)	Very good quality RCT	Details adverse events, absenteeism and vaccine uptake rate in HCW, but no placebo control (also took acetominophen if had side effects)
Aoki	B(b)	Good quality Randomised trial	Trial of acetominophen. Adverse events, absenteeism in HCW, but no placebo control
Mostow	B(b)	Poor quality RCT	Adverse events and absenteeism in HCW, but with no placebo control
Saxen	B(b)	Poor quality RCT	Vaccine vs placebo. Adverse events and absenteeism in HCW with placebo control
Weingarten	B(b)	Good quality RCT	Vaccine vs placebo. Adverse events, influenza rates, absenteeism and costs in HCW
Wilde	B(b)	Very good quality RCT	Trial over 3 seasons with flu vaccine vs other vaccines or placebo. Adverse events, influenza rates and absenteeism in HCW
Cooper	C	Poor quality Before-after intervention	Uptake rates with and without promotion and HCW attitudes to vaccination, costs.
Harbath	C	Good quality Before-after intervention + questionnaire	Uptake rates with and without promotion + attitudes and beliefs (see questionnaire below) with control arm
Nishi	C	Adequate quality Controlled trial	Adverse events, absenteeism and associated costs with no vaccine control arm
Schiefele	C	Adequate quality Feasability/ safety style	Uptake rates with promotion programme, absenteeism and adverse events in HCW
Tannenbaum	C	Good quality Controlled trial	Uptake rates with and without promotion with control arm
Thomas	C	Adequate quality Before-after intervention	Uptake rates with and without promotion (before-after) and reasons for non- vaccination
Elorza Ricart	D	Descriptive analysis	Vaccination rates in 2 consecutive campaigns with characteristics of vaccinated HCW
DeAngelis	D	Questionnaire	Vaccination state & reasons for non-vaccination
Doebbeling	D	Multiple logistic regression model	Vaccination rates during campaign and characteristics of vaccinees
Ganguly	D	Questionnaire	Vaccination rates and reasons for non-vaccination. HCW beliefs concerning vaccination
Harbath	D	Questionnaire (part of study)	Vaccination state before and after campaign and reasons for non-vaccination
Manuel	D	Questionnaire	Rates of and attitudes/beliefs about vaccination
Murray	D	Questionnaire	Vaccination rates
Nichol	D	Questionnaire	Vaccination rates with vaccination programme, vaccinee characteristics and reasons for vaccination and non-vaccination
Stephenson	D	Questionnaire	Vaccination rates, vaccinee characteristics and reasons for vaccination and non-vaccination
Watanakun-akorn	D	Questionnaire	Vaccination rate following vaccination program. Side-effects, characteristics of vaccinees and reasons for non-vaccination
Yassi	D	Questionnaire	Vaccination rates and characteristics of vaccinees. Reasons for non-vaccination and attitudes and beliefs about vaccination

Notes : Study quality refers mainly to the methodological quality of the study and the internal validity. External validity/generalisability is given by the 'relevance' column i.e. its ability to answer the review question or it's use in this review.

Appendix 9: Tabulation of Study Quality

Quality checklist for Dey 2001 (cluster RCT of HCW vaccination uptake).

Trial Criteria	**Dey 2001**
Was the study randomised appropriately?	Yes – although method not stated
Was the control arm appropriate?	Yes, for study, but for our review it would have been more useful to have no intervention at all
Where cluster numbers were small, did researchers attempt to balance trial arms for baseline characteristics relevant to the outcome?	Not relevant (cluster sizes large and no patient outcomes measured)
Was the response rate given for each arm?	Yes
Were appropriate methods used to determine sample size i.e. intra-class correlation coefficient?	Yes
Was an appropriate analysis carried out*?	Yes
Where the same individuals were studied repeatedly at follow-up, were attrition rates given?	Not relevant
Was the balance of baseline characteristics and potential confounders between arms given?	No
Where differences existed, were regression methods for clustered data used to allow for confounding at both the individual and cluster level?	Not known

* Cluster level analysis should use the cluster means, proportions or log odds and apply standard parametric or non-parametric statistical methods. If individual level data is used i.e. individual patient outcomes, then the design effect must be incorporated into the analysis i.e. estimating the intra-class correlation coefficient.
For dichotomous outcomes a random effects meta-analysis can be used by pooling the cluster specific outcomes, however these should be weighted where clusters differ in size.

Quality of RCTs assessing outcomes of vaccination in HCW

A summary of quality of Group B(b) trials i.e. RCTs is given by the following. One point given for each of the following; adequate randomisation method, presence of concealment of allocation, blinding of participants, loss to follow-up of less than 20%. 0 points = very poor, 1 point=poor, 2 points=adequate, 3 points=good, 4 points=very good.

