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Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age

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NHS R&D HTA Programme

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This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure was replaced in 2000 by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

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Abstract

Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age

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Objectives: To determine the cost-effectiveness of influenza vaccination in people aged 65–74 years in the absence of co-morbidity.
Design: Primary research: randomised controlled trial.
Setting: Primary care.
Participants: People without risk factors for influenza or contraindications to vaccination were identified from 20 general practitioner (GP) practices in Liverpool in September 1999 and invited to participate in the study. There were 5875/9727 (60.4%) people aged 65–74 years identified as potentially eligible and, of these, 729 (12%) were randomised.
Intervention: Participants were randomised to receive either influenza vaccine or placebo (ratio 3:1), with all individuals receiving pneumococcal vaccine unless administered in the previous 10 years. Of the 729 people randomised, 552 received vaccine and 177 received placebo; 726 individuals were administered pneumococcal vaccine.
Main outcome measures and methodology of economic evaluation: GP attendance with influenza-like illness (ILI) or pneumonia (primary outcome measure); or any respiratory symptoms; hospitalisation with a respiratory illness; death; participant self-reported ILI; quality of life (QoL) measures at 2, 4 and 6 months post-study vaccination; adverse reactions 3 days after vaccination. A cost-effectiveness analysis was undertaken to identify the incremental cost associated with the avoidance of episodes of influenza in the vaccination population and an impact model was used to extrapolate the cost-effectiveness results obtained from the trial to assess their generalisability throughout the NHS.
Results: In England and Wales, weekly consultations for influenza and ILI remained at baseline levels (less than 50 per 100,000 population) until week 50/1999 and then increased rapidly, peaking during week 2/2000 with a rate of 231/100,000. This rate fell within the range of 'higher than expected seasonal activity' of 200–400/100,000. Rates then quickly declined, returning to baseline levels by week 5/2000. The predominant circulating strain during this period was influenza A (H3N2). Five (0.9%) people in the vaccine group were diagnosed by their GP with an ILI compared to two (1.1%) in the placebo group [relative risk (RR), 0.8; 95% confidence interval (CI) = 0.16 to 4.1]. No participants were diagnosed with pneumonia by their GP and there were no hospitalisations for respiratory illness in either group. Significantly fewer vaccinated individuals self-reported a single ILI (4.6% vs 8.9%, RR, 0.51; 95% CI for RR, 0.28 to 0.96). There was no significant difference in any of the QoL measurements over time between the two groups. Reported systemic side-effects showed no significant differences between groups. Local side-effects occurred with a significantly increased incidence in the vaccine group (11.3% vs 5.1%, $p = 0.02$). Each GP consultation avoided by vaccination was estimated from trial data to generate a net NHS cost of £174.
Conclusions: No difference was seen between groups for the primary outcome measure, although the trial was underpowered to demonstrate a true difference. Vaccination had no significant effect on any of the QoL measures used, although vaccinated individuals were less likely to self-report ILI. The analysis did not suggest that influenza vaccination in healthy people aged 65–74 years would lead to lower NHS costs. Future research should look at ways to maximise vaccine uptake in people at greatest risk from influenza and also the level of vaccine protection afforded to people from different age and socio-economic populations.

Contents

List of abbreviations

ANOVA	analysis of variance	OTC	over-the-counter
CI	confidence interval	QALY	quality-adjusted life year
CIA	Confidence Interval Analysis	RCGP	Royal College of General Practitioners
HAD	Hospital Anxiety and Depression scale	RCT	randomised controlled trial
ILI	influenza-like illness	RR	relative risk
OTA	Office of Technology Assessment	SD	standard deviation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

To determine the cost-effectiveness of influenza vaccination in people aged 65–74 years in the absence of co-morbidity.

Design

Primary research: randomised controlled trial.

Setting

Primary care.

Subjects

People without risk factors for influenza (diabetes, asthma, chronic heart, lung or renal disease, immunosuppression or living in an institution) or contraindications to vaccination were identified from 20 general practitioner (GP) practices in Liverpool in September 1999 and invited to participate in the study. There were 5875/9727 (60.4%) people aged 65–74 years identified as potentially eligible for entry into the study and, of these, 729 (12%) were randomised. The remaining 39.6% of people in this age group had one or more risk factors for influenza making them eligible for vaccination according to guidance from the Department of Health and so could not be included in this study.

Intervention

Participants were randomised in a ratio of 3:1 to receive either influenza vaccine or placebo (physiological saline solution), with all individuals receiving pneumococcal vaccine unless administered in the previous 10 years. Of the 729 people randomised, 552 received vaccine and 177 received placebo; 726 individuals were administered pneumococcal vaccine. Influenza vaccine was manufactured in accordance with the WHO recommendation (Northern Hemisphere) for 1999–2000 and contained the following antigens: A/Beijing/262/95 (H1N1), A/Sydney/5/97 (H3N2) and B/Beijing/184/93.

Main outcome measures

GP attendance with influenza-like illness (ILI) or pneumonia (primary outcome measure); GP attendance with respiratory symptoms; hospitalisation with a respiratory illness; death; participant self-reported ILI; quality of life (QoL) measures (EuroQoL EQ-5D and Hospital Anxiety and Depression scale) at 2, 4 and 6 months post-study vaccination; adverse reactions 3 days after vaccination. All outcome measures were recorded between 1 October 1999 and 31 March 2000.

Methodology of economic evaluation

The economic analysis was undertaken from a societal perspective and incorporated both public and privately borne costs associated with the vaccination programme. A cost-effectiveness analysis was undertaken to identify the incremental cost associated with the avoidance of episodes of influenza in the vaccination population. As many episodes of influenza may not lead to a GP consultation (sufferers simply 'take to their bed'), a patient-held diary was employed to identify such 'invisible' episodes of ILI. An impact model was used to extrapolate the cost-effectiveness results obtained from the trial to assess their generalisability throughout the NHS.

Results

Background influenza rate

The background influenza rate in Liverpool in 1999–2000 was very similar to the overall rate in England and Wales where weekly consultations for influenza and ILI remained at baseline levels (less than 50 per 100,000 population) until week 50/1999 and then increased rapidly, peaking during week 2/2000 with a rate of 231/100,000. This rate fell within the range of 'higher than expected seasonal activity' of 200–400/100,000. Rates then quickly declined, returning to baseline levels by week 5/2000. The predominant circulating strain during this period was influenza A (H3N2).

Clinical outcome

Five (0.9%) people in the vaccine group were diagnosed by their GP with an ILI compared to two (1.1%) in the placebo group [relative risk (RR), 0.8; 95% confidence interval (CI) = 0.16 to 4.1]. No participants were diagnosed with pneumonia by their GP and there were no hospitalisations for respiratory illness in either group. Significantly fewer vaccinated individuals self-reported a single ILI (4.6% vs 8.9%, RR, 0.51; 95% CI for RR, 0.28 to 0.96). There was no significant difference in any of the QoL measurements over time between the two groups. Reported systemic side-effects (feverishness, aching limbs, fatigue, rash, cough, runny nose, headache and sore throat) showed no significant differences between groups. Local side-effects occurred with a significantly increased incidence in the vaccine group (11.3% vs 5.1%, $p = 0.02$).

Economic evaluation

Each GP consultation avoided by vaccination was estimated from trial data to generate a net NHS cost of £174.

Conclusions

No difference was seen between groups for the primary outcome measure (GP attendance with ILI or pneumonia), although the trial was underpowered to demonstrate a true difference. Vaccination had no significant effect on any of the QoL measures used, although vaccinated individuals were less likely to self-report ILI.

Implications for healthcare

Our analysis did not suggest that influenza vaccination in healthy people aged 65–74 years would lead to lower NHS costs. A significant protective effect of influenza vaccine was found for the reduction of self-reported ILI, but the study was not sufficiently powered to examine the effect of influenza vaccination on mortality, GP consultations for respiratory illness or hospital admissions for pneumonia- and influenza-associated respiratory illness.

Recommendations for future research

Following the introduction in 2000–1 of new Department of Health guidelines to include all people aged 65 years or more in the national vaccination programme, future research should look at ways to maximise vaccine uptake in people at greatest risk from influenza, especially older people (>80 years) and those living in nursing and residential accommodation. Research is also needed to investigate the level of vaccine protection afforded to people from different age and socio-economic populations.

Chapter 1
Introduction

In 1999 the recommendations for influenza vaccination in the UK were as follows:[1]

- people aged 75 years or older
- people with chronic heart, lung or renal disease
- people with asthma
- people with diabetes
- people living in an institution
- people with immunosuppression due to disease or treatment.

This was different to advice given in the USA and the rest of Europe, where vaccination was routinely available for all individuals aged 65 years or more regardless of health status.[2] Despite the UK recommendations, many family doctors working in the UK were already following European and American guidelines and vaccinating healthy older people who requested vaccination.

This study was funded to assess the clinical and economic implications of reducing the age limit for routine vaccination in the UK to 65 years, thus incorporating healthy 65–74-year-olds who were the target group for this research. In 2000 (during the period of this research), the policy was altered with influenza vaccine becoming available for all people aged 65 years and over.[3] This report is therefore unique given that it is the only one whose research environment has been significantly affected by a policy change during the period of the research, which raises questions about coordination between research and policy in ensuring optimum use of available evidence. The incorporation of healthy 65–74-year-olds into the target group for influenza vaccination altered the ethical basis of the research, making the continued use of a randomised controlled trial (RCT) unacceptable. As a consequence, the analysis had to be fundamentally restructured and only results obtained over a 1-year rather than the originally planned 2-year RCT framework were incorporated into the economic model.

Our initial aim was to use the results of the trial to inform an impact model evaluating cost-effectiveness under a range of different scenarios relating to different 'attack' rates and different qualities of 'match' between circulating strain and vaccine. Unfortunately, as the scale of the clinical analysis became more limited, greater reliance had to be placed on using other sources of evidence (national and local) to inform the scenario analyses, supported by appropriate use of sensitivity analysis.

Chapter 2

Literature review

Prior to commencing the study, a computer-aided literature search was initiated using OVID MEDLINE, Silver Platter MEDLINE, PubMed and the Cochrane Library. The purpose of the search was to review the clinical evidence for vaccine effectiveness in older people. The search terms used were influenza, influenza vaccine, pneumococcal vaccine, aged, elderly, efficacy, community, institutionalised, adverse reaction and pneumonia. References in the identified papers were used to search earlier studies (i.e. published before 1966). Evidence for vaccine cost-effectiveness is considered in more detail in Chapter 5. The search was restricted to articles published in English involving human subjects aged 55 years or above and relevant review articles were also included. The search was repeated at the end of the study and updated if new relevant literature had been published between September 1999 and September 2001.

Background to the research

Influenza is an acute respiratory disease that typically presents with a sudden onset of fever, usually accompanied by a headache, sore throat, myalgia, malaise and a dry cough.[4] Most illness is self-limiting with fever lasting between 1 and 5 days. Influenza is spread by inhalation of microdroplets and can cause periodic epidemics and pandemics.

The influenza virus was first identified in 1933, although influenza pandemics have affected human populations since ancient times (Hippocrates is known to have written about their occurrence) and it has been estimated that at least 12 pandemics have occurred within the past 400 years, 11 of these originating from China.[5] The pandemic of 1918–20 ('Spanish' influenza) is extensively documented as are the other pandemics of 1957–8 ('Asian' influenza) and 1968–9 ('Hong Kong' influenza). Pandemics are caused by substantial antigenic shifts, which lead to the appearance of new influenza subtypes against which little natural population immunity exists, resulting in exceptionally high morbidity and mortality. Since the pandemic of 1977–8 only one major epidemic of influenza has occurred (1989–90) and influenza has only exceeded 'normal seasonal activity' on four occasions since 1990 (1993–4, 1996–7, 1998–9 and 1999–2000), each associated with increased activity of influenza A (H3N2) virus.

Older people are much more likely to develop serious complications as a result of influenza infection. In the USA between 1957 and 1960 two influenza epidemics were estimated to have caused a total of 86,000 excess deaths, two-thirds of which occurred in people aged 65 years or above. Additionally, excess influenza associated mortality during this period in the USA was demonstrated in people with cardiovascular disease, renal disease, bronchopulmonary disease and diabetes mellitus.[6] During the influenza epidemics of 1968–9 and 1972–3 in Portland, OR, USA, it was demonstrated in a case control study that of 310 private healthcare members hospitalised with pneumonia or influenza, 26 of 38 (68%) deaths occurred in those over 65 years; the other 12 deaths occurring in individuals aged 45–64 years and chronic disease was present in 95% of those who died.[7] The highest death rates occurred in people with both cardiovascular and pulmonary disease. The authors estimated that fewer than 10 pneumonia and influenza deaths per 100,000 occurred in healthy individuals aged 65 years or more during this period.

In 1989–90, during the last influenza epidemic to affect England and Wales, it was estimated that 24,877 excess deaths occurred; 82% of these were in individuals aged 75 years and older, 15% in those aged 65–74 years and only 3% in people aged less than 65 years.[8] Institutional care, chronic obstructive pulmonary disease, asthma and neurological disease were all identified as independent risk factors for certified influenza death in the UK during this period.[9]

The consequences of an influenza epidemic are perhaps best illustrated by Burnet,[10] who, in 1953, writing for *Scientific American* commented that, "Whenever an epidemic of influenza passes through a community, there is a sharp peak of deaths from various causes among the aged. Any elderly person rendered frail by physical disability is likely to succumb to an attack of influenza. This

was heavily underlined during the 1951 influenza outbreak in Great Britain. In Liverpool the epidemic passed like an angel of death amongst the old … An investigation of the saving of life that might be effected by appropriate immunisation of the aged against influenza would seem to be a very worthwhile project."

Although mortality statistics provide an indicator of influenza activity among older people, mortality from influenza is still, however, a comparatively rare event and hence is at best a very partial indicator of influenza activity. At the population level the usual method of monitoring clinical influenza activity is based on sentinel general practitioner (GP) surveillance schemes. For example, the Royal College of General Practitioners (RCGP) reports the number of patients consulting each week with an influenza-like illness (ILI). While such schemes are useful in assessing the level of influenza activity in the population, the non-specific nature of the symptomatology means that increases in recorded 'influenza' may be apparent in the absence of true underlying disease. The sentinel GP surveillance schemes report the number of patients consulting with an ILI as a weekly rate, with normal seasonal activity leading to between 50 and 200 consultations per 100,000 population. A definitive diagnosis of influenza requires laboratory confirmation, with virus isolation from clinical specimens (e.g. throat and nasal swabs) being the gold standard. Serology is an alternative method of diagnosis and is based on the detection of a fourfold or greater rise in specific antibody titre in paired serum samples, the first sample collected as soon as possible after onset of illness and the second collected 10–14 days later. The extent of agreement between virological and clinical diagnosis can only be analysed in schemes where specimens are analysed from patients presenting to GPs with ILI. Virological surveillance also plays a crucial role in identifying and characterising the influenza viruses currently active in the community. Such surveillance informs decisions concerning the strain components contained in the current vaccines, and allows monitoring for evidence of significant antigenic change. Information from UK virological surveillance assists the WHO in deciding on the strains to be included in vaccines to be developed for the next influenza season.

The availability of an influenza vaccine provides the opportunity to protect people at high risk due to either age or co-morbidity. As evidence of the benefits of vaccination becomes available for each subsequent high-risk group, that risk group will then become routinely incorporated into the target population offered vaccination. The provision of vaccination, however, is complicated by the ability of the influenza virus to mutate each year through antigenic drift. As a consequence, influenza has been described as "a constant disease, caused by a variable virus".[11] Such variability requires a newly formulated vaccine to be administered each year that matches as closely as possible the circulating strain of influenza. Such mutability also contributes to a reduced level of vaccine efficacy in comparison to that of other viral vaccines (e.g. polio and measles) even in years with a good antigenic match.

Vaccination in nursing and residential homes

Some of the earliest studies to demonstrate vaccine effectiveness in high-risk groups were conducted in nursing homes. Vaccine effectiveness is determined by many factors, including the match between vaccine and circulating virus and whether seroconversion occurs to individual vaccine strains following vaccination. Residents of nursing homes are at high risk of influenza and its related complications for various reasons; many are over 75 years of age, have multiple underlying medical conditions and live in a closed environment. Goodman and colleagues[12] described an outbreak of influenza A in a nursing home that resulted in 30 (25%) reported cases of ILI, 13 (10.8%) hospitalisations and nine (7.5%) deaths. There have, however, been relatively few RCTs carried out owing to the ethical concerns about the use of a placebo in frail, older people.

Many of the earlier studies that demonstrated a better outcome in vaccinated, institutionalised individuals were non-randomised, uncontrolled, observational designs and therefore allowed considerable scope for the introduction of bias. Studies by Howells and colleagues,[13]; Patriarca and colleagues,[14] Deguchi and colleagues,[15] and Monto and colleagues[16] have shown that unvaccinated residents of nursing homes are significantly more likely to be hospitalised, develop bronchopneumonia and/or die of ILI when compared with vaccinated residents. Such studies are difficult to compare because of inconsistencies in descriptions of residents' functional abilities and co-existing morbidity. It is possible that the unvaccinated residents in each of these studies were a sicker, frailer group, who may not have been able to give informed consent for vaccination. As a consequence, they would have

been at greater risk of death and serious morbidity during an influenza outbreak irrespective of vaccination status. The behaviour of physicians and/or nurses towards them may also have been different compared to vaccinated individuals. Alternatively, the unvaccinated residents may actually have been a healthier group with a lower risk of morbidity and mortality and less of a perceived need for vaccination.

In a meta-analysis of 20 cohort trials involving individuals over 65 years of age the pooled estimates of vaccine effectiveness were 56% for preventing respiratory illness, 53% for preventing pneumonia, 48% for preventing hospitalisations and 68% for preventing all-cause mortality.[17] Only cohort observational studies were included in the meta-analysis; nine of the studies were prospective and 11 retrospective. Nineteen of the 20 studies involved institutionalised older people and the controls used were residents who had not been vaccinated. These studies were carried out in US (n =14), French (n = 2), UK (n = 1), Canadian (n = 1) and Australian (n = 1) nursing homes. The sample size in each study varied from 17 to >1000 with only six studies describing sex distribution, with the majority being female. The mean or median age of participants in most of the studies was 80 years or more. Vaccine effectiveness may actually have been underestimated as other infections can cause hospitalisation and death, which in the studies may have been attributed to influenza. It is impossible to say to what extent selection bias occurred in any of the studies. Sicker patients may have been more likely to be vaccinated or alternatively vaccine may have been withheld from such patients if they were unwell at the time of vaccination or were considered to have a very poor quality of life (QoL). In addition, patients who could not consent or who were considered to have the least to gain may not have been included in the vaccination programme. The authors state that documentation as to whether a person actually received vaccine may have been poor in some studies. Some of the homes in the studies may therefore have relied on memory rather than written evidence of vaccination status (information bias).

The effectiveness of vaccination depends on a good match between circulating virus and vaccine administered. Fourteen studies described the strain as identical, and similar vaccine effectiveness was seen when the circulating virus was a 'drift' variant. When the influenza strain circulating in the community showed antigenic 'shift' no benefit was gained from vaccination.

Coles and co-workers[18] also highlighted the importance of a good match between circulating virus and vaccine in a study that found 30% (37/124) of the residents of a New York nursing home suffered from an ILI despite vaccine uptake of 90%. Three influenza-related deaths and six cases of pneumonia were described in nine of the vaccinated residents. Along with the advanced age of many of the residents, the authors speculated that antigenic drift of the circulating influenza A virus and poor vaccine uptake in staff (10%) might have been to blame for this apparent vaccine failure. Eight cases of ILI in staff preceded resident cases by 16 days, suggesting that staff may have introduced influenza into the home. It has been shown in clinical trials that vaccination of healthcare workers is associated with reduced mortality among older patients in long-term care.[19]

Vaccination in the community

Studies have shown that influenza vaccination can reduce mortality from pneumonia and influenza in non-institutionalised people aged 65 years or more, for example, Barker and Mullooly,[20] 87% reduction; Fleming and colleagues,[21] 75% reduction; Nichol and colleagues,[22] 50% reduction; Christenson and colleagues,[23] 57% reduction. These were retrospective[20,21] or prospective[22,23] cohort studies. The trials were conducted over 1,[21,23] 2[20] and 6[22] years. Christenson and colleagues[23] vaccinated participants with both influenza and pneumococcal vaccines, unlike the other trials where the majority of participants were administered only influenza vaccine. All of the above studies included both healthy and chronically ill individuals and came from different populations (USA, UK and Sweden).

A UK case control study[9] demonstrated a 41% reduction in certified influenza death in vaccinated individuals aged 16 to 95+ years during the 1989–90 epidemic. In addition to reducing deaths from pneumonia and influenza, Fedson and colleagues[24] demonstrated in a case control study that vaccination also reduced deaths from any cause by about 30% in non-institutionalised Canadian individuals aged 45 years or older.

Nichol and colleagues[22] attempted to clarify the benefits of vaccination for older individuals over a 6-year period by grouping them according to risk status: high risk (having heart or lung disease), intermediate risk (having diabetes, renal disease,

stroke and/or dementia or rheumatological disease) and low risk (none of these conditions); 69% of individuals observed over the 6-year period were in the low-risk group, 10% in the intermediate-risk group and 21% in the high-risk group. Within the vaccine group there was an overall reduction of 39% for pneumonia hospitalisations, a 32% decrease in hospitalisations for all respiratory conditions and a 27% decrease in hospitalisations for congestive heart failure. Within the risk groups, vaccine reduced hospitalisations for all respiratory conditions by 33% (low-risk group), 39% (intermediate-risk group) and 19% (high-risk group). For all risk groups, all-cause mortality was reduced by 50%. There were important differences in overall baseline characteristics between vaccinated and unvaccinated subjects, although these were controlled for in the final analysis. Vaccinated subjects were more likely than unvaccinated subjects to be male, to have underlying heart or lung disease, to have received pneumococcal vaccine in the previous year and to utilise more healthcare resources, such as physician visits. Unvaccinated subjects were, on the other hand more likely to have a history of dementia or stroke. In keeping with all observational studies, bias may have been introduced as a result of other unknown differences that may have existed between vaccinated and unvaccinated individuals.

It was demonstrated in the prospective cohort study by Christenson and colleagues[23] that combined influenza and pneumococcal vaccination in a large sample of non-institutionalised older people aged 65 years or more reduced hospitalisation for influenza by 46% and for pneumonia by 29%.

Two case control studies[25,26] have also demonstrated the effectiveness of influenza vaccination in preventing hospitalisation among older people when using pneumonia- and influenza-related diagnoses as an outcome measure. Puig-Barbera and colleagues[25] found that vaccination reduced hospital admissions for pneumonia by 79% during a 4-month study period (November 1994–March 1995) in non-institutionalised Spanish people aged 65 years or more. Ohmit and Monto[26] showed that vaccination over two consecutive years was 31% and 32% effective in reducing the likelihood of hospitalisation from pneumonia- and influenza-related diagnoses in non-institutionalised American individuals aged 65 years or more. Ohmit and Monto[26] noted that vaccination offered no protection against hospitalisation when influenza activity was low or absent in the community.

The only RCT involving older people was conducted in The Netherlands by Govaert and colleagues[27] and involved 1838 mainly healthy, non-institutionalised people aged 60–91 years (median age 66 years). Over 80% of individuals who participated were in the age range 60–74 years and over a quarter of individuals had one or more chronic illnesses (cardiac disease, pulmonary disease or metabolic problems), although these were not considered by the researchers to be serious enough to warrant exclusion. Eligible individuals were identified by family physicians working from 15 practices in the southern region of The Netherlands. Vaccination was shown to reduce the risk of influenza by 58% in individuals with typical clinical symptoms confirmed serologically. No benefit was shown for people over 70 years of age, possibly because there were fewer participants in this group. Interestingly, 67 participants had serologically confirmed influenza but showed no clinical symptoms, suggesting that over-reliance on serological diagnosis may be misleading. People who had a history of repeated immunisations appeared to get the greatest protection from serologically confirmed influenza. Ahmed and colleagues[9] also found a greater protective effect (in terms of reduction in mortality) when influenza vaccine had been administered in previous years. Both of these findings are important when making a case for an annually administered age-based vaccination policy.

Adverse reactions

Margolis and colleagues[28] and Govaert and colleagues[29] investigated the incidence of side-effects following inactivated influenza vaccination in older people living in the USA and The Netherlands, respectively. The Govaert study included participants who were aged 60–91 years and the Margolis study involved people aged over 65 years. The mean age of the participants in the Margolis study was 70.6 years, with 95.5% being men, and in the Govaert study the mean age was 67 years, with an approximately equal proportion of males and females.

The Govaert study used mainly healthy individuals whereas the Margolis study considered outpatients, two-thirds of whom self-reported

having an unspecified chronic illness. Both studies were randomised placebo controlled, although Margolis' study employed a crossover design type study in contrast to the Govaert study which used a parallel design.

No significant difference was seen in either study in the incidence of systemic side-effects between the vaccine and placebo groups: 27.7% vaccine versus 22.9% placebo (Margolis) and 11% vaccine versus 9.4% placebo (Govaert). However, a significant number of individuals administered vaccine did complain of local symptoms when compared with placebo, the proportion being similar in both studies; 20.1% (Margolis) and 17.5% (Govaert).

Govaert and colleagues recorded symptoms via a questionnaire sent to participants 4 weeks after the initial injection, which could have led to recall bias, whereas Margolis and colleagues conducted a telephone interview 1 week later. The shorter time period between injection and interview used in the Margolis study may explain the greater proportion of systemic symptoms reported in their trial, with individuals probably more likely to report symptoms when asked a short time after the injection. Alternatively, many of the systemic symptoms recorded in the Margolis study (which had a similar incidence in both groups) may have been secondary to underlying chronic illness rather than vaccination. The Govaert study showed that those individuals with an unspecified lung condition were more likely to report systemic side-effects.

No severe side-effects were reported in either study. Women reported more side-effects than men in the Govaert study. The number of women in the Margolis study was too small to provide useful data.

Although RCTs investigating adverse reactions have found no increase relative to placebo when side-effects were recorded 1–4 weeks after vaccination, case reports have been published highlighting an association between auto-immune disease and influenza vaccination.[30]

In 1976, an association was reported in the USA between inactivated influenza vaccine and Guillain–Barré syndrome.[31] This was not found in later studies[32,33] but more recently the relationship has again been reported, although the calculated risk has been estimated to be only one additional case of Guillain–Barré syndrome per million people vaccinated.[34]

Pneumococcal vaccination

The indications for pneumococcal vaccination are almost identical with those for influenza vaccination.[35] A meta-analysis of nine randomised placebo controlled trials carried out between 1976 and 1987 demonstrated vaccine effectiveness in reducing pneumococcal bacteraemia and pneumococcal pneumonia in healthy adults aged 18–55 years.[36] Pneumococcal vaccination did not reduce all-cause mortality and did not protect against other causes of pneumonia. No benefit was seen for people classified as high risk (adults aged over 55 years or those with one or more chronic illnesses). The vaccine was found to be safe in all trials, with a febrile reaction occurring in less than 2% of people vaccinated and local reactions occurring in up to one-third. There were no reported severe reactions. Of the nine trials, two were from South Africa, three were conducted in the USA and there was one each from New Guinea, Canada, Belgium and France. Five of these studies involved over 4000 people with a mean age > 60 years, all of whom had one or more chronic illnesses. The analysis was unable to determine if the benefits seen in healthy people aged under 55 years could also be extrapolated to healthy older people.

Örtqvist and colleagues[37] conducted a randomised placebo controlled trial in an attempt to determine the effectiveness of pneumococcal vaccine in people aged 50–85 years living in Sweden who had already been treated once in hospital for community-acquired pneumonia. No reduction was seen in overall pneumonia or pneumococcal pneumonia and there was no difference in death rates between the two groups. However, a non-significant increase in the rate of bacteraemia was seen in the placebo group. The risk of pneumonia recurrence for all participants was 17% during a mean follow-up period of 2.5 years, indicating that this sample of patients had an unusually high risk of recurrent pneumonia. Only 42% of the vaccine group and 43% of the placebo group were described as previously healthy. It seems unlikely, therefore, that these results can be generalised to include all older people living in the community.

A case control study by Farr and co-workers[38] demonstrated a reduction in pneumococcal bacteraemia in individuals aged 65 years or more and people of all ages with chronic illness administered pneumococcal vaccine. All cases had been selected from a list of previously hospitalised patients at a US university hospital.

In a RCT conducted in Finland, 2837 participants aged 60 years or more were randomised to receive either influenza vaccine alone or influenza and pneumococcal vaccines.[39] No significant difference in the incidence of radiologically confirmed pneumococcal pneumonia (the primary outcome variable) was seen overall between the two groups, although a subgroup analysis showed a 56% protective efficacy for pneumococcal pneumonia in people classified to be at increased or high risk. Pneumococcal aetiology was identified by serological methods and the overall incidence of serologically diagnosed pneumococcal pneumonia in the study population was seven per 1000 person-years.

A study of the cost-effectiveness of pneumococcal vaccination of people aged ≥ 65 years in five Western European countries (Belgium, France, Scotland, Spain and Sweden) found vaccination to be cost-effective against invasive pneumococcal disease when administered either alone or concurrently with influenza vaccine.[40] Both influenza and pneumococcal vaccines can be given safely at the same vaccination session with no increase in the frequency of systemic side-effects.[41–44]

Summary

Following a thorough review of the literature pertinent to influenza vaccination in older people, the following conclusions could be drawn:

- Influenza vaccination is effective in reducing morbidity and mortality in people aged 65 years or more with co-existing chronic illness.
- Influenza vaccination is effective in reducing morbidity and mortality in institutionalised older people.
- Influenza vaccination is safe and does not cause an increase in systemic side-effects compared with placebo.
- Pneumococcal vaccination may reduce pneumococcal bacteraemia and can be safely co-administered with influenza vaccine in different sites at the same vaccination session.

In 1999 a study was undertaken in Liverpool to determine the cost–benefits to the NHS of vaccinating healthy people aged 65–74 years who at the time were not included in UK influenza immunisation guidelines.

Chapter 3
Methodology

Participants

Healthy individuals registered with 20 practices in Liverpool were identified in September 1999 from computerised GP records, excluding individuals with known indications for vaccination (chronic heart, lung or renal disease, asthma, diabetes, immunosuppression due to disease or treatment and living in long-stay residential or nursing accommodation). Thirteen of the 20 practices were unable to use a computer to search for patients by disease category. In these practices, suitable people were identified either by their doctor or practice nurse or by manually searching patient prescriptions to identify key medications. Patients prescribed immunosuppressants or medications for diabetes or chronic heart, lung or renal disease were excluded. Invitations were sent on behalf of the GP in accordance with Caldicott guidelines.

In January 2000, a questionnaire and pre-paid envelope were sent to all individuals who declined to participate. People were asked to reply yes or no to statements describing different reason(s) for non-participation. A space at the bottom of the questionnaire enabled any other reason(s) to be given. The questionnaire was designed by the research team and labelled with a unique identifying code that enabled confidentiality to be maintained (Appendix 1).

The vaccination status of eligible individuals who did not participate but who may have been vaccinated by their own GP outside the study was also determined. Additionally, the Carstairs deprivation score[45] was calculated for each person from the postcodes of all eligible individuals. Negative scores on the index indicate relative affluence whereas positive scores indicate relative deprivation.

To increase the power of the trial and to attempt to account for the natural annual variation that occurs in baseline influenza attack rates, recruitment and randomisation were originally planned to have taken place over two consecutive winter seasons (1999–2000 and 2000–1). This was not possible following the change in UK influenza immunisation policy in May 2000.[3] Thus in 2000–1, a RCT could not be carried out and all people who participated in 1999–2000 were offered influenza vaccine only.

Intervention

Recruitment took place in September and October 1999 and vaccinations were administered at participants' local GP surgery during October and November. Participants were block randomised using computer-generated numbers, stratified by GP practice, to receive either a trivalent, split virion influenza vaccine or placebo (0.5 ml physiological saline) in a ratio of 3:1. This ratio was chosen to encourage participation in the study, with participants three times more likely to receive vaccine than placebo. Each dose of influenza vaccine (0.5 ml) contained 15 µg of A/Beijing/262/95 (H1N1), 15 µg of A/Sydney/5/97 (H3N2) and 15 µg of B/Beijing/184/93 in accordance with the WHO recommendation (Northern Hemisphere) for 1999–2000. As a further incentive to join the study, all participants were given the 23-valent pneumococcal polysaccharide vaccine unless it had been administered in the previous 10 years. The indications for pneumococcal and influenza vaccines are almost identical.

Influenza vaccine or placebo was always administered into the right deltoid muscle and pneumococcal vaccine into the left deltoid.

Each participant on arrival was given a numbered, sealed, opaque envelope containing a card revealing a letter A, B, C or D. The project statistician, prior to each vaccination session, assigned one letter to placebo and the envelopes were prepared in the researchers' office before each session commenced.

Influenza and pneumococcal vaccines were supplied by Wyeth Laboratories (Maidenhead, Berkshire, UK). Other vaccine manufacturers had been approached, but only Wyeth expressed an interest in supplying vaccine for the trial. Owing to the seasonal demands placed upon the company by influenza vaccine production, they were unable to open a new production line for the

manufacture of a placebo specifically for this trial. However, the manufacturer of syringes used for influenza vaccine administration (Becton-Dickinson) did supply us with empty syringes, which were then manually filled with physiological saline solution. This meant that influenza vaccine and placebo were identical in appearance and delivered in identical syringes provided by the same manufacturer, thus ensuring that participants were unaware of the type of injection given. Owing to the limited number of personnel involved it was not possible to make the trial double blinded. One member of the research team was responsible for the administration of all vaccinations and was aware of which participants received placebo.

The local research and ethics committee approved the trial protocol and written informed consent was obtained from all individuals before entry into the trial.

Clinical outcomes and follow-up

Side-effects

At the time of the study injection, all participants were given a side-effects questionnaire (Appendix 2) and each person was given instructions to complete this after 3 days (the period when any side-effects attributable to vaccination are most likely to occur[46]) and return to the researchers in a pre-paid envelope. A reminder letter was sent to individuals not returning questionnaires followed by a telephone call if still outstanding. This was repeated in year 2 (when only influenza vaccine was given) and the paired responses from both years were compared, thus allowing assessment of the contribution of pneumococcal vaccine to the incidence of systemic side-effects in year 1.

Respiratory illness

All participants were given a three-page illness calendar (Appendix 3) and asked to record symptoms of any respiratory illness for 6 months following the study injection. One page of the calendar was returned to the researchers in pre-paid envelopes at 2-monthly intervals following a reminder letter. Individuals who had recorded respiratory symptoms were contacted by telephone and interviewed by one researcher blinded to treatment allocation to ascertain a more qualitative description of their illness.

For the purposes of this study, based on the criteria as described in the International Classification of Health Problems in Primary Care,[47] individuals were classified as suffering from influenza or ILI if all of the following symptoms were present: sudden onset of ILI, cough, feverishness, prostration and weakness, myalgia and widespread aches and pains. Serology was not analysed owing to the logistical difficulties of obtaining serum from individuals with ILI throughout Merseyside. Clinical judgement has been shown to have the highest predictive value in the diagnosis of influenza when influenza is known to be circulating in the community.[4] Those individuals reporting a doctor's consultation secondary to their illness had their medical records and prescribed medication scrutinised. Additionally, the medical records of those individuals who did not return their calendar to the researchers and were not contactable by telephone were also examined.

Hospitalisation secondary to acute or chronic respiratory illness

The hospital records of patients admitted with a respiratory illness and post-mortem reports and medical records of individuals in the study who died from any cause were examined.

QoL scores

The EuroQol EQ-5D health questionnaire (Appendix 4) was used to assess quality of life for 6 months following vaccination. The Hospital Anxiety and Depression scale (HAD) was also included in the study to assess the psychological impact of an acute influenza infection as defined by anxiety and depressive symptoms (Appendix 5). The HAD consists of 14 items on two subscales (seven anxiety and seven depression) and ratings are made on four-point scales representing the degree of distress associated with any anxiety or depressive symptoms suffered during the previous week. The two scales are then scored separately. On both scales, a score of $\leqslant 7$ indicates non-cases, 8–10 doubtful cases and 11+ definite cases. In the original paper[48] the authors argued that "should the researcher require inclusion of all possible cases, i.e. a low proportion of false negatives", then a score of eight and over should be used, and "where the research requires the inclusion of only those patients who have a high probability of suffering from the mood disorder, i.e. a low proportion of false positives", then a score of 11 and over should be used. The HAD has been shown in different studies to have good reliability and validity when used as a psychological screening tool.[49]

The EQ-5D questionnaire was developed as a practical way of measuring the health of a population, allowing a self-description of current

health-related QoL to be recorded easily and has been validated for use in this population.[50] Current health state can be measured either in the form of a weighted score based on five different health dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) or by a visual analogue 'thermometer' scale where 100 represents the best imaginable health state and zero the worst.

Immediately prior to vaccination, participants were asked to self-complete the EQ-5D, HAD and Barthel index (Appendix 6). The Barthel index[51] was used to check the level of dependence of people recruited to the study. Both the EQ-5D and HAD were additionally sent to participants at 2-monthly intervals after the study vaccination and were returned to the researchers in pre-paid envelopes.

Data analysis and sample size calculation

The primary outcome variable was occurrence of influenza as measured by patient attendance at the GP with pneumonia-like illness or ILI. Chi-squared, Fisher's exact test and Mann–Whitney *U*-test were used to compare baseline characteristics. Vaccine efficacy was expressed in terms of the relative risk with 95% confidence intervals. QoL outcomes were analysed by a repeated measure analysis of variance (ANOVA) (general linear model) with factors for time, injection type and time–injection type interaction. Missing values were excluded on a list-wise basis.

All tests were two sided (unless specified), with significance shown by $p < 0.05$. The p values quoted were not adjusted for multiple hypotheses testing, either within or across families of parameters.

Power calculations for the primary outcome variable based on a 1-year analysis were difficult in view of the annual variation in influenza incidence and the unknown benefit of vaccination in this population. If the baseline rate of influenza was 15% we calculated that a total of 2135 patients randomised 3:1 vaccine:placebo would achieve 80% power to detect a true 5% difference between the two groups. All data were password protected and held in Microsoft Access 97. Only authorised users of the University Managed Network Service could access this database. Anonymity was maintained using a unique identifying number assigned to each participant in the study. Data were analysed using SPSS version 10.7 and Confidence Interval Analysis (CIA) software.

Chapter 4
Results

Outline of recruitment

In September 1999, 9727 people aged 65–74 years were registered with practices participating in the study.

Of these individuals, 6058 (62.3%) were initially considered suitable (i.e. fit, healthy and non-institutionalised) and invited to join the study. Of these people, 5875 (60.4%) were subsequently found eligible to participate.

In the remaining 183 individuals:

- 76 invitations were returned by the Royal Mail, 'not at this address'
- 84 individuals were subsequently found to have one or more chronic illnesses requiring vaccination out of the study
- nine individuals were older than 75 years
- 10 claimed to be allergic to the vaccine
- four were deceased.

Of the 5875 eligible individuals, 4047 (68.9%) replied to the invitation to participate and 729 (12.4%) were subsequently randomised. Baseline characteristics of people randomised are given in *Table 1*. There were no clinically important differences between participants randomised to receive influenza vaccine or placebo.

Of the 5146 (87.6%) individuals who did not consent:

- 2583 informed us that they did not want to participate
- 1828 did not reply
- 568 informed us that they had already been vaccinated by their own doctor
- 167 agreed to participate but did not attend when given an appointment.

Participant flow through the study is summarised in *Figure 1*.

There were no clinically important median age differences between participants and eligible non-participants (68.9 years versus 69.6 years, respectively, at 1 October 1999).

Females were significantly less likely to participate:

- 341/729 (46.8%) participants were female
- 2962/5146 (57.6%) non-participants were female
- odds ratio for being female and participating in the study = 0.65 (95% CI = 0.56 to 0.76, $p < 0.001$).

Reasons for non-participation

Of the questionnaires distributed, 1173/2583 (45.4%) were returned. A total of 2621 reasons

TABLE 1 *Participant characteristics*

	Vaccine (*n* = 552)	**Placebo (*n* = 177)**	***p* Value**
Median age (years) (IQR)[a]	68.9 (4.4)	69.1 (5.2)	0.64[a]
Male (%)	51.8	57.6	0.21[b]
Current smoker (%)	19.7	20.9	0.82[b]
Ex-smoker (%)	44.6	36.7	0.08[b]
Never smoked (%)	35.7	42.4	0.13[b]
Median (range) Barthel score	100 (60–100)	100 (65–100)	0.90[a]
Immunised with pneumococcal vaccine prior to consenting for trial (%)	0.2	1.1	0.15[c]

IQR, interquartile range.
[a] Mann–Whitney *U*-test.
[b] χ^2 test.
[c] Fisher's exact test.

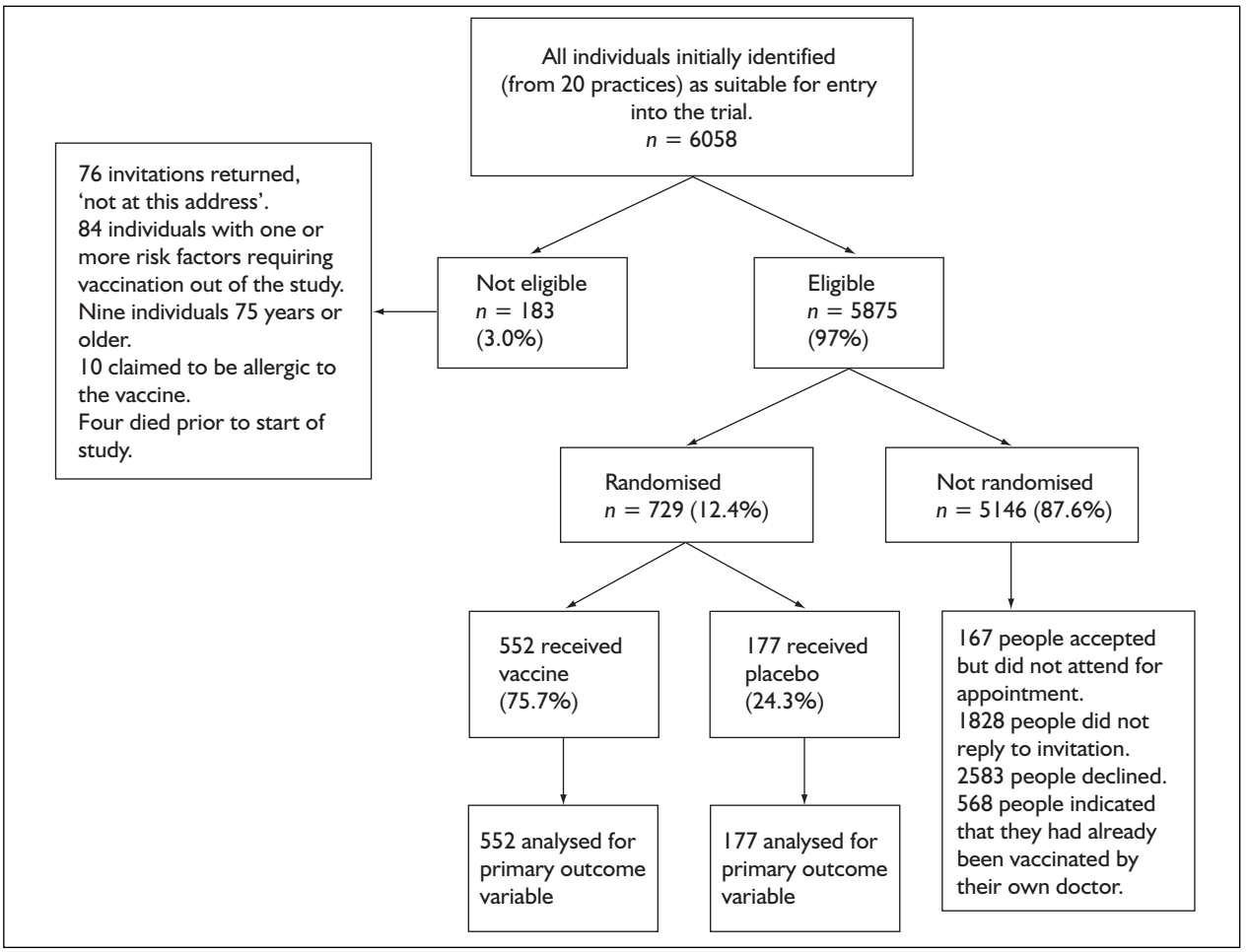

FIGURE 1 *Trial profile*

were given for non-participation, i.e. a mean of 2.2 reasons per questionnaire returned. The breakdown of their responses is shown below:

	n	(%)
• do not wish to be involved in a research project	622	(53.0)
• concerned about side-effects of vaccine	399	(34.0)
• do not require the vaccine	372	(31.7)
• if required, would rather the GP gave the vaccine	341	(29.1)
• objection to name 'Geriatric Medicine' on invitation letter	296	(25.2)
• already received the vaccine this year	203	(17.3)
• illness exclusion criteria for study	162	(13.8)
• previous bad reaction to the vaccine	75	(6.4)
• unable to attend any of the sessions	51	(4.3)
• unable to get to GP surgery	47	(4.0)
• already involved in a clinical trial	29	(2.5)
• fear of needles/dislike of injections	19	(1.6)
• doubts about vaccine efficacy	3	(0.3)
• egg allergy	2	(0.2)

Claims of vaccination out of the study were verified with the individual's own GP. In 16 of the 20 participating practices we were able to obtain these data. Of the 203 individuals who indicated on the questionnaire that they did not take part because they had been vaccinated out of the study, 177 were registered with these 16 practices and a total of 134 (76%) of those in whom verification was possible were listed as having received vaccination. There was no evidence to suggest that vaccine had been administered in the remaining 24%.

Adverse reactions following influenza vaccination

Initially 699 (96%) side-effect questionnaires were returned, and a further 25 were received following a postal or telephone reminder; 724 (99%) questionnaires were returned in total, from 385 males and 339 females. The five missing questionnaires were all from patients in the vaccine group. Pneumococcal vaccine was

TABLE 2 *Adverse reactions (1999–2000)*

	Vaccine: *n* (%)	Placebo: *n* (%)	Difference in reported symptoms (%) (95% CI)	*p* Value
Sore right arm	62 (11.3)	9 (5.1)	6.2 (1.3 to 10.0)	0.02
Feverishness	20 (3.7)	8 (4.5)	–0.8 (–5.2 to 2.1)	0.77
Aching limbs	56 (10.2)	20 (11.3)	–1.0 (–7.0 to 3.7)	0.80
Fatigue	78 (14.3)	19 (10.7)	3.6 (–2.5 to 8.4)	0.29
Rash	17 (3.1)	8 (4.5)	–1.4 (–5.7 to 1.5)	0.51
Cough	29 (5.3)	17 (9.6)	–4.3 (–9.8 to 0)	0.06
Runny nose	91 (16.6)	42 (23.7)	–7.1 (–14.5 to –0.5)	0.05
Headache	51 (9.3)	23 (13.0)	–3.7 (–9.8 to 1.3)	0.21
Sore throat	23 (4.2)	10 (5.6)	–1.4 (–6.1 to 1.8)	0.56
Any systemic symptom	192 (35.1)	75 (42.4)	–7.3 (–15.6 to 0.9)	0.10

administered to 175/177 (98.9%) individuals in the placebo group and 546/547 (99.8%) individuals in the vaccine group.

There was no significant difference in systemic symptoms between the two groups. There was, however, a significant difference in local symptoms of 6.2% between the vaccine and placebo group (95% CI 1.3 to 10.0; $p = 0.02$).

All results were analysed using Pearson χ^2 test, correction factor applied.

The results are summarised in *Table 2*.

Females were significantly more likely to complain of local but not systemic side-effects:

- 129/339 (38.1%) females complained of one or more systemic side-effects
- 138/385 (35.8%) males complained of one or more systemic side-effects
- odds ratio for females and one or more systemic side effects = 1.1 (95% CI = 0.8 to 1.5)
- 42/339 (12.4%) females complained of local symptoms;
- 29/385 (7.5%) males complained of local symptoms;
- odds ratio for females and local symptoms = 1.74 (95% CI = 1.1 to 2.9).

Adverse reactions 2000–1

As in 1999–2000, all individuals were asked to complete a side-effect questionnaire 3 days after receiving the vaccine in 2000–1. To investigate the contribution of pneumococcal vaccine in adverse reactions, the incidence of systemic side-effects in the second year (when people received influenza vaccine only) were compared in people who participated in both years and who received simultaneous influenza and pneumococcal vaccine in year one.

TABLE 3 *Total number of systemic side-effects over two consecutive years (n = 356)*

Adverse reaction	Influenza and pneumococcal vaccination (1999): *n* (%)	Influenza vaccination (2000): *n* (%)
Fever	11 (3.1)	18 (5.1)
Aching limbs	33 (9.3)	36 (10.1)
Rash	10 (2.8)	25 (7.0)
Fatigue	48 (13.5)	56 (15.7)
Runny nose	59 (16.6)	66 (18.5)
Cough	18 (5.1)	36 (10.1)
Headache	27 (7.6)	45 (12.6)
Sore throat	9 (2.5)	25 (7.0)
Any systemic symptom	121 (34.0)	125 (35.1)

In total, 674/714 (94%) questionnaires were returned in year 2 and, of these, 356 people received influenza and pneumococcal vaccines in the first year of the trial. The total number of systemic side-effects recorded by these individuals in both years is given in *Table 3*.

Higher frequencies of systemic symptoms in 2000 compared with 1999 could be explained by different exposure to common viral or bacterial pathogens, for example enteroviruses or *Streptococcus pyogenes*.

Clinical outcomes

Primary outcome

The results of the primary outcome measure are contained in *Table 4*. There were no hospitalisations for respiratory illness and no GP diagnoses of pneumonia during the study period.

TABLE 4 *Clinical outcomes involving medical intervention*

	Vaccine: *n* (%)	**Placebo: *n* (%)**	**RR (95% CI)**
GP diagnosis of ILI	5 (0.9)	2 (1.1%)	0.8 (0.16 to 4.1)
GP diagnosis of pneumonia	0	0	N/A
GP consultation for any respiratory symptom	44 (8.0)	17 (9.6)	0.83 (0.49 to 1.42)
GP prescribed antibiotic for any respiratory symptom	38 (6.9)	9 (5.1)	1.35 (0.67 to 2.74)
Hospitalisation for any respiratory illness	0	0	N/A
Death[a]	3 (0.5)	1 (0.6)	0.96 (0.1 to 9.19)

[a] Cause of death = bronchial carcinoma (2), oropharyngeal carcinoma (1), metastatic adenocarcinoma (1).

TABLE 5 *Self-reported ILI*

	Vaccine: *n* (%)	**Placebo: *n* (%)**	**RR (95% CI)**
At least one or more[a] episodes of self-reported ILI	24 (4.6)	15 (8.9)	0.51 (0.28 to 0.96)[b]
At least one or more episodes of self-reported ILI involving a GP consultation[c]	9 (1.7)	4 (2.4)	0.72 (0.23 to 2.32)
Self-reported ILI not requiring a doctor consultation but involving use of OTC medication	11 (2.1)	7 (4.2)	0.50 (0.2 to 1.28)

OTC, over the counter.
[a] No participants self-reported more than one ILI during the monitoring period.
[b] Significant, $p = 0.031$ (Fisher's exact test, one-sided).
[c] Not necessarily diagnosed by the GP as ILI.

Self-reported illness data

Self-reported illness data are contained in *Table 5*.

There were 538 participants who returned all illness calendar sheets and a further 153 individuals who failed to return one or more sheets were contacted by telephone; 38 individuals (29 vaccine and nine placebo) did not return all or part of the illness calendar and could not be contacted. Complete self-reported illness data were thus obtained from 691 (95% of vaccine and 95% of control group) people.

Significantly fewer vaccinated individuals self-reported a single ILI.

Vaccine efficacy for prevention of ILI =
$1 - \text{RR} \times 100\%$
$1 - 0.51 \times 100 = 49\%$
(95% CI = 4 to 72%)

Over-the-counter (OTC) medicines self-administered were paracetamol, Co-codamol, Lemsip®, Sudafed®, Beechams® Powders, Benylin® cough mixture, 'homeopathic remedies', aspirin, Strepsils®, TCP® and linctus cough preparations.

The median age of people (56% male) who self-reported ILI was 69.9 years at 1 October 1999 and the mean Carstairs score of this group was 3.2.

Seventeen (44%) individuals with a self-reported ILI took paracetamol either alone or in combination with other medication.

Two-thirds of the people who self-reported an ILI in 1999–2000 did not seek medical attention. Thirty-four (87%) people reported their symptoms in either December 1999 or January 2000 (*Figure 2*), mirroring local and national data for GP consultation rates for ILI during the same period (*Figure 3*).

Background rate of influenza

The predominant circulating influenza strain in 1999–2000 was influenza A (H3N2). The match between influenza vaccine components and circulating strains in 1999–2000 was good and the vaccine provided substantial protection.[52] Data from eight Liverpool Health Authority 'spotter'

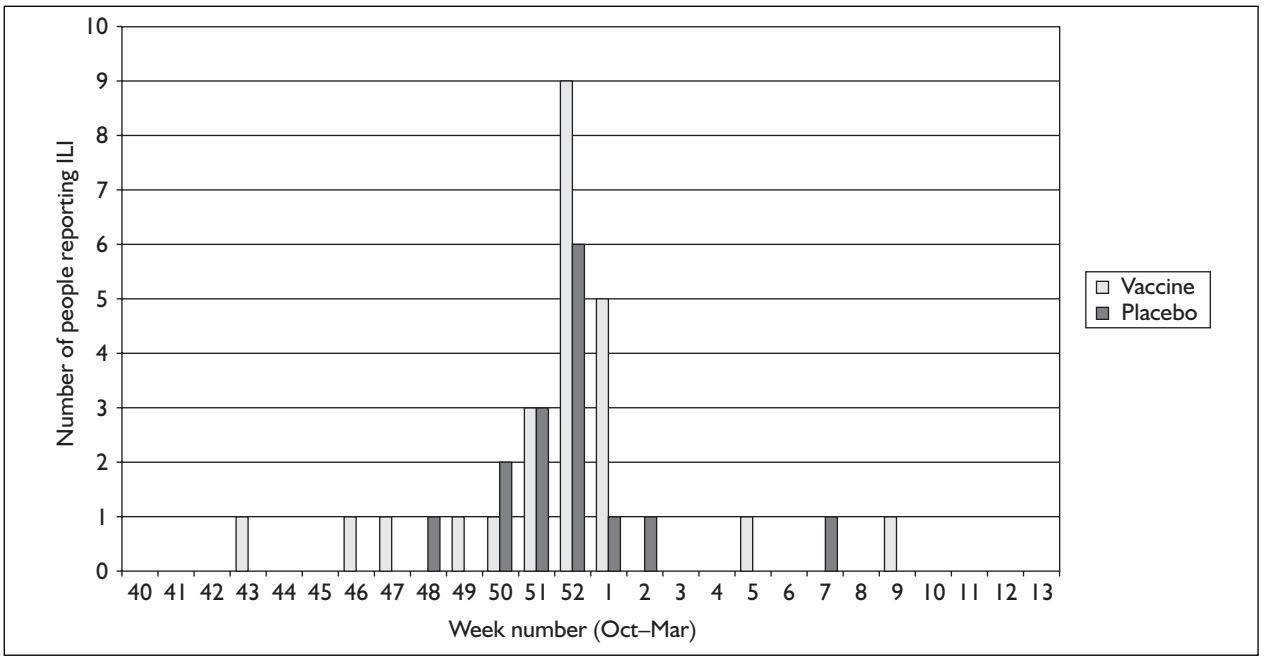

FIGURE 2 *Self-reported ILI 1999–2000*

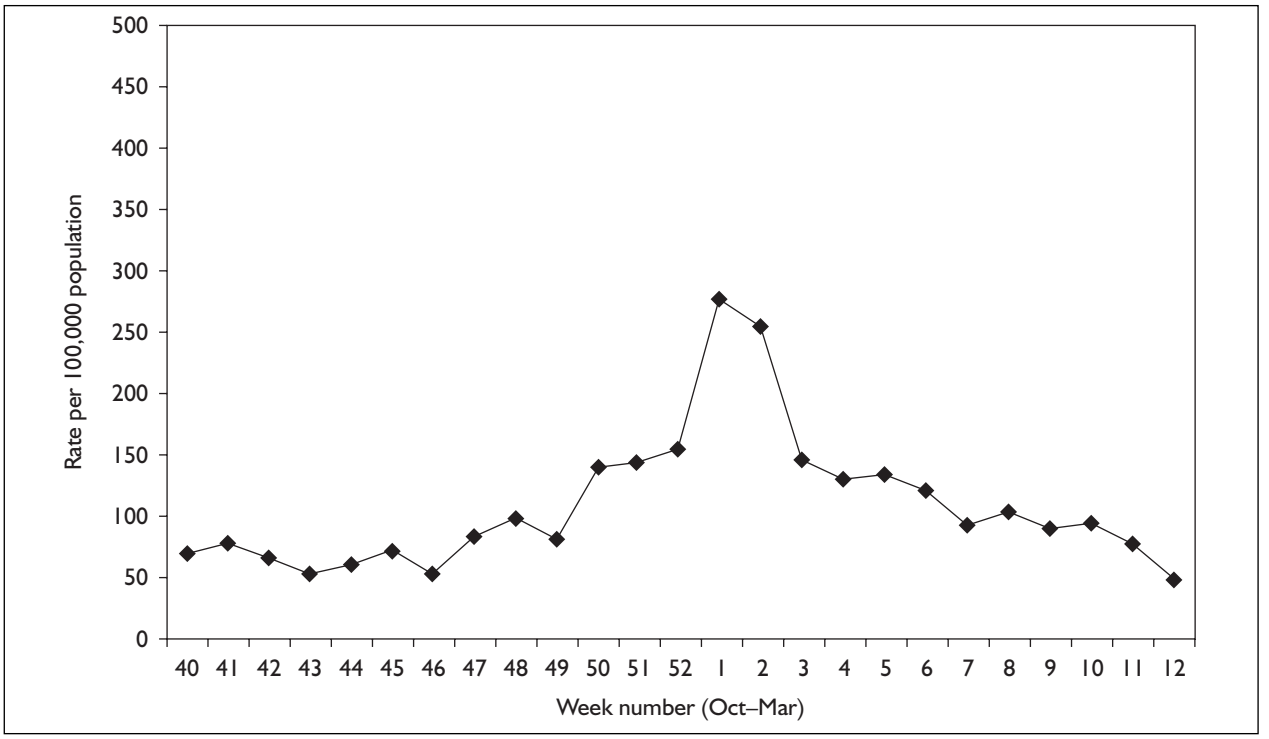

FIGURE 3 *Consultation rate per 100,000 population in Liverpool in 1999–2000 for influenza and ILI (primary care information initiative)*

practices covering a population of 52,500 showed a peak GP consultation rate for ILI of 278 per 100,000 population in the week beginning 3 January 2000 (*Figure 3*) compared with a peak rate of 231 per 100,000 seen overall for England and Wales during the same period. This rate fell within the range of 'higher than expected seasonal activity" of 200–400 per 100,000.

Variation in EQ-5D (QoL) scores

- Immediately prior to vaccination, 696/729 (95%) individuals completed all five dimensions included in the section 'Your own health state today' and 692/729 (95%) people marked a score on the visual analogue 'thermometer' scale.

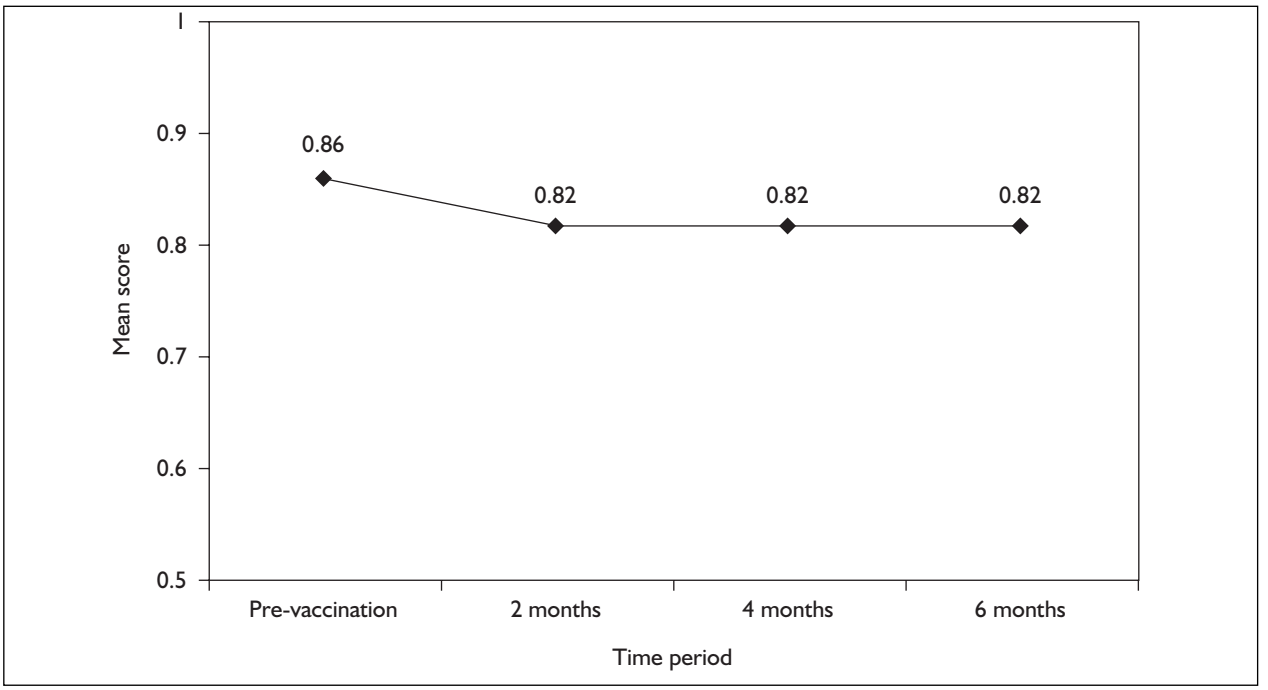

FIGURE 4 *Mean EQ-5D weighted score (*n *= 557)*

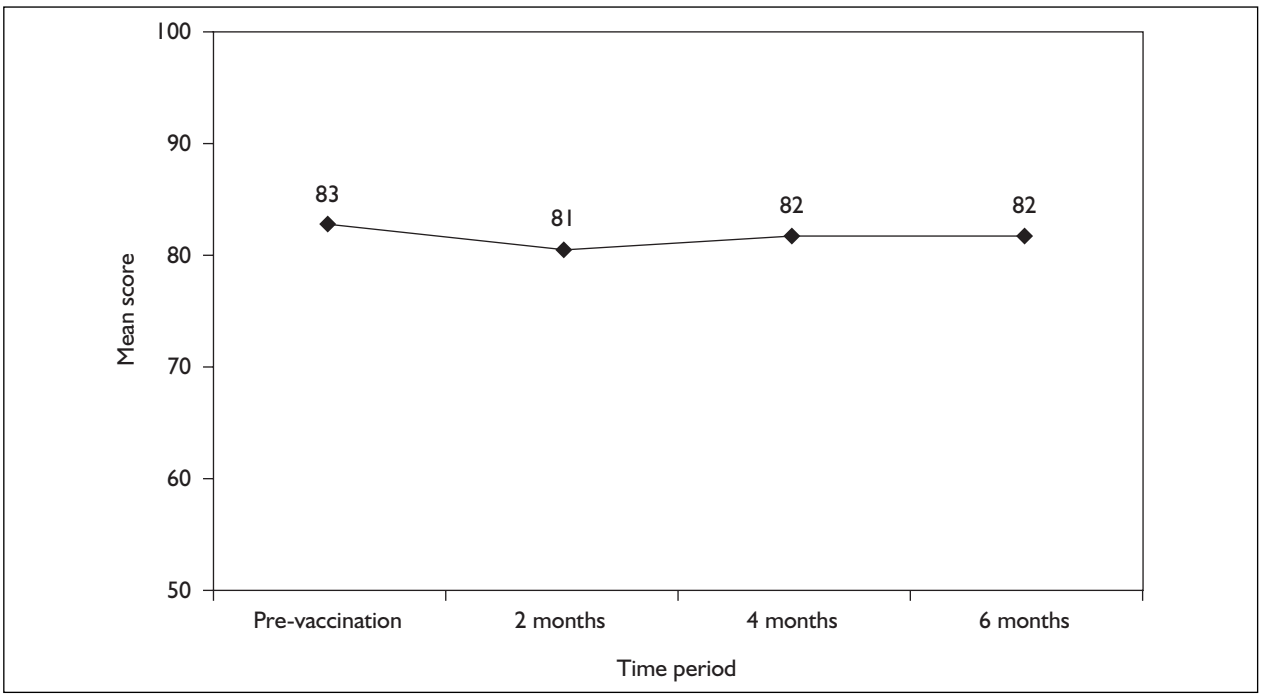

FIGURE 5 *Mean EQ-5D visual analogue score (*n *= 575)*

- 671/729 (92%) EQ-5D questionnaires were returned at 2 months, 664/729 (91%) at 4 months and 683 (94%) at 6 months.
- 650/671 (97%), 635/664 (96%) and 668/683 (98%) individuals completed all five dimensions in the section 'Your own health state today' at 2, 4 and 6 months, respectively.
- 657/671 (98%), 647/664 (97%) and 675/683 (99%) individuals completed the visual analogue 'thermometer' scale at 2, 4 and 6 months, respectively.
- 557 (75% of vaccine group and 81% of placebo group) and 575 (78% of vaccine group and 82% of placebo group) participants had a weighted health state and visual analogue scale score, respectively, for every monitoring period (four separate time periods). The mean (standard deviation, SD) weighted scores were 0.86 (0.2),

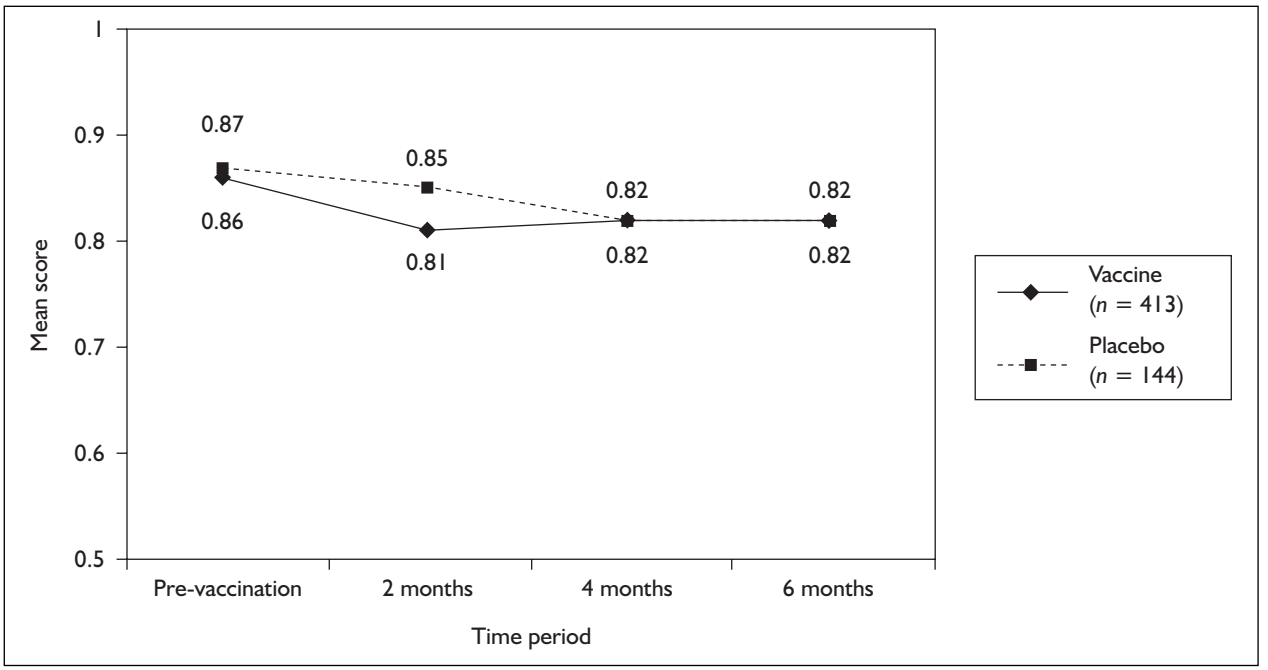

FIGURE 6 *Mean EQ-5D weighted score compared between groups*

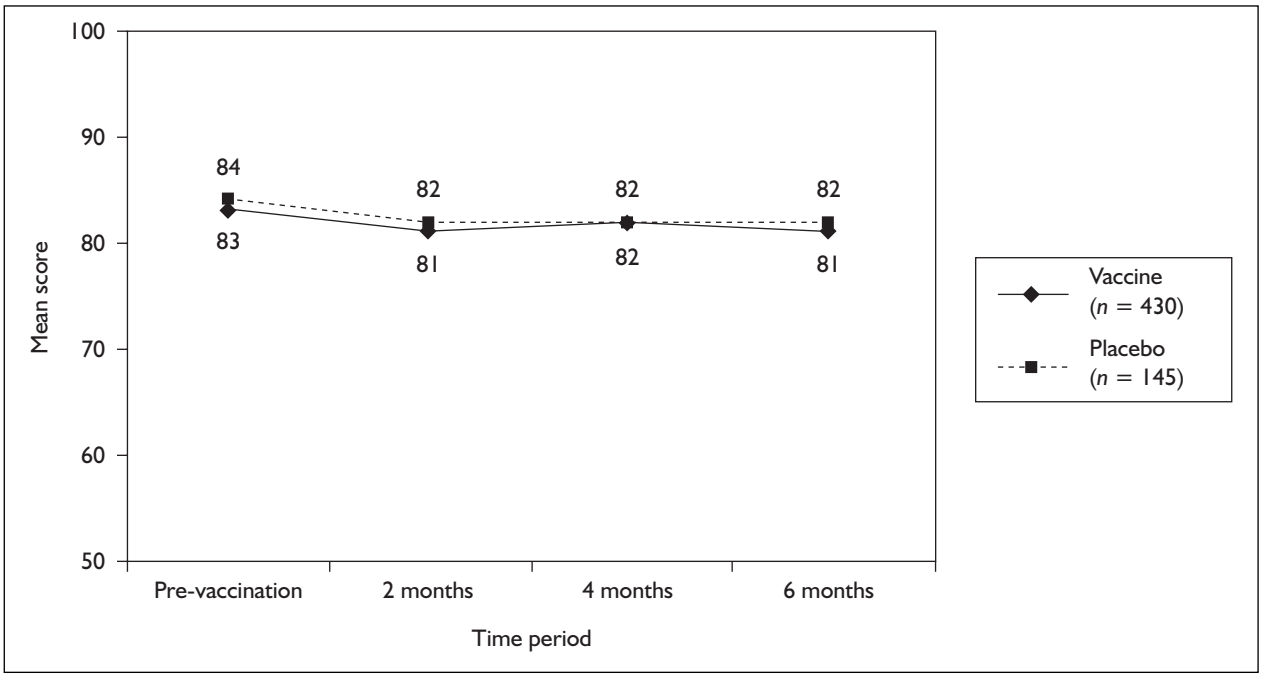

FIGURE 7 *Mean EQ-5D visual analogue score compared between groups*

0.82 (0.22), 0.82 (0.21), 0.82 (0.21) at baseline, 2, 4 and 6 months, respectively (*Figure 4*).

- The mean (SD) visual analogue scores were 83 (15), 81 (15), 82 (15), 82 (15) at baseline, 2, 4 and 6 months, respectively (*Figure 5*).
- A significant decrease over time was seen in both mean weighted [F (2.871, 1593.442) = 15.298, $p < 0.001$] and visual analogue scores [F (2.361, 1353.092) = 4.841, $p = 0.005$].
- For all time periods combined, there was no significant difference between vaccine and placebo on either the weighted score [F (1,555) = 0.519, $p = 0.47$] or visual analogue scale [F (1, 573) = 0.68, $p = 0.41$].
- No significant difference over time was seen between vaccine and placebo (injection type × time period interaction) on either the weighted score scale [F (2.87, 1593.4) = 1.96, $p = 0.12$, *Figure 6*] or visual analogue scale [F (2.36, 1353.1) = 0.23, $p = 0.83$, *Figure 7*].

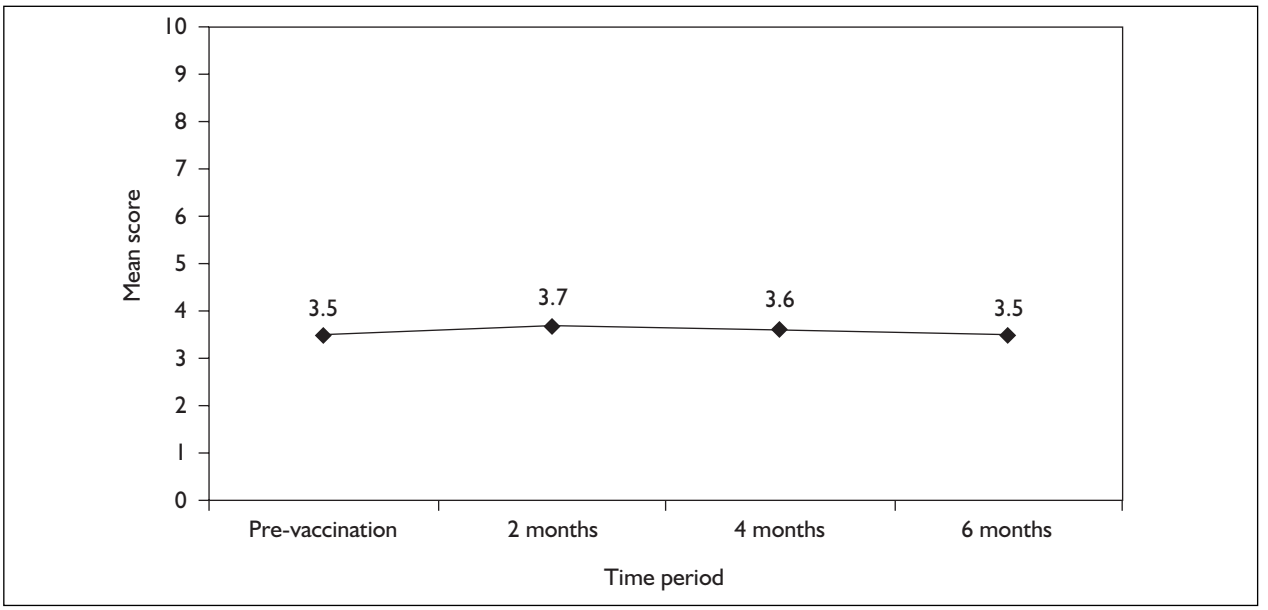

FIGURE 8 *Mean HAD anxiety score (n = 523)*

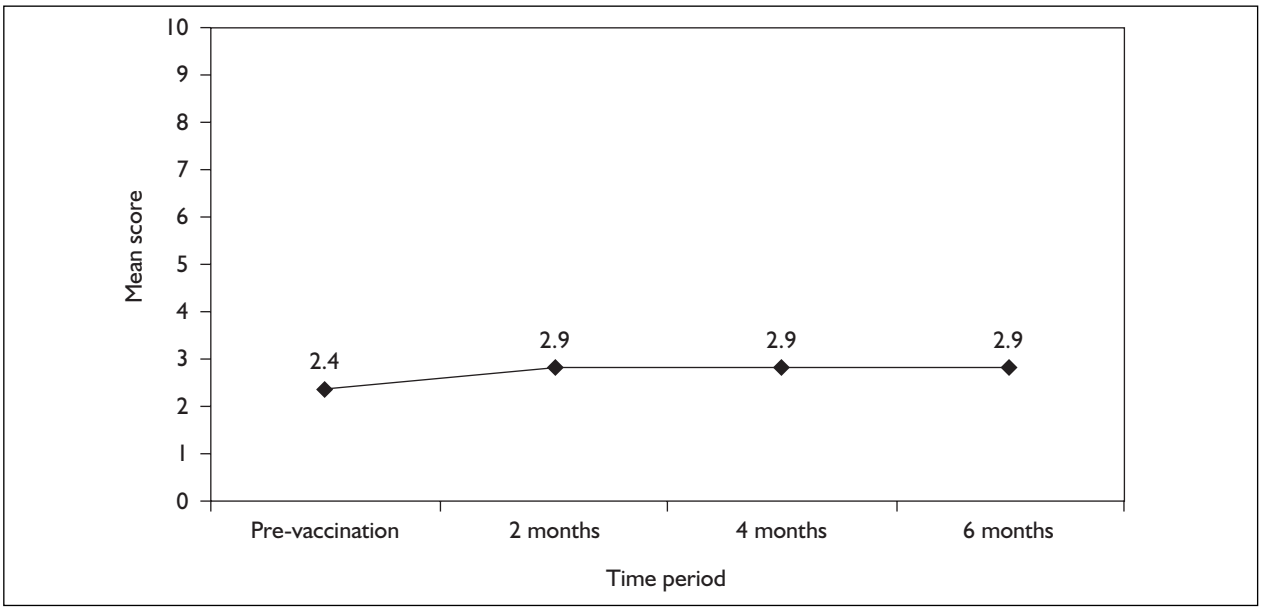

FIGURE 9 *Mean HAD depression score (n = 529)*

Variation in anxiety and depression scores

- 702/729 (96%) anxiety and 707/729 (97%) depression scales were fully completed at baseline.
- 679/729 (93%), 656/729 (90%) and 666/729 (91%) HAD questionnaires were returned at 2, 4 and 6 months, respectively.
- At 2 months, 662/679 anxiety (97%) and 660/679 (97%) depression scales were fully completed.
- At 4 months, 630/656 (96%) anxiety and 626/656 (95%) depression scales were fully completed.
- At 6 months, 627/666 (94%) anxiety and 630/666 (95%) depression scales were fully completed.
- 523/729 (72% of vaccine group and 71% of placebo group) individuals completed the anxiety scale at every 2-month period. Mean (SD) anxiety scores for these individuals were 3.5 (3.1), 3.7 (3.3), 3.6 (3.4) and 3.5 (3.3) at baseline, 2, 4 and 6 months, respectively (*Figure 8*).
- 529/729 (72% of vaccine group and 73% of placebo group) individuals completed the depression scale at every 2-month period. Mean (SD) depression scores for these individuals were 2.4 (2.3), 2.9 (2.6), 2.9 (2.8) and 2.9 (2.6)

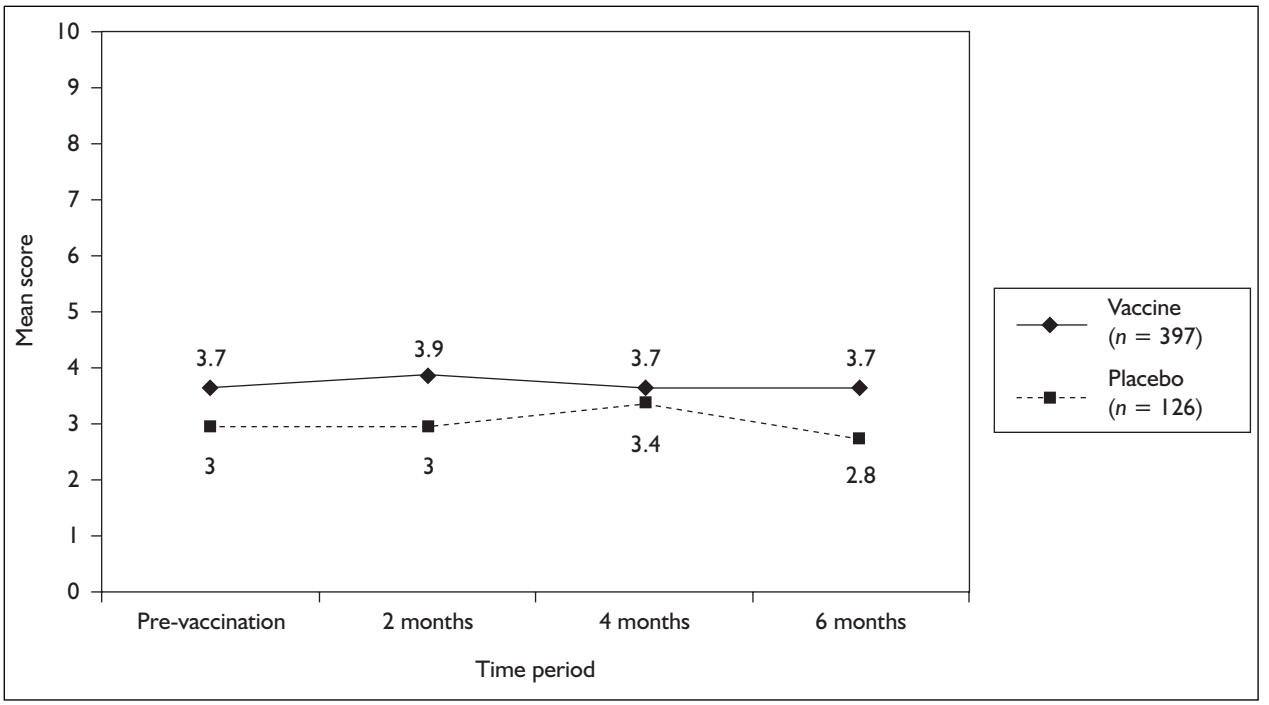

FIGURE 10 *Mean HAD anxiety score compared between groups*

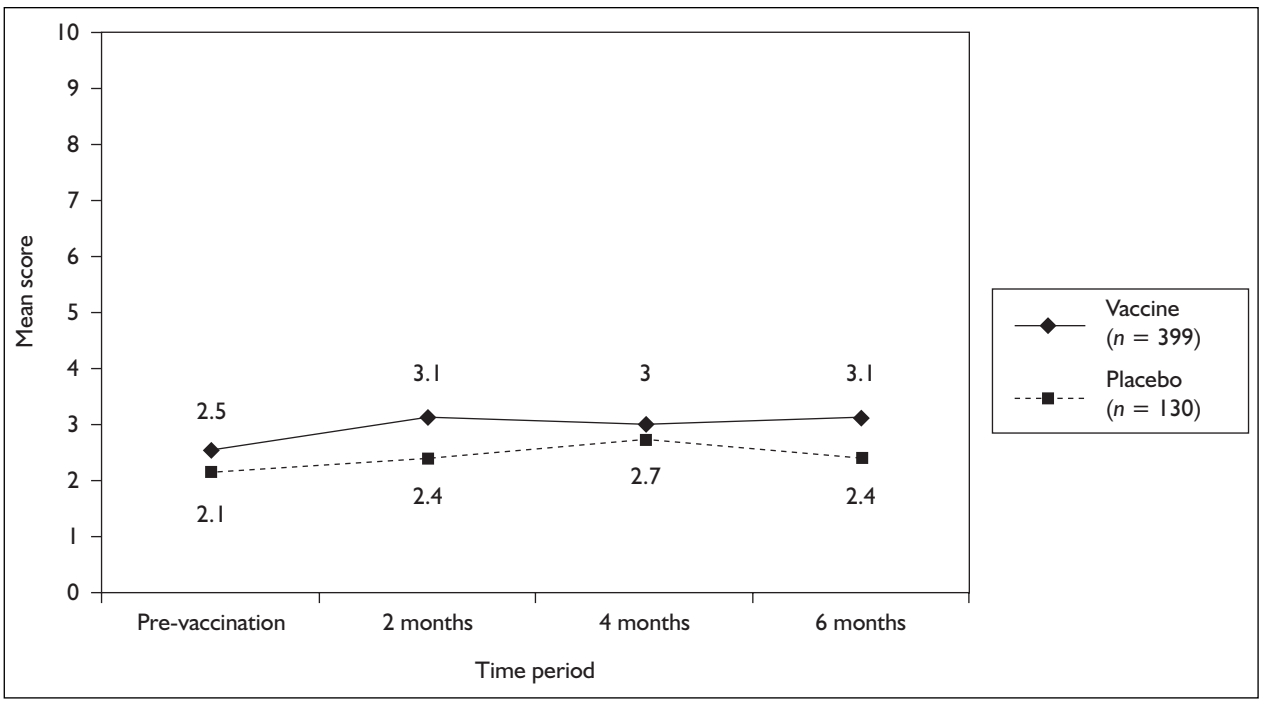

FIGURE 11 *Mean HAD depression score compared between groups*

at baseline, 2, 4 and 6 months respectively (*Figure 9*).

- There was no significant change over time in anxiety scores [F (2.846, 1482.681) = 2.072, p = 0.11] but there was a significant increase in depression scores [F (2.792, 1471.329 = 12.731, $p < 0.001$].
- For all time periods combined, scoring was significantly higher in the vaccine group for both anxiety [F (1, 521) = 5.882, p = 0.016] and depression [F (1, 527) = 4.878, p = 0.028].
- There was no significant difference over time between vaccine and placebo (injection type × time period interaction) for either anxiety [F (2.8, 1482.7) = 2.46, p = 0.065, *Figure 10*] or depression [F (2.8, 1471.3) = 2.1, p = 0.1, *Figure 11*].

TABLE 6 *Age, sex and deprivation scores for participants versus eligible non-participants*

	Consented for study (*n* = 729)	**Non-participant but vaccinated by GP out of study[a] (*n* = 1102)**	**Non-participant and not vaccinated by GP out of study[a] (*n* = 3604)**
Median age (years)	68.9	70.0	69.4
Mean Carstairs score (SD)	3.9 (4.3)	3.6 (4.1)	4.3 (4.3)
Female (%)	46.8	59.2	57.9

[a] Validated vaccination data available from 16 practices.

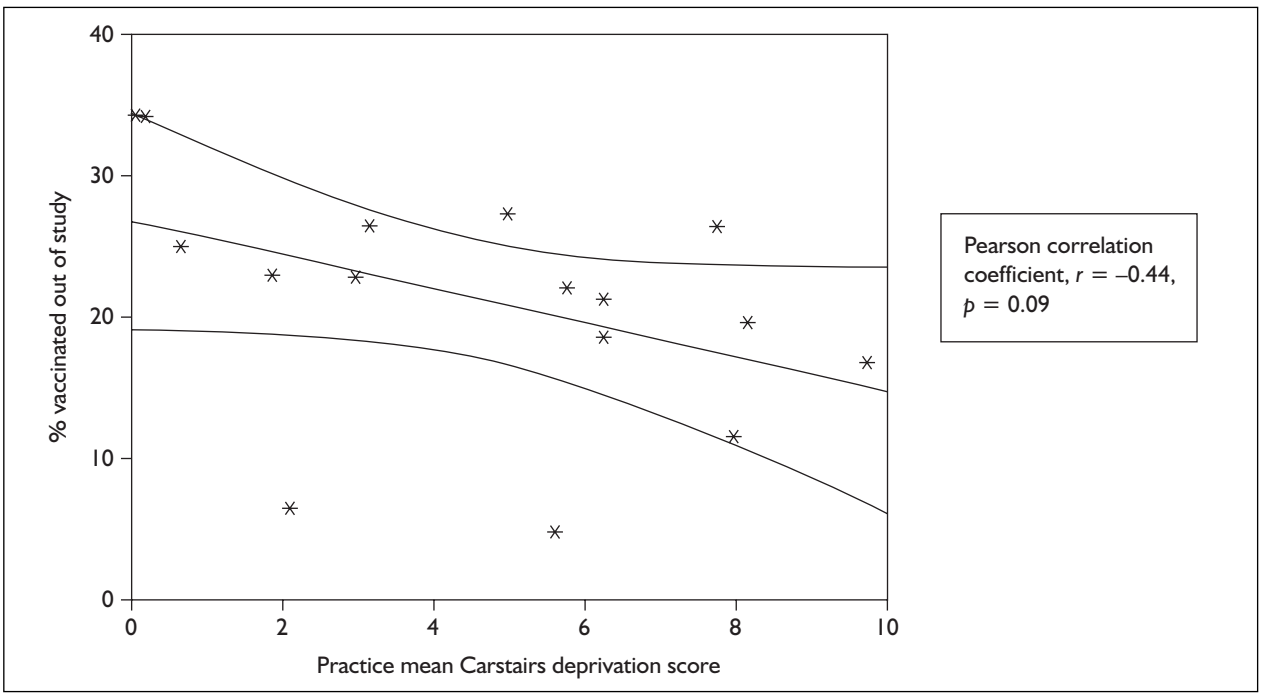

FIGURE 12 *Regression line of percentage of people vaccinated out of the study on GP practice mean Carstairs score, with 95% confidence intervals*

Vaccination out of study

For the winter season 1999–2000 we obtained data from 16/20 practices regarding the vaccination status of eligible individuals who did not participate. Total vaccine uptake (including vaccine and placebo administered in this trial) was 40% (3626/9037) for all people aged 65–74 years who were registered with these 16 practices. Half of the people vaccinated (i.e. 20%) had one or more risk factors making them ineligible for this study. The 1102 (23.4%) eligible individuals who declined participation in the study received vaccination from their own GP. The median age, mean deprivation score and sex was recorded for participants and eligible non-participants who were or were not vaccinated out of the study. This is summarised in *Table 6*.

There were no clinically important age or sex differences between non-participants who were or were not vaccinated outside the study.

The mean Carstairs score was significantly higher for non-participants who were not vaccinated out of the study (4.3 versus 3.6, difference = 0.7, $p < 0.001$, independent samples *t*-test).

A weak non-significant negative correlation was seen between deprivation and uptake of vaccine out of the study (*Figure 12*).

Chapter 5

Economic evaluation: introduction and methods

Economic modelling: the methodological approach

Rapidly escalating healthcare costs have led to increased emphasis on evidence-based medicine supported by economic modelling to assess the comparative clinical and cost-effectiveness of alternative therapeutic strategies. Economic modelling is a means of representing the complexity of the real world in a simplified and comprehensible form using mathematical and/or statistical relationships.[53] Modelling is essential in circumstances such as those faced in this analysis where the availability of trial data is limited for ethical, political or cost reasons. However, in constructing an economic model to evaluate influenza vaccination in healthy older people, it is essential to maximise both the internal and external validity of the model. Internal validity can be maximised by ensuring a high methodological quality in study design, ensuring that the underlying assumptions are appropriate and that the structure of the model mirrors reality as closely as possible. External validity depends on the extent to which the results obtained in the influenza trial are generalisable either from place to place or from a trial situation into practice. The generalisability of our findings depends on local variations in structures of service delivery for influenza vaccine, which are likely to lead to significant differences in the privately borne costs of being vaccinated. In deciding whether to attend for immunisation, each individual will balance the anticipated benefits with the costs (time, inconvenience, privately borne costs) that he or she will incur through such an attendance. Local programmes must therefore minimise such privately borne costs if they are to maximise the use of vaccination by their local population – a key factor underlying the comparative cost-effectiveness of local influenza vaccination programmes. In order to reflect cost-effectiveness that would arise in actual clinical practice, all trial-generated costs and consequences were extracted when assessing their real-world implications to ensure that the model reflects actual conditions through the alteration of key variables. For example, although placebo costs are incorporated in the trial analysis, these and all other protocol-driven costs are not considered in the extrapolation of trial results into mainstream clinical practice. In addition, the economic model has been made as transparent as possible to ensure that the methodology, underlying assumptions and causal relationships are clearly explained and therefore open to criticism and reinterpretation should circumstances change.

Such transparency also highlights areas in which the information base underlying the model is either of poor quality or totally lacking.[54] Given such data deficiencies, sensitivity analysis has been used extensively to assess the robustness of the results obtained. Knowledge of the robustness of results and particular areas in which data are either limited or completely absent is also of value in prioritising future research and to highlight the key variables influencing cost-effectiveness.[55] However, although sensitivity analysis can do much, it is important to remember that the clinical trial on which this economic analysis is based was truncated as a direct consequence of a change in national vaccination policy. As such, our results should be treated with circumspection as being largely indicative and hypothesis generating rather than definitive and final.

The costs associated with influenza vaccination

The evaluation of the costs arising from any intervention must be as comprehensive as possible to ensure that consumption of all resources are incorporated into the analysis regardless of their source. As the population being analysed in this study is not of working age, it is unlikely that any direct productivity gains to the economy will arise as a consequence of the vaccination programme. Equally, although the maintenance of a healthy older population is likely to reduce demands on social service and the public welfare system, the impact of such changes was not felt to be significant enough to warrant detailed analysis.

NHS costs should include the cost of the vaccine, all expenditure associated with vaccine

administration and complications or side-effects relating to the vaccine. Any savings in healthcare resources arising from reductions in the incidence of the disease should be netted off from this initial cost. The implications of influenza vaccination for primary care costs and workload are likely to be complex. Obviously, the immediate and direct implication of the vaccination programme is to increase GP workload through the need to vaccinate healthy older people. However, once the vaccination has been provided, its protective effect means that the patient is less likely to contract influenza and hence less likely to visit the GP. Thus, the cost analysis must compare the savings arising from reduced attendance due to lower levels of influenza with the additional cost and time required to vaccinate relevant patients within the GP's population.

The impact upon hospital costs depends on the extent to which beds can be 'freed up' as a consequence of the vaccination programme. However, it is not just the number of beds that can be released that is important, but also the timing of their release. The value of a freed-up bed depends largely on the level of patient demand being experienced by the hospital sector. In periods of low demand, a freed-up bed may simply be left unoccupied whereas in periods of peak demand lack of available beds may constitute the greatest constraint on the ability of the NHS to expand its care provision. Enhanced rates of vaccination may therefore reduce winter pressures on NHS hospitals by reducing bed utilisation at this exact period of peak demand. Thus, by reducing demand at this time, the benefits to the hospital service will be significantly greater than by freeing up beds at other times of the year.

The implications of the vaccination programme on privately borne costs were also found to be complex. In order to receive vaccination, people have to travel to a specified location (normally the GP surgery), which may prove difficult for people with limited access to private transport and who may experience mobility difficulties. To assess this aspect of privately borne cost, a questionnaire was used to analyse the time taken and mode of transport utilised by patients attending for vaccination (Appendix 7). In addition, the impact on 'significant others' was assessed to obtain a picture of the time commitment and costs imposed on patients, friends and relatives. Finally, privately borne costs associated with adverse events or side-effects of immunisation were captured to assess the extent of the health burden imposed by local and systematic reactions to vaccination.

Epidemiology

A detailed understanding of the epidemiology of influenza is crucial to delineating accurately the benefits arising from influenza vaccination, as only such an understanding will adequately capture the complexity of the transmission dynamics of influenza. Developing such an understanding requires access to an accurate and robust dynamic epidemiological model, the development of which was outside the scope of our study. It is important to recognise, however, the strong link between the transmission and population dynamics of influenza and the comparative cost-effectiveness in any defined year of influenza vaccination, particularly given the high degree of inter-annual variation in transmission that exists. In particular, an enhanced understanding of the epidemiology of influenza is crucial to the implementation of an effective vaccination policy. In particular, in order to maximise the uptake of influenza vaccination in targeted groups, it is essential to enhance our understanding of the micro-epidemiology of influenza vaccination and, in particular, in identifying factors that promote or reduce the uptake of vaccine.[56] This is a crucial area, which is analysed in greater detail in the section 'The crucial relationship between cost-effectiveness and vaccination levels' (p. 26).

One of the major epidemiological problems relates to the 'isolation of effect' between vaccination and its impact on the influenza virus. Estimating levels of ill health directly related to influenza is complicated by the fact that influenza occurs during periods when other respiratory infections are also prevalent, thus making it difficult to isolate acute respiratory disease that can be directly related to influenza. Many other respiratory viruses and pathogens cause an ILI which is indistinguishable from that caused by the true influenza virus. Conversely, although the influenza virus typically manifests itself in symptoms such as fever, malaise, muscle aches, sore throat and headache, its symptomatology may range from mild cold symptoms to fulminant pneumonia, or it may even present as an asymptomatic illness. This overlap poses problems for those wishing to evaluate the effectiveness of vaccination strategies on population health and resource use. Such problems are compounded by the fact that most patients developing an ILI are unlikely to seek medical attention: hence a combination of measures will be required to assess the prevalence of influenza in the populations receiving active vaccine and placebo. Developing an accurate understanding of the relationship

between influenza and other acute respiratory diseases is therefore a crucial element in determining the cost-effectiveness of influenza vaccine. Most analyses assume that influenza activity is additive to all other acute respiratory agents; however, a number of studies have suggested that para-influenza viruses and rhinoviruses are less active in mid-winter when influenza epidemics tend to occur.[57] If such offsetting seasonal effects do occur in other acute respiratory diseases, then the observed relationship between vaccination and reductions in ILIs may actually underestimate the protective effect of vaccination against influenza as a greater proportion of ILIs are actually likely to consist of influenza.

The benefits associated with influenza vaccination in healthy older people

The benefits to society as a result of vaccination of healthy older people relate to the reduced incidence of influenza in the population as a whole in addition to the health gains arising for individual patients. The benefits to the individual relate to the health gains arising from the avoidance of influenza. The effect of influenza on individual patients can range from asymptomatic infection to a life-threatening pneumonia with secondary bacterial infection. A recent systematic review found that vaccination reduced cases of respiratory illness, episodes of hospitalisation and influenza-related mortality by 50%.[17] The number of vaccinations required to prevent one influenza-related death will depend on the attack rate of the virus. In an epidemic year such as 1989, only 40 patients in high-risk groups and 240 patients in other groups would have had to be vaccinated to prevent one influenza-related death.[21,58] However, in 1993 where a lower attack rate was seen, 80 high-risk and 500 low-risk patients would have had to be vaccinated to prevent one influenza-related death.

In older people, influenza is a major cause of mortality with more than 13,000 deaths being attributed to influenza in Britain during 1993.[59] The most recent epidemic year (1989–90) resulted in 29,000 influenza-related deaths in the UK, with over 85% being over the age of 65 years.[60] Excess deaths represent the most visible impact of influenza in older people. Unfortunately, excess mortality is an extremely limited outcome measure and studies have shown that between 10 and 15 people are likely to be hospitalised for each person who dies of complications from influenza.[61,62] Estimating mortality rates is also complicated by the fact that relatively few deaths are certified as being directly caused by influenza. For example, during the 1989–90 influenza epidemic, 26,080 excess deaths occurred in comparison with the three previous years; however, only 2440 of these deaths were directly attributed to influenza with 5260 being attributed to pneumonia.[63] An analysis of mortality data in The Netherlands indicated that the true impact of influenza on mortality exceeded registered influenza mortality by a factor of 3.6.[64]

Between 39 and 52% of all influenza-related illnesses will require formal medical attention[62] and the cost of excess hospitalisations directly attributable to influenza in the USA has been estimated at between US$750 million and US$1000 million.[65] In addition, influenza will also cause a significant reduction in functional status and associated quality of life, which is less visible as the majority of healthy older people will simply self-medicate, retire to bed and endure the symptoms. Indeed, significant health education effort is extended to persuade people suffering from uncomplicated influenza to follow exactly this course of action.

Given that many episodes of influenza in healthy older people would be unlikely to lead to a GP consultation, it was essential for our analysis to uncover this 'invisible' cost of influenza. In order to achieve this, patients were requested to record details of their symptomatology throughout the winter months to provide details of occasions in which influenza-like symptoms arose. In cases where a combination of symptoms arose on particular days that were indicative of influenza, a clinician contacted the patient directly and used his clinical judgement to confirm the likely diagnosis of influenza. It is reassuring to recognise that the self-recorded influenza symptoms peaked in the exact 2-week period (between the last week of December 2000 and the first week of January 2001) that was nationally recognised as the peak period for influenza. In addition, patients were asked to record any GP attendance or hospital visits that were related to influenza.

Such symptoms may also impose physical or psychological limitations that lead to a temporary or permanent decline in their QoL. To capture this element, the QoL of each person participating in the trial was evaluated using the EuroQol (EQ-5D) analysis. This is a well-validated and widely used

QoL questionnaire that has shown to be useful in assessing QoL losses in a range of therapeutic areas. To assess any potential psychological implications arising from influenza, participants were asked to complete the HAD throughout the period of this study. One study[66] found a decline in major physical functioning in 9% of older nursing home residents suffering from influenza. Such deterioration may result from direct damage caused by the virus or indirectly as a consequence of the deconditioning associated with the extended bed rest necessitated by influenza.[67] The extent to which vaccination may attenuate any QoL or functional loss even in cases where it does not actually prevent influenza is an important area for further research. However, such research would need to utilise more sensitive measures of QoL than it was possible to use in this study.

In the USA, a new federal programme for vaccination reimbursement for older people helped to increase vaccine distribution by two-thirds.[68] Overall influenza vaccination levels amongst persons aged 65 years or older increased from 23% in 1985 to approximately 66% in 1997 in the USA.[69] This increase surpassed the national health objective target in the USA for 2000 of 60%. Unfortunately, this more intensive use of influenza vaccine in the USA has not produced a noticeable reduction in excess mortality.[70] The important factor to consider, however, is the extent to which vaccination has controlled an upward trend in influenza mortality that would inevitably have occurred in its absence. Population ageing and rapid human transport have contributed to the enhanced spread of influenza leading to an increase in infection rates. Increased urbanisation resulting from greater population density also accelerates the transmission of influenza. These trends are likely to continue and the benefits derived from vaccination programmes are likely to become of ever greater importance in the future.

The crucial relationship between cost-effectiveness and vaccination levels

Little information is available concerning factors underpinning the decision of older people either to seek or to avoid influenza immunisation. Health education has been found to be effective in increasing immunisation rates among the elderly. Even brief interventions on behalf of health professionals to encourage vaccination appear to be effective in improving immunisation rates. The advice of health professionals, therefore, appears to be crucial and uptake is high (about 80%) when vaccination is actively promoted by a member of the primary care team.[71] It is unusual for older people to actively avoid vaccination and more likely that they simply do not afford it a high enough priority to justify the personal cost and inconvenience involved in accessing vaccination services.

To maximise uptake, it is necessary continuously to reinforce health education messages provided to older people. The messages should be emphasised by health professionals in close contact with older people who should also be provided with training opportunities to improve their knowledge and involvement in information campaigns. The role of financial incentives to suppliers to enhance immunisation levels has been analysed elsewhere.[72] This study found that, despite high background immunisation rates, a modest financial incentive (US$0.80 per shot) led to an approximately 7% increase in immunisation rates among older people. One study[73] identified seven factors acting in favour of influenza vaccination (perceived benefits, perceived severity, living together with another person, advised by GP, age, vaccinated in previous influenza seasons and living in an urban environment) and two factors acting against vaccination (perceived barriers to vaccine and living in a nursing home or sheltered housing). This study found that free vaccinations and active advocacy on behalf of health professionals were exceptionally effective means of promoting higher vaccine coverage and that having previously been vaccinated also increased the likelihood of seeking vaccination in subsequent years. One crucial area of further research is to develop accurate empirical models that reliably predict influenza vaccination behaviour amongst older people.

It is essential to optimise communication with the public to inform potential recipients of the small risks and large benefits arising from the vaccination programme. One problem that arises is in the separation of private and social costs that arise through the presence of externalities in this area. From the perspective of the individual, if the incidence of a disease has become low (perhaps owing to a successful vaccination programme) then the risk of disease to the individual is also low but the privately borne cost related to obtaining vaccination remains constant. In such circumstances, the rational individual who obtains protection from the disease by 'herd immunity' may reject vaccination if the privately borne costs exceed the privately borne benefits. Thus, as rates of influenza diminish, the likelihood of significant

divergence between public and privately borne costs becomes greater. To persuade rational individuals to continue to be vaccinated when the vaccination programme has reduced the incidence of disease requires a reduction in the privately borne costs inherent in obtaining vaccination. In such circumstances, taking the service to the patient or reimbursing travel, time and expenses may be required to balance privately borne costs and benefits. In contrast, from the social perspective, avoidance of vaccination is not in the best interest of public health because 'herd immunity' diminishes as coverage falls. The challenge is to 'internalise' externalities to ensure that public and individual interests can be served simultaneously.[74]

Irrespective of the cost-effectiveness of influenza vaccination, the policy of providing influenza vaccination to the healthy elderly will not succeed unless patients choose to attend for vaccination. Such a choice will be based on the privately borne costs and benefits perceived from the perspective of each individual person. The simple availability of influenza vaccination to healthy older people will not ensure delivery of this service and hence protection of this target group. New and multifactorial approaches are needed. Such interventions combine patient reminders with implementation of walk-in clinics and extensive patient and health professional education reducing barriers to vaccination. The extension of the nursing role, including vaccination in hospital discharge planning, vaccine delivery by pharmacists and other interventions aimed at reducing the privately borne costs of obtaining vaccination, are necessary to improve vaccination rates in the older population. All high-risk patients should be entered into vaccine registers to allow annual call and recall in a more systematic and organised manner. Greater imagination could be used in delivering vaccine at non-conventional sites such as day-care centres, pharmacies and old-age facilities. Developing a cost-effective service requires the identification and use of all available methods for maximising uptake if we are to maximise the potential benefit arising from this important healthcare intervention.

The cost-effectiveness of influenza vaccination in the healthy elderly: the current evidence base

The earliest and most comprehensive cost-effectiveness analysis was undertaken by the US Office of Technology Assessment (OTA),[75] which found that influenza vaccination of all persons 65 years of age and above cost US$1782 per year of healthy life gained (1978 prices). Influenza vaccination was found actually to be cost saving when the analysis excluded future healthcare costs arising as a consequence of avoided mortality. The conclusions of the OTA report were reinforced by the US Medicare demonstration project[76] which found that influenza vaccination represented a highly cost-effective intervention for Medicare recipients. The Medicare influenza demonstration project estimated a cost per life year gained through influenza vaccination in older people of US$145. A more recent study[77] estimated a cost saving of US$117 for each person aged 65 years and over who is vaccinated. Thus, although the individual estimates appear to vary significantly between studies, a significant body of evidence has been generated in the North American context emphasising the cost-effectiveness of influenza vaccination in older people.

Three large population-based studies have been undertaken in North America analysing the impact of influenza vaccination in older populations. The Michigan and Manitoba studies[24,26,78] used a case control structure, whereas the Minnesota study[77] employed a retrospective cohort analysis. Studies were carried out in Michigan to assess the value of influenza vaccination for older people.[26] In two years (1990 and 1991) which covered both Type A and Type B influenza seasons, influenza vaccination was estimated to lead to a 31% reduction in the likelihood of hospitalisation in 1990–1 and a 32% reduction in 1991–2. All analyses measured the 'outcome' of vaccination by the estimated percentage reduction in pneumonia and influenza admissions to hospital. In each case, influenza vaccination was found to lead to a 30–50% reduction in such admissions and demonstrated that, with influenza vaccination, little if any 'replacement' morbidity or mortality appeared to occur. One benefit of such large-scale retrospective studies is their ability to identify comparatively rare events such as influenza-related mortality. These three studies provide important clinical evidence of the health benefits underlying influenza vaccination in North America. The methods for conducting such studies are straightforward and would generate equally valuable evidence if applied in the UK context. Again, this is another important area in which further research would prove invaluable.

More recent US studies have been less comprehensive in their scope and have largely concentrated on analysing the savings associated

with avoided cases of influenza. Despite this limited scope, the results obtained in such studies frequently appear to be inconsistent. For example, Mullooly and colleagues[79] analysed the cost-effectiveness of vaccination in older people and identified a direct health care cost saving of US$1.10 per vaccination, whereas a similar study[77] identified a substantially greater direct health care cost saving of US$117 per older person vaccinated. Helliwell and Drummond[80] identified one of the major causes of such inconsistency between the results of individual studies by emphasising the paucity of accurate information regarding many of the key variables underlying the cost-effectiveness estimates. In response to such uncertainty, they produced their results in the form of a range of possible outcomes from a cost saving of US$53.52 to an additional cost of US$6.82 per person vaccinated. Their best point estimate was that vaccination would lead to a cost saving of US$11.40 per older person vaccinated. This wide range of cost-effectiveness estimates emphasises the significant uncertainty underpinning cost and effectiveness calculations of influenza vaccination in older people.

For reasons that are not readily understood, Spain appears to be the most successful country in Europe in extending influenza vaccination coverage to its population. A Spanish study[25] estimated the probability of influenza vaccination preventing admission to hospital for pneumonia at 0.21 (95% CI, 0.09 to 0.55).

The impact of influenza on older people's health was also estimated in a study comparing three periods (epidemic, non-epidemic and influenza-free).[65] The study analysed hospitalisation rates for pneumonia, influenza, acute bronchitis, chronic respiratory disease, congestive heart failure and coronary heart disease in each of these three periods. The risk of hospitalisation was significantly greater in both the epidemic and non-epidemic periods for respiratory conditions such as pneumonia and influenza. In addition, hospitalisations for congestive heart failure were also significantly increased in both the epidemic and non-epidemic periods. In comparison to the influenza-free period the excess costs of these hospitalisations were over US$1000 million in an epidemic period and US$750 million in a non-epidemic period.

Schoenbaum and colleagues[81] used formal decision analysis to analyse whether or not to vaccinate the entire US population against a possible epidemic of a new influenza virus. The net benefits of immunisation were calculated by subtracting the total costs of the vaccine programme from the total benefits. Total benefits were calculated by multiplying the costs incurred as a result of an epidemic by the probability of an epidemic occurring and then by vaccine efficacy. Vaccination programme costs were calculated for different target age groups using the cost of past public vaccine programmes, the estimated cost of the vaccine and the cost of vaccine adverse reactions (calculated using the human capital approach). Benefits were calculated from the estimated direct costs of treating the estimated number of patients and the indirect costs of influenza illness and death in terms of lost productivity (again using the human capital approach). Estimates of vaccine efficacy, acceptance and adverse reaction rates, the probability of an epidemic occurring and its likely severity in terms of age-specific morbidity and mortality were obtained using the Delphi survey technique. The study identified acceptance rates where the cost of the programme equalled the benefits for each of the alternative target age ranges of the vaccination programme. As the probability of the epidemic increased, the break-even acceptance rates were reduced. Expected benefits also increased or decreased in line with increases or decreases in vaccine efficacy. The authors concluded that if the programme was limited to adults of 25 years or older and acceptance rates were 59% or above, the programme would be economically justifiable. They also identified the advantages of structuring the problem as a formal decision analysis. First, once the framework was developed, it could be used for analysing a range of alternative vaccination strategies. Second, it enabled a break-even analysis to be undertaken for each individual strategy, and third, it could be used to identify conditions for obtaining maximum benefits from the vaccination programme.

The applicability of international evidence to the UK

Meta-analyses undertaken on evidence generated in international studies indicate that vaccination of older people significantly reduces the risk of respiratory disease, hospital admission and deaths.[17] Unfortunately, the majority of studies have been undertaken in North America where RCTs could not be undertaken as such analyses would have been unethical. The majority of analyses are, therefore, undertaken in the form of cohort studies which exhibit a range of potentially confounding factors such as selection bias

(differences between vaccinated and unvaccinated people) and information bias (incorrect ascertainment of vaccination status and outcomes) which may directly affect comparative health outcomes.[82] RCTs avoid such biases and perhaps represent a more reliable source of evidence. A Dutch RCT reported a 50% reduction in serologically confirmed infection and ILI through influenza vaccination in people aged 60 years and over.[27] Although the trial was too small to assess comparatively rare events such as hospital admissions or deaths, it provides useful support for results obtained from observational studies.

International studies have, therefore, identified significant vaccine effectiveness in preventing hospitalisation during periods of peak surveillance confirmed influenza. If such results could be translated into the UK context, then it would result in a significant reduction in the 'winter pressures' imposed on the NHS during the period of peak demand on hospital services.

A range of problems arise in directly applying international sources of evidence to the NHS. For example, the study undertaken by Mullooly and colleagues[79] utilised a highly restricted perspective with only the direct costs and benefits to the health provider (health maintenance organisation) being analysed. Such analyses also use a different structure of costs than those found in the NHS. For example, Mullooly and colleagues costed inpatient episodes (for both pneumonia and influenza) at US$3234 and outpatient episodes at US$1375 and utilised a unit cost for each vaccination of US$7.11 (US$2.76 for overheads, US$2.35 for giving the injection, US$1.45 for vaccine and supplies, US$0.29 for promotion and US$0.26 for wastage). Such a structure of comparative costs results from a pattern of care provision and costs that strictly restrict their applicability to the NHS.

Transferring economic models of influenza vaccination generated in other countries to the NHS requires a far more complex analysis than simply changing the unit of currency. The strategic environment of each healthcare system (e.g. resource availability) establishes the broad structures within which care is provided. Equally, variations in patterns of care provision result from the complex interaction between resource availability (physical and financial) and structures of medical education and training. Therefore, in assessing the applicability of internationally generated evidence to the NHS, factors such as international variations in influenza consultation rates and hospitalisation rates must be taken into account. Significant discrepancies also exist in the structure of health service costs between North America and the UK. Vaccine costs in the UK appear to be twice as high as those in the USA, whereas the cost of treatment and hospitalisation is significantly lower. Given the higher immunisation costs and lower treatment costs in the UK, North American evidence is of strictly limited value in directing policy within the context of the NHS.[83]

A great deal of international evidence has therefore been generated, but its applicability to the context of the NHS appears to be limited. The extent to which such international evidence can be used to guide NHS decision-making is also limited. Evidence-based decision-making is crucial in optimising the cost-effectiveness of service provision within the NHS; however, to be of value, such evidence must be relevant within the unique context of the NHS.[84] Huge variations exist in levels of influenza vaccination cost-effectiveness calculated in different North American studies. Although sensitivity analysis can assist in testing the robustness of the results with respect to alternative structures of costs and patterns of care, such analyses can only be of limited value in enhancing the applicability of such evidence.

International research evidence strongly suggests that extending influenza vaccination to all people over 65 years of age is likely to be cost-effective. Unfortunately, the results of the international studies undertaken are unlikely to be directly applicable to the UK because of differences in the pattern and utilisation of health services and the direct costs of immunisation. The overall financial impact of influenza vaccination of the healthy older population on the NHS will depend upon factors such as the influenza attack rate, GP consultation and hospital attendance. Such practice variations (differential admission rates to hospital, lengths of stay in hospital, availability of hospital beds and use of primary care facilities) require NHS-specific data to inform an NHS-specific model that generates results that are directly relevant to the NHS.[85] The results obtained from the development of such an NHS-specific model are described in the following chapters.

Chapter 6

Results: economic evaluation of trial

Introduction

In this chapter we consider incremental costs and outcomes as measured in the first year of the RCT, prior to the change of national policy which led to truncation of the planned trial.

Participants in both arms of the trial received anti-pneumococcal vaccination. In undertaking this evaluation it is necessary to assume that interactions between the two types of vaccine are negligible both in terms of their immediate effects (side-effects, etc.) and in terms of their impact on episodes of acute illness. If later research shows this assumption to be inaccurate then it is likely that the impact of influenza vaccination alone will have been underestimated, that is, the current assumption is conservative relative to the independent efficacy of influenza vaccination.

Vaccination costs

The influenza vaccine used in the trial cost £3.30 per patient, whereas the materials cost of control arm injections is estimated to be £0.20 per patient. The mean time spent in vaccination per patient was estimated to be 10 minutes, which was combined with salary costs for the administrator to yield an average cost of administration of £2.92 per patient. Thus, the overall cost of vaccination in the RCT is estimated to be £6.22 per patient in the intervention arm and £3.12 per patient in the control arm. Applied to patients enrolled in the first year of the trial, the total cost of vaccination is calculated to £3433 and £552, respectively. No side-effects requiring medical intervention were reported in either group.

Privately borne costs

The private costs incurred by patients travelling to the vaccination centre were very low. Over 40% were able to walk to the centre and incurred no direct cost; 36% travelled by car with a mean journey cost of £1.00 and 21% used bus or taxi costing £1.81 on average. Overall, the mean cost of travel to the vaccination centre is estimated as £0.76 per patient. Comparison of the modes of transport between the trial arms showed no significance differences, so there is no reason to expect any increment in direct patient-borne costs attributable to the intervention.

The rates of patient self-reported ILI are shown in *Table* 7, together with 95% CIs for a binomial variable. The probability of suffering ILI was approximately halved by vaccination, although the difference obtained was only of borderline significance owing to the reduced sample size.

A total of 26 patients reported episodes of ILI but did not visit their GPs. Of these, 69% took OTC medication for symptom relief during the episode. There was no evidence of any difference between the trial arms in the propensity of patients to use OTC medicines, and therefore the same probability is used for all patients suffering a self-reported ILI episode. Assuming an average medication cost of £1.50 per episode, the total estimated direct cost of OTC medication is £15.53 in the control arm and £24.84 in the intervention arm, equivalent to a cost per trial participant of £0.088 and £0.045, respectively.

TABLE 7 *Incidence of self-reported ILI*

	Vaccine (n = 523)	**Placebo (n =168)**	**Difference: vaccine – control**
No. of patients reporting ILI	24	15	–
Probability of ILI (%)	4.59	8.93	–4.34[a]
Lower 95% CI (%)	3.03	5.26	–9.05
Upper 95% CI (%)	6.85	14.56	+0.37

[a] p = 0.031, Fisher's exact test (one-sided).

TABLE 8 *NHS costs attributable to vaccination and ILI*

NHS costs	Total costs (£)		Cost per person (£)		
	Control	Vaccine	Control	Vaccine	Difference
Vaccine/placebo	35.40	1821.60	0.20	3.30	+3.10
Administration	516.84	1611.84	2.92	2.92	0.00
Total vaccination cost	552.24	3433.44	3.12	6.22	+3.10
GP consultations	323.00	836.00	1.82	1.51	–0.31
GP prescribed drugs	79.14	278.44	0.45	0.50	+0.05
Total GP costs	402.14	1114.44	2.27	2.02	–0.25
Hospital episodes	0.00	0.00	0.00	0.00	0.00
Total NHS costs	954.38	4547.88	5.39	8.24	+2.85

Use of health services related to ILI

In isolating the health gains directly associated with 'influenza vaccination', it was necessary to accurately identify cases of ILIs in both areas of the trial. The structure of the research made formal serological confirmation of influenza impossible as specimens were not available for laboratory examination. Given that the clinical diagnosis was reached in the absence of serological confirmation of influenza, it is possible that a range of other respiratory conditions were incorporated within the general definition of ILI. If it is assumed that such respiratory illnesses are equally distributed between the active and placebo arms of the trial (given that the influenza vaccine has no known effect on other respiratory diseases), any reduction in the incidence of illness in the vaccinated group will be diluted by the existence of a common and unaffected amount of other ILIs. It is possible, therefore, that the use of a very sensitive but non-specific clinical case definition may bias the study against identifying an impact for vaccination.

During the trial there were no recorded cases of hospitalisation attributable to ILI in either arm of the trial. This suggests that the rate of hospitalisation among this healthy group of patients is very low. It was therefore not possible to estimate the risks applicable to patients in either arm, without a much larger sample, and no costs were calculated for hospital admission in the trial evaluation.

The principal cost of ILI is therefore that involved in GP consultations with patients seeking relief from influenza-like symptoms. In the intervention arm, 44 patients visited their GP during the first year of the study, that is, 8.0% (95% CI 5.9 to 10.6%), compared with 17 patients in the control arm, that is, 9.6% (95% CI 5.9 to 15.2%). This modest reduction did not achieve statistical significance. Assuming a mean consultation cost of £19.00 per patient (PSSRU Costs of Health and Personal Social Services 1999), the total cost of trial consultations is estimated as £323 in the control arm and £836 in the intervention arm. The corresponding mean cost estimates per participant are £1.82 and £1.51, respectively.

The other cost incurred by the health service is the cost of medicines prescribed by the GP. Instances where the doctor prescribed a course of antibiotics were recorded, and revealed similar levels of prescribing in the two arms of the trial: 5.1% (95% CI 2.5 to 9.7%) in the control arm and 6.9% (95% CI 5.0 to 9.4%) in the intervention arm. Assuming a mean cost of a course of antibiotics to be £5.00 and the mean cost of other medicines for symptomatic relief to consultees to be £2.00, the total cost of GP prescribing for ILI is estimated as £79 in the control arm and £278 in the intervention arm, implying mean costs per participant of £0.45 and £0.50, respectively.

Taken together, the overall costs attributable to ILI in the first year of the trial amount to £954.38 in the control arm and £4547.88 for the vaccination arm. Equivalent per-person costs are £5.39 and £8.24, respectively, suggesting an incremental cost of £2.85 per person vaccinated. These results are summarised in *Table 8*.

Mortality

There were no reported instances of mortality in either arm of the trial that could be attributed to

causes influenced in any way by ILI. It is therefore not possible from the trial to make any estimates of absolute mortality rates or of the supposed efficacy of vaccination in reducing mortality risk.

Cost-effectiveness indicators

From an NHS perspective, we wish to relate the additional cost per person vaccinated (£2.85) to an appropriate measure of outcome benefit. Since neither deaths nor hospital admissions were recorded in either trial arm, these natural outcome indicators are not meaningful. Since the only contacts recorded with health services were some GP consultations, the most appropriate outcome measure is the number of GP consultations avoided as a result of introducing vaccination for this group of people. The resulting cost-effectiveness ratio is then £174 per GP consultation avoided.

From the perspective of the individual participating in the trial, vaccination led to a minimal reduction in direct costs (£0.043). Relating this to the most natural metric of benefit for patients (the number of self-reported ILI episodes), results in a cost-effectiveness ratio of £0.99 per episode avoided.

Sensitivity analyses

Although a range of parameters and probabilities has been estimated from trial results, few of these have the potential to influence the cost-effectiveness indicators to any extent.

From the perspective of patients, only the probability of requiring OTC medicines and the assumed cost of OTC medicines can affect the findings. Sensitivity analyses were carried out on both variables – the former by considering half and double the trial-derived probabilities and the latter by increasing and decreasing the mean cost of OTC medicines by £1.00. In all cases, a small reduction in net direct costs is evident, varying between £0.34 and £1.70 (central estimate £0.99).

The cost per GP consultation avoided from the NHS perspective is influenced by three parameters: the risk of a GP consultation being required, the risk of an influenza-related hospitalisation episode and the mean cost per GP consultation. Using the lower and upper confidence limits for the probability of a GP consultation had the largest effect. The cost per GP consultation avoided varied between £49 and a saving of £6230. Varying the mean cost per GP consultation by ±£5 produces a directly equivalent variation in cost per GP consultation avoided (£169 to £179, central estimate £174).

Although hospitalisation and mortality were unrecorded for any patients in the trial, it is still possible to estimate notional upper confidence limits on the risk of each event for the relevant sample. This suggests that upper limits for hospitalisation and mortality risk are the same as 2.65% and 0.86% for control and intervention arms, respectively.

The effect of the greater hospitalisation limits on NHS cost per GP consultation avoided is to generate a net cost saving of £1019. The upper confidence limit also allows calculation of a cost per hospitalisation episode avoided ratio of £932. Similarly, using the higher mortality risk suggests a cost per death avoided of £159.

Summary

Although the economic evaluation of the RCT presented above is based on less than ideal evidence, the results of costing and sensitivity analysis suggests that some clear and robust conclusions can be drawn. First, from the viewpoint of a member of the group of healthy 65–74-year-olds, it is clear that the direct financial impact of vaccination is minimal, and could even be expected to be slightly cost saving. In addition there is a good indication of a halving of the number of ILIs that can be expected in a winter season. It seems that the absolute risk of a serious influenza-related illness risking hospitalisation or premature death is minimal in this group, so that the benefits to be expected to the individual are mainly in terms of avoiding the inconvenience and discomfort of a bout of illness. Assuming that virtually all members of the group will have retired from economic activity, issues of loss of earnings are not relevant.

From the NHS perspective, the primary concern is the demands made by influenza sufferers of their GP. Our best estimate from the trial is a net NHS cost of £174 for each GP consultation avoided by vaccination. Sensitivity analysis suggests that this figure is unlikely to exceed £200, and may equally be turned into a substantial net cost reduction.

Chapter 7

Economic evaluation applied to national implementation of vaccination programme against influenza for healthy 65–74-year-olds

Introduction

In this chapter we develop an economic model to analyse the levels of incremental costs and outcomes which might be expected to arise if the main findings of the first year of the RCT were typical of the effects which could be expected across England. Privately borne costs are not considered here, since it would not be appropriate to generalise transport costs, etc., from a city environment to the whole country, and the broad conclusion of the previous section that privately borne costs are not generally important is unlikely to alter.

Assumptions underlying the model

Population

The population aged 65–74 in England was estimated by the Office for National Statistics to be 4,090,000 in 2001 based on 1998-based projections.

Healthy group

In the 1991 census, 40% of the population of Liverpool aged 65–74 years was recorded as suffering from a long-term limiting illness. In view of the improved survival and life expectancy in those suffering many chronic diseases (e.g. coronary heart disease, stroke) we expect that an increased proportion of this age group will be in one or other of the designated 'at-risk' categories for priority vaccination against influenza. Therefore, we have assumed that the healthy 65–74-year-olds constitute 50% of their contemporaries, that is, they number approximately 2,045,000.

Current and target coverage

In 'The Winter Plan 2000', the Department of Health set a target uptake rate for vaccination in this group of 60%. It is not clear what the preceding voluntary coverage rate had been; for the purposes of this exercise we assume that 20% of healthy 65–74-year-olds would actively seek vaccination without any promotional campaign.

Hospitalisation

In order to obtain an estimate of the normal impact of influenza on emergency hospital services for this population group, we obtained details of all non-elective hospital admissions to the Royal Liverpool University Hospital in 2000–1 for respiratory conditions normally associated with influenza, eliminating all cases where there was evidence of existing 'at-risk' conditions. This identified a total of 64 admissions which was then compared to the estimated 65–74-year-old population of the local GP practices normally considered within the hospital's 'catchment area'. Although not a precise calculation, it nonetheless provides a realistic approximation to the hospitalisation rate applying in the target group: 0.32% per year. The impact of vaccination on this rate is difficult to assess from the trial evidence, but we took the relative reduction in GP consultation rates (–17%) as a reasonable conservative first estimate.

Mortality

Following the same logic, we determined that only two of the above admission episodes proved fatal, and on this evidence we estimated the relevant mortality rate to be 0.01% per year and the relative reduction to be expected from vaccination to be the same as that for hospitalisations.

Vaccination costs

In line with the national GP renumeration scheme, the cost of vaccination is set at £6.45 per person. The 'Winter Plan 2000' earmarked £22.6 million for promoting and facilitating the extended vaccination scheme to achieve the national coverage target. We therefore used this figure as the direct cost of health promotion required to achieve a 40% increase in take-up.

TABLE 9 *Sensitivity analysis of incremental cost-effectiveness ratios for national implementation scenario*

Variation from baseline scenario	Incremental cost per death avoided (£)	Incremental cost per hospital episode avoided (£)	Incremental cost per hospital bed-day not used (£)	Incremental cost per GP consultation avoided (£)	Incremental cost per life-year gained (£)	Incremental cost per QALY gained (£)
Central estimate scenario	1948071	60877	8388	2013	243509	304386
1. Increase target coverage to 80%	1402603	43831	6039	1450	175325	219157
2a. Reduce hospital admission risk to 0.25%	1955879	78708	10844	2022	244485	305606
2b. Increase hospital admission risk to 0.41%	1938115	47134	6494	2003	242264	302830
3a. Reduce mortality risk to 0.0017%	11247073	60877	8388	2013	1405884	1757355
3b. Increase mortality risk to 0.04%	483086	60877	8388	2013	60386	75482
4. Increase efficacy of vaccine to 50% relative reduction	626182	19568	2696	647	78273	97841
5. Increase all incident rates ×3	602450	18827	2594	623	75306	94133
6. Zero programme promotional costs	311667	9740	1342	322	38958	48698
7a. Reduce cost per hospital episode to £807.11	1957184	61162	8427	2023	244648	305810
7b. Increase cost per hospital episode to £1376.63	1938959	60592	8348	2004	242370	302962
8a. Reduce life expectancy to 5 years	1948071	60877	8388	2013	389614	487018
8b. Increase life expectancy to 10 years	1948071	60877	8388	2013	194807	243509

QALY, quality-adjusted life year.

Patient experience and associated costs

Using the rates of self-reported ILI from the Liverpool trial, we estimate that 6.0% of the group would suffer an episode of ILI with 60% vaccination coverage compared with 7.65% with only 20% coverage. This translates into 33,800 fewer bouts of influenza, a relative reduction of 21.6%. The corresponding reduction in money spent on OTC medicines only amounts to about £34,000.

Use of health services related to ILIs

The expected incidence of respiratory symptoms suggestive of ILI leading to a GP consultation rate reduction from 9.6% to 8.0% under this scenario results in 13,400 fewer consultations, and a notional cost saving of £254,000 together with £235,000 less spent on prescription drugs.

Acute hospital episodes are estimated to reduce by 442 owing to increased vaccination coverage, and hospital costs reduce by about £483,000. This is based on analysis of the Liverpool admissions, which showed an average length of hospital stay of 7.26 days at a mean cost of £1093 per episode. Using these figures, we anticipate that increased vaccination would lead to 3208 fewer hospital bed-days being required, and reduced hospital costs of £483,000.

Mortality

The evidence obtained in Liverpool suggests that mortality attributable to ILI is rare in the healthy 65–74-year-old age group. The scenario in which vaccination increases from 20% to 60% results in only 14 fewer deaths across the whole of England in a year (from 196 to 182).

Cost-effectiveness indicators

Utilising the assumptions outlined above, the economic model provides estimates of several cost-effectiveness ratios:

- incremental NHS cost per GP consultation avoided will be approximately £2000
- incremental NHS cost per hospital admission avoided will be approximately £61,000
- incremental NHS cost per hospital bed-day unused will be approximately £8400
- incremental NHS cost per death avoided will be approximately £1,900,000.

If we assume further that patients suffering premature death from influenza, could have expected a further 8 years of life and that the utility value of those years would average 80%, we can calculate two further ratios:

- incremental NHS cost per life-year gained will be approximately £244,000
- incremental NHS cost per QALY gained will be approximately £304,000.

Sensitivity analyses

Table 9 provides the results of eight sensitivity analyses undertaken around the central estimates of national cost-effectiveness. The most optimistic scenario assumes that target uptake rates can be achieved with no additional expenditure on promoting vaccination. This has the effect of reducing net NHS costs by about 85%, and hence reduces all cost-effectiveness ratios by the same proportion.

Other trials of influenza vaccination have reported much higher efficacy rates. The effect of this was tested by increasing the efficacy of influenza vaccine to 50% relative risk reduction. It has also been noted that the absolute magnitude of annual influenza peaks can be much higher once or twice a decade. We therefore considered the consequences to multiplying all incidence rates by three. Both of these scenarios produced similar results with all ratios approximately double those obtained with the most optimistic scenario.

Other sources of uncertainty were more selective in their effects, and generally showed less remarkable changes in ratios.

Chapter 8
Discussion

Economic analysis of trial evaluation

Given the societal perspective from which the economic analysis was undertaken, it was necessary to evaluate all sources of resource consumption and savings arising from influenza vaccination. This required the analysis to assess not only the publicly funded sources of resource consumption (GPs and hospitals), but also privately funded sources (OTC medication and 'taking to one's bed'). Such a broad analysis was essential to identify all episodes of influenza irrespective of whether they led to formal consultation with a healthcare professional. In an attempt to verify the reliability of the self-reported symptom information obtained from the patient diary, the research clinician telephoned each patient reporting symptoms to clarify the nature and severity of the symptoms suffered and used his clinical judgement to assess whether they were indicative of an ILI. Although reliance on patient diaries may be open to criticism, such an approach was essential in unlocking episodes of illness that would otherwise not have been identified.

One further potential criticism concerns the nature of the comparison undertaken in the trial. It was felt that the use of a double placebo (influenza and pneumococcal vaccines) would make GP and patient recruitment difficult and therefore all patients in the trial who had not previously been vaccinated were provided with pneumococcal vaccination. The trial evaluation therefore took the form of a direct comparison of influenza plus pneumococcal vaccination with placebo plus pneumococcal vaccination.

Given this broad perspective, the economic analysis had three main aims: first, to evaluate the net incremental resource implications of routine influenza immunisation in healthy 65–74-year-olds; second, to evaluate the impact on QoL experienced by patients on and off immunisation; and third, using the combined results, to assess the incremental cost-effectiveness ratio underlying immunisation, incorporating both public sector resource use and privately borne costs. The model developed from the results of the trial enabled the impact of a nationwide immunisation programme for this population cohort to be assessed in terms of its costs and benefits for both individual patients and for society as a whole. The methodology will also provide useful guidance to future research given that it was designed to be appropriate to evaluating any proposed extension to the influenza immunisation programme. Although it was recognised that the comparatively small scale of the clinical trial did not enable definitive answers to be obtained to the range of questions addressed, the analysis provides valuable indicative results that should be developed in subsequent analyses.

A fundamental determinant of the cost-effectiveness of influenza vaccination is the willingness of people to attend for vaccination. As such, it is important also to investigate why recruitment was difficult in this study. The commonest reason given for non-participation was an unwillingness to participate in research. Many of these people wanted the certainty of knowing that they had received actual vaccine rather than placebo and were thus vaccinated outside the study, although not all claims of vaccination by the GP could be validated. Some 34% of people were concerned about side-effects and 32% felt that they did not require the vaccine. When interpreting these responses it should be remembered that fewer than 50% of questionnaires were returned. However, people sent questionnaires had already declined to participate in a clinical trial and would be less likely to want to be involved in further projects. Interestingly, 25% of people who returned questionnaires objected to the name 'Department of Geriatric Medicine' printed on the original invitation letter. Anecdotal comments made to us by some non-participants during the recruitment period suggested that the word 'Geriatric' had caused sufficient offence to be the sole reason for them not to participate. Perhaps no reference should be made to age or ageing in any terminology used when inviting older people to participate in a clinical trial.

Similar reasons for poor uptake of influenza vaccine have also been given in other studies.[73,86–90] Fear of side-effects is consistently reported in all papers as a barrier to influenza

vaccination, but evidence from this study and others[28,29] demonstrates that there is no significant difference in the incidence of systemic side-effects between people administered influenza vaccine and those who receive placebo. Such barriers to influenza vaccine should be taken into account when planning national vaccination campaigns. An important point to note is that there was also no decrease in the incidence of side-effects in year 2 when only influenza vaccine was administered compared with year 1 when both influenza and pneumococcal vaccines were used.

Females were less likely to participate and more likely to report local side-effects following vaccination, a phenomenon also observed in other trials.[91,92] Non-participants were slightly older than participants, although this is unlikely to be clinically important. A weak association was found between the mean deprivation score for each practice and the proportion of people vaccinated out of the study (*Figure 12*). This negative (although non-significant) correlation between increased deprivation and decreased uptake of influenza vaccine needs to be confirmed in future studies.

The results obtained from this trial identified a marked reduction in the number of ILIs suffered in the vaccinated population that would otherwise not have been brought to the attention of the NHS. We found no significant change over time in psychological factors such as depression or anxiety between the two groups, indicating that the psychological impact of the higher rate of influenza experienced in the placebo group is not significant. However, our analysis does not allow us to assess the extent to which vaccination improves the psychological welfare of recipients through the provision of reassurance that their chances of contracting influenza have been minimised. Many of the patients had travelled a significant distance over a significant time period at not insignificant inconvenience and cost to themselves to attend for vaccination. This comparatively high privately borne cost together with the additional cost imposed on scarce healthcare resources needs to be taken into account and balanced against the potential benefits both to patients and to the health service when considering an extension to the vaccination programme. The patients who are in greatest need of vaccination are 'unhealthy' older people and much greater research is required concerning policies to facilitate their attendance rather than simply extending the vaccination net.

Because of the enforced limitation on the length of the study, it is important to recognise that the results obtained are significantly underpowered. This is of particular importance in assigning costs to comparatively rare events such as deaths and hospitalisations which will not occur with the frequency that would enable sensible conclusions to be drawn from the clinical trial. In assessing results obtained in the artificial environment of randomised controlled clinical trials, it is important to analyse the extent to which the efficacy data reported in the trial are likely to be replicated and translated into actual effectiveness in clinical practice. The greater the extent to which the efficacy measured in the trial depends on elaborate patient management systems designed to maximise compliance, the less likely it is that the results obtained will be replicated in actual clinical practice. Trial conditions are specifically designed to maximise efficacy by optimising patient compliance in a manner that may be difficult to replicate in normal clinical practice.

Evidence appears to indicate that annual vaccination over a number of years may enhance the protective impact of each subsequent year's vaccination. As such it is arguable that annual vaccination provides benefits in future years that are not captured in the trial. Unfortunately, the extent of such a cumulative protective effect (even if it exists) is uncertain. As such the assumption was made in this analysis that the full protective benefits of the vaccination are contained within the year of analysis. In such circumstances, discounting of future costs and benefits became unnecessary as the protection offered by the vaccination programme was assumed to be entirely contained within the year of analysis. Should strong and quantitative evidence arise of a cumulative protective effect then obviously this assumption would have to be relaxed and the benefits of annual vaccination would have to be allocated over a number of years.

A disproportionately large element of the cost associated with influenza is derived from a small number of patients suffering from comparatively rare events (death or severe complications) that a study of this scale cannot adequately capture. In such circumstances it is important to recognise that the cost and effectiveness estimates can suffer from a high level of uncertainty. Such uncertainty can only be reduced by introducing other forms of evidence to support the modelling process in order to assess the implications for the NHS as a whole.

National implications: implementation model

Because of the truncated nature of the RCT, the level and quality of evidence obtained from this source was limited. Even in the absence of the enforced limitation of the RCT, it would still have proved necessary to supplement the clinical trial results with other sources of information, particularly with regard to rare events such as severe morbidity or death. The aim of the implementation model was to assess the extent to which national implementation of screening for the healthy 65–74-year-olds would affect the health of the UK population and the utilisation of scarce NHS resources.

The methodology utilised compared the direct costs of vaccination with the excess treatment costs arising in the non-vaccinated population using a societal perspective. The cost analysis used a number of sources. The net vaccination cost included the unit costs of vaccines and supplies and the cost of delivery and overheads. The costs of medical care averted related to the anticipated reduction in episodes of hospitalisation, primary care attendance and OTC medication. The direct cost of the vaccine was based on the total expenses of vaccination that could be reclaimed by GPs plus the cost of the GP attendance required to deliver the vaccination. The costs of episodes of ill health averted by the vaccination were based on estimates derived from the RCT with local unit costs applied. The medical care costs associated with avoided episodes of influenza were estimated in collaboration with the finance and information departments of the Royal Liverpool University Hospital.

Any economic analysis is inevitably subject to a range of sources of uncertainty and it is important that such uncertainty is recognised and, wherever possible, incorporated into the analysis. As such, a detailed sensitivity analysis was undertaken around crucial decision points to assess their implications for the overall cost-effectiveness of screening in healthy older people.

The degree of prevalence of influenza varies significantly from year to year and calculation of the cost-effectiveness of influenza vaccination will vary inversely with the prevalence rate. Such mutability inevitably limits the usefulness of cost-effectiveness calculations based on a single year and robust cost-effectiveness calculations must be based on expected values averaged over distributions of prevalence covering a number of years. Influenza seasons vary significantly in terms of the timing, aetiology and virulence of the circulating strains. Levels of influenza activity over the past 10 years appear to be dichotomised between years of low activity and years of high activity. Overall, there appears to be of the order of a 10:1 variation in influenza activity between low- and high-activity years. Years of pandemic were not analysed, as by definition they were exceptionally rare events that are caused by factors against which influenza vaccination would have little or no impact. As such, in order to estimate separate cost-effectiveness ratios in periods of different influenza prevalence, a range of scenarios were modelled to assess how the attack rate of influenza alters the cost-effectiveness of vaccination. The scenarios analysed simultaneously varied estimates of vaccine effectiveness, proportion of patients needing medical care and median length of hospital stay over a plausible range of results.

Although this projected national evaluation of extending influenza vaccination to the healthy 65–74-year-old population is necessarily speculative and imprecise, it nevertheless gives strongly suggestive answers to some key questions:

1. Does vaccination of this population lead to significantly lower NHS costs? Clearly this cannot be supported from our analysis.
2. Is vaccination of this population consistent with currently accepted measures of value for money as measured by cost per QALY or cost per life-year? Even on the most optimistic assumptions, vaccination rates very poorly compared with standards applied in recent National Institute for Clinical Excellence assessments.
3. Does vaccination in this population offer value for money in substituting for specific NHS resource use (i.e. GP's time, hospital beds, etc.)? In cash terms, vaccination is many times more expensive than the normal cost of the resources it would save.

It may be argued that vaccination is valuable in relieving pressure on scarce resources at times of particular pressure. However, we estimate that only about 3200 bed-days will be saved per year, which amounts to only 0.015% of the national annual total bed-days used for general non-elective admissions. Even in the most extreme scenarios this does not rise above 0.05%. Similarly, the expected benefit in reduced demand for GP consultations (under 13,500 in a year) is only the equivalent of three less consultations per practice per year.

This model was also developed at a time in which a new range of drugs for the treatment of influenza was being introduced into the NHS. The development of these expensive new antiviral drugs for the treatment of influenza was felt likely to impose a significant additional commitment of NHS resources, as a greater proportion of patients suffering from influenza would seek formal medical attention. The availability of such costly treatments will increase influenza costs above those identified in the model. This therefore emphasises the need to optimise the protective benefits of influenza immunisation in order to constrain expenditure on such new drugs to affordable levels. Simple age-based audits should therefore be undertaken in each practice to monitor progress in enhancing vaccination coverage and to assess its impact on the utilisation and cost of influenza treatments in the target population.

Routine annual vaccination must remain the mainstay of influenza management policy. The cost-effectiveness of vaccination in any particular year depends on the extent to which the vaccine and prevailing virus strain are appropriately matched. The targeting of influenza vaccination is based on its proven efficacy in healthy volunteers combined with recognition that influenza complications are most likely to occur in older people and those with chronic medical conditions. Unfortunately, very little robust evidence is available concerning the comparative efficacy of influenza vaccine in the older population. It is generally accepted that older people may have a more limited response to influenza vaccine than younger recipients; however, the extent of the reduced effectiveness remains unclear.

If the protective effects of the vaccine on older people are found to be significantly lower then alternative policies need to be examined to optimise the level of protection provided to them from this source. For example, priorities for vaccination could be extended to incorporate care staff and household contacts who are most likely to transmit the virus to older patients. One study[93] identified immunisation of care providers as being at least as important in protecting older patients in long-term care facilities from influenza as the immunisation of patients themselves. The cost-effectiveness of such alternative strategies should be evaluated and compared with the cost-effectiveness information provided in this report.

Chapter 9

Recommendations for future research

Following the change in the UK to an age-based immunisation policy, it is important to ensure that uptake is maximised in people who will benefit most from vaccination. A recent audit of general practices in Northern Ireland found a decline in vaccine uptake amongst people aged over 85 years and suggested that people living in nursing or residential accommodation were less likely to be vaccinated.[94] Closer monitoring of immunisation rates in people at greatest risk from influenza is therefore required, and future research should focus on ways to maximise vaccine uptake in the highest risk groups, especially frail, institutionalised, older people. Research is also needed to investigate differences in vaccine protection between people from different age and socio-economic populations.

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Long Lane Medical Centre, Long Lane, Liverpool, L9 6DQ

Garston Family Health Centre, Moss Street, Liverpool, L9 2NA

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References

1. Department of Health. Influenza immunisation: extension of current policy to include all those aged 75 years and over. London: The Stationery Office; 1998.
2. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunisation Practices (ACIP). *Morb Mortal Wkly Rep* 1999;**48**:1–28.
3. Department of Health. Influenza immunisation. London: The Stationery Office; 2000.
4. van Elden LJ, van Essen GA, Boucher CA, van Loon AM, Nijhuis M, Schipper P, *et al*. Clinical diagnosis of influenza virus infection: evaluation of diagnostic tools in general practice. *Br J Gen Pract* 2001;**51**:630–4.
5. Kuszewski K, Brydak L. The epidemiology and history of influenza. *Biomed Pharmacother* 2000; **54**:188–95.
6. Eickhoff TC, Sherman IL, Serfling RE. Observations on excess mortality associated with epidemic influenza. *JAMA* 1961;**176**:104–10.
7. Barker WH, Mullooly JP. Pneumonia and influenza deaths during epidemics: implications for prevention. *Arch Intern Med* 1982;**142**:85–9.
8. Curwen M, Dunnell K, Ashley J. Hidden influenza deaths 1989/90. *Popul Trends* 1990;**61**:31–3.
9. Ahmed AE, Nicholson KG, Nguyen-Van-Tam JS. Reduction in mortality associated with influenza vaccine during 1989–90 epidemic. *Lancet* 1995; **346**:591–5.
10. Burnet M. The influenza virus. *Sci Am* 1953; **188**:27–31.
11. Kilbourne ED. The influenza viruses and influenza. Academic Press: New York; 1975.
12. Goodman RA, Orenstein WA, Munro TF, Smith SC, Sikes RK. Impact of influenza A in a nursing-home. *JAMA* 1982;**247**:1451–3.
13. Howells CH, Vesselinova-Jenkins CK, Evans AD, James J. Influenza vaccination and mortality from bronchopneumonia in the elderly. *Lancet* 1975;**1**:381–3.
14. Patriarca PA, Weber JA, Parker RA, Hall WN, Kendal AP, Bregman DJ, *et al.* Efficacy of influenza vaccine in nursing homes. Reduction in illness and complications during an influenza A (H3N2) epidemic. *JAMA* 1985;**253**:1136–9.
15. Deguchi Y, Takasugi Y, Nishimura K. Vaccine effectiveness for influenza in the elderly in welfare nursing homes during an influenza A (H3N2) epidemic. *Epidemiol Infect* 2000;**125**:393–7.
16. Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. *Am J Epidemiol* 2001; **154**:155–60.
17. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med* 1995;**123**:518–27.
18. Coles FB, Balzano GJ, Morse DL. An outbreak of influenza A (H3N2) in a well immunised nursing home population. *J Am Geriatr Soc* 1992;**40**:589–92.
19. Carman WF, Elder AG, Wallace LA, McAulay K, Walker A, Murray GD, *et al*. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* 2000;**355**:93–7.
20. Barker WH, Mullooly JP. Influenza vaccination of elderly persons. Reduction in pneumonia and influenza hospitalisations and deaths. *JAMA* 1980;**244**:2547–9.
21. Fleming DM, Watson JM, Nicholas S, Smith GE, Swan AV. Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989–90 using a general practice database. *Epidemiol Infect* 1995;**115**:581–9.
22. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch Intern Med* 1998; **158**:1769–76.
23. Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. *Lancet* 2001; **357**:1008–11.
24. Fedson DS, Wajda A, Nicol JP, Hammond GW, Kaiser DL, Roos LL. Clinical effectiveness of influenza vaccination in Manitoba. *JAMA* 1993;**270**:1956–61.
25. Puig-Barbera J, Marquez-Calderon S, Masoliver-Fores A, Lloria-Paes F, Ortega-Dicha A, Gil-Martin M, *et al*. Reduction in hospital admissions for pneumonia in non-institutionalised elderly people as a result of influenza vaccination: a case-control study in Spain. *J Epidemiol Community Health* 1997; **51**:526–30.

26. Ohmit SE, Monto AS. Influenza vaccine effectiveness in preventing hospitalisation among the elderly during influenza type A and type B seasons. *Int J Epidemiol* 1995;**24**:1240–8.

27. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomised double-blind placebo-controlled trial. *JAMA* 1994; **272**:1661–5.

28. Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. *JAMA* 1990;**264**:1139–41.

29. Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double-blind placebo-controlled trial. *BMJ* 1993;**307**:988–90.

30. Mader R, Narendran A, Lewtas J, Bykerk V, Goodman RCJ, Dickson JR, *et al*. Systemic vasculitis following influenza vaccination – report of 3 cases and literature review. *J Rheumatol* 1993;**20**:1429–31.

31. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, *et al*. Guillain–Barré syndrome following vaccination in the National Influenza Immunisation Program, United States, 1976–1977. *Am J Epidemiol* 1979; **110**:105–23.

32. Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain–Barré syndrome and the 1978–1979 influenza vaccine. *N Engl J Med* 1981;**304**: 1557–61.

33. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain–Barré syndrome in the United States, 1979–1980 and 1980–1981. Lack of an association with influenza vaccination. *JAMA* 1982;**248**: 698–700.

34. Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, *et al*. The Guillain–Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *N Engl J Med* 1998;**339**: 1797–802.

35. Hattotuwa KL, Hind CR. Pneumococcal vaccine. *Postgrad Med J* 1997;**73**:222–4.

36. Fine MJ, Smith MA, Carson CA, Meffe F, Sankey SS, Weissfeld LA, *et al*. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomised controlled trials. *Arch Intern Med* 1994;**154**:2666–77.

37. Örtqvist A, Hedlund J, Burman LA, Elbel E, Hofer M, Leinonen M, *et al*. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet* 1998;**351**:399–403.

38. Farr BM, Johnston BL, Cobb DK, Fisch MJ, Germanson TP, Adal KA, *et al*. Preventing pneumococcal bacteremia in patients at risk. Results of a matched case-control study. *Arch Intern Med* 1995;**155**:2336–40.

39. Koivula I, Sten M, Leinonen M, Makela PH. Clinical efficacy of pneumococcal vaccine in the elderly: a randomised, single-blind population-based trial. *Am J Med* 1997;**103**:281–90.

40. Ament A, Baltussen R, Duru G, Rigaud-Bully C, de Graeve D, Ortqvist A, *et al*. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 Western European countries. *Clin Infect Dis* 2000;**31**:444–50.

41. DeStefano F, Goodman RA, Noble GR, McClary GD, Smith SJ, Broome CV. Simultaneous administration of influenza and pneumococcal vaccines. *JAMA* 1982;**247**:2551–4.

42. Honkanen PO, Keistinen T, Kivela SL. Reactions following administration of influenza vaccine alone or with pneumococcal vaccine to the elderly. *Arch Intern Med* 1996;**156**:205–8.

43. Grilli G, Fuiano L, Biasio LR, Pregliasco F, Plebani A, Leibovitz M, *et al*. Simultaneous influenza and pneumococcal vaccination in elderly individuals. *Eur J Epidemiol* 1997;**13**:287–91.

44. Fletcher TJ, Tunnicliffe WS, Hammond K, Roberts K, Ayres JG. Simultaneous immunisation with influenza vaccine and pneumococcal polysaccharide vaccine in patients with chronic respiratory disease. *BMJ* 1997;**314**:1663–5.

45. Carstairs V, Morris R. Deprivation and health in Scotland. Aberdeen: Aberdeen University Press; 1991.

46. Parkman PD, Hopps HE, Rastogi SC, Meyer HM Jr. Summary of clinical trials of influenza virus vaccines in adults. *J Infect Dis* 1977;**136** Suppl:S722–30.

47. Classification Committee of WONCA. ICHPPC-2-Defined (International Classification of Health Problems in Primary Care). 3rd ed. Oxford: Oxford University Press; 1983. p. 72.

48. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**:361–70.

49. Herrmann C. International experiences with the hospital anxiety and depression scale – a review of validation data and clinical results. *J Psychosom Res* 1997;**42**:17–41.

50. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;**316**:736–41.

51. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Maryland State Med J* 1965;**14**:61–5.

52. Goddard NL, Joseph CA, Zambon M, Nunn M, Fleming D, Watson JM. Influenza surveillance in England and Wales: October 1999 to May 2000. *Commun Dis Public Health* 2000;**3**:261–6.

53. Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? *Pharmacoeconomics* 2000;**17**:445–59.

54. Sheldon TA. Problems of using modelling in the economic evaluation of health care. *Health Econ* 1996;**5**:1–11.

55. Buxton MJ, Drummond MF, VanHout BA, Prince RL, Sheldon TA, Szucs T, *et al*. Modelling in economic evaluation: an unavoidable fact of life. *Health Econ* 1997;**6**:217–27.

56. Fedson DS. Evaluating the impact of influenza vaccination. A North American perspective. *Pharmacoeconomics* 1996;**9** Suppl 3:54–61.

57. Glezen WP, Paredes A, Taber LH. Influenza in children. Relationship to other respiratory agents. *JAMA* 1980;**243**:1