	Al Mazrou 1992	Aoki 1993	Mostow 1977	Saxen 1999	Weingarten 1988	Wilde 1999
Trial described as randomised?	Y	Y	N	Y	Y	Y
Randomisation procedure described?	Y	Y	Y	N	Y	Y
Randomisation method adequate?	Y	Y	N	?	Y	Y
Was there a statement regarding concealment?	Y	N	n/a	N	N	Y
Method of concealment described?	Y	N	n/a	N	N	Y
Was the method adequate?	Y	?	n/a	?	?	Y
Trial described as double-blind?	N	Y	Y	Y	Y	Y
Treatment allocation masked from participants?	Y	Y	Y	Y	Y	Y
Treatment allocation masked from investigators	SOME	?	Y	?	Y	Y
Treatment allocation masked from outcome assessors?	Y	Y	Y	?	Y	?
Withdrawals stated for each group?	None	None	?	N	None	Y
Loss to follow-up stated for each group?	None	N	Y	N	N	Y
Was loss to follow-up less than 20%?	None	Y	N	N	Y	Y
Was loss to follow-up higher in one group than another?	n/a	?	?	?	?	N
Intention-to-treat analysis carried out?	n/a	n/a	n/a	n/a	n/a	n/a
Quality Score	4-Very good	3-Good	1-Poor	1-Poor	3-Good	4-Very good

Quality checklist for other intervention studies assessing uptake rates and outcomes in HCW.

Study	Quality 'score'	Reasons
Cooper	Adequate	A retrospective control was used but details only given for all staff and not for staff with patient contact ('after' rates only given for this group of HCW) Also the comparison group is from 4 years previous. However study useful for giving a baseline uptake rates and costs of a vaccination promotion program. Results as % only
Harbath	Good	Initial survey to determine reasons for non-compliance. Focused on changes in uptake rates in 2 intervention groups with retrospective controls. Gives confidence intervals and p-values
Nishi	Adequate	A concurrent controlled trial at the same hospital with relatively large numbers of HCW (727) although there were 5x more in the control group. Main outcomes of absenteeism and ILL in following season given as rate per 100 persons and statistical difference measured using Fisher's exact test. Complicated by fact that only had partial translation at time of completing review.
Schiefele	Adequate	Gives details of uptake rates with a promotion program only but useful for adverse events data and absenteeism from vaccination
Tannenbaum	Good	The control group used was a concurrent control at a similar nursing home with similar initial vaccination rates. The baseline characteristics of both are listed. Odds ratios are given with confidence intervals and a logistic regression analysis carried out to examine effect when controlling for possible confounding factors. Odds ratios given with confidence intervals
Thomas	Adequate	Retrospective control used, therefore details effectiveness of promotion. Provides information on vaccination rates and reasons for non-vaccination- Good response rate for survey (89%)Results given as % only

Quality of observational studies assessing uptake rates and attitudes to vaccination

Study	**External validity and methods**	**Response rate**
Christian	Yes/No 40-item self-administered questionnaire in US 123-bed acute care hospital	63% (239/379)
Elorza Ricart	Descriptive analysis of 4500 HCW in Spanish tertiary hospital using 2 years data from human resources dept. Some ambiguity in paper as to methods.	n/a
DeAngelis	All HCW (working with children i.e. PHCP) in US city (except registered nurses and licensed practical nurses) included in 4 question telephone survey (or in person)	99% (117/119)
Doebbeling	Multiple logistic regression model in US hospital using linked data from vaccination clinic to personnel dept. database for demographics, all staff included during vaccination campaign	n/a
Ganguly	USA veterans hospital where HCW vaccination advised. All staff included. Random selection 62 HCW with self-administered written questionnaire	100% (62/62)
Harbath	All staff in geriatrics, paediatrics and obstetrics (high-risk) in University hospital in Switzerland. 24 multiple-choice self-administered questionnaire	73% (797/1092)
Heimburger	Anonymous, self-administered questionnaire in US large chronic care psychiatric facility. Vaccination rates from before and after vaccination campaign.	71% (1222/1293)
Manuel	Canadian long-term care facilities, all staff included. 58-item self-administered written questionnaire.	58% (231/401)
Murray	Australian tertiary adult hospital where there are guidelines for HCW vaccination (admin. Keep records of vaccination and consent/refusal) Only staff with patient contact included. Pre-tested telephone questionnaire by single interviewer lasting 5 mins. Used random sample	87% (269/308)
Nafziger	32 item questionnaire given during clinics in 891-bed university tertiary referral hospital and 278-bed veterans hospital in US.	73% (79/108)
Nichol	US veterans hospital. Doctors and nurses included. All eligible staff received 35-item mailed self-administered survey	38% (392/1031)
Stephenson	UK ward staff (medical and non-medical) with regular patient contact in 3 acute hospitals. 17% sample received hand delivered 18-item self-administered questionnaire	99% (597/604)
Watanakunakorn	USA community teaching hospital, all staff included. Self-administered written questionnaire in pay slip	34.3% (1203/3501)
Yassi	Ward staff on wards with high-risk patients in Canadian acute care teaching hospital. Self-administered multi-choice written questionnaire	55% (519/948)

Appendix 10: Tabulation of Economic Studies

	Postma 1999	**Buxton Bridges 2000**	**Akazawa 2003**	**Allsup 2003**	**OTA 1981**	**Levy 1996**
Assessment of:	Influenza vaccine in 65+	Influenza vaccine in healthy working adults	Influenza vaccine in employed adults	Influenza vaccine in 65-74yrs	Influenza vaccine in 1. High risk 2. Socioeconomic risk 3. School children	Influenza vaccine in employed adults
Country	Netherlands	US	US	UK	US	France
Study type	Cost Effectiveness Cost of illness	Cost benefit	Cost benefit	Cost-effectiveness	Cost effectiveness	Cost-benefit
Type of analysis/model used	Simple accounting	Simple accounting	Simple accounting	Simple accounting	Simple accounting	Simple accounting
Population	65+	Healthy working adults aged 18-64yrs	Employed adults aged 22-64 yrs	Low risk 65-74yrs	As above	Employed adults aged 25-65yrs
Perspective	Healthcare	Societal & healthcare payer	?Employers	Societal	Societal & medicare	Societal
Source of costs/benefits	Government data Literature	RCT and other dbases	1996 Medical Expenditure Panel Survey Literature	RCT Literature Other data sources	Government data Literature	Government data Literature
Year of costs	1995 & 1997/8	1999?	1996	2000	1971-78	1989-90
Currency	Euros	Dollars	$	£	$	FF
Sensitivity analysis?	Y	Y	Y	Y	Y	Y
COMMENTS	Elderly in Netherlands	Healthy workers in US	Healthy workers in US	Elderly In UK	Out of date Not group of interest - US	Brief details Workers in France

	Lee 2002	**Fitzner 2001**	**Nichol 2001**	**Nichol 1995**	**Scuffham 2002**	**Wood 1999**
Assessment of:	Influenza vaccine in healthy working adults	Influenza vaccine in 1. Elderly 2. Children 3. Working-age adults	Influenza vaccine in healthy working adults	Influenza vaccine of healthy working adults	Includes influenza vaccine strategies in Europe	Influenza vaccine in working population
Country	USA	Hong Kong	USA	USA	E&W, France, Germany	Russia
Study type	Cost benefit	Cost effectiveness Cost benefit	Cost benefit	Cost benefit	Cost-effectiveness	Cost benefit
Type of analysis/model used	Simple accounting	Simple accounting	Monte Carlo Simulation	Simple accounting	Simple accounting	Simple accounting
Population	Health working adults aged 18-50 yrs	Includes working-age adults	Healthy working adults	Healthy working adults Aged 18-64 yrs	Elderly	Working adults
Perspective	Societal	Individual Societal	Societal	Societal	Healthcare payer	Healthcare payer?
Source of costs/benefits	Survey data, Conjoint analysis, Literature	Survey Government data Literature	Published literature	RCT	Literature National data sources Expert panels & clinicians	Retrospective study from database
Year of costs	2001	1993-94	1998	1994	2000	1998
Currency	US $	Hong Kong $ US $	US $	US $	Euros	Russian rubles
Sensitivity analysis?	Y	Y	Y	N	Y	N
COMMENTS	Healthy working adults in USA	Includes healthy working-age adults Different type of 'flu seasons?	Healthy workers in USA	Healthy workers in USA	Elderly in Europe	Healthy workers in Russia

	Yassi 1991	**Burchel 1999**	**Nichol 1999**	**Campbell 1997**	**Kumpulainen 1997**	**Dille 1999**
Assessment of:	Influenza vaccine for HCW	Influenza vaccine campaign in workplace	Influenza vaccine for elderly	Influenza vaccine for healthy working adults	Influenza vaccine for healthy workers	Influenza vaccine programme for healthy workers
Country	Canada	Brazil	US	US	Finland	US
Study type	Cost benefit	Cost benefit	Cost-benefit	Cost-effectiveness	Cost-effectiveness	Cost benefit
Type of analysis/model used	Simple accounting	Simple accounting	Simple accounting	Simple accounting	Simple accounting	Simple accounting
Population	All HCW High risk HCW	Workers in pharma-chemical co.	Elderly 65-74 yrs	Employees of textile plants	Healthy care workers (of the elderly and families small children)	Workers
Perspective	Employer?	Employer	Societal	Employer	?Societal	Employer?
Source of costs/benefits	Before/after study	Literature Company data	Administrative claims data for 2 cohorts	Controlled trial	Controlled study	Retrospective survey?
Year of costs	1987-88?	1997	1995-6	1992-3?	1991	1994
Currency	$ Canadian	$Brazil $ US	$US	$US	Finnish marks	$US
Sensitivity analysis?	Y	Y	N	Y	?	N
COMMENTS	HCW in Canada No pt outcomes	Healthy workers in Brazil	Elderly in US	Healthy workers in US	Care workers No patient outcomes	Healthy workers in US

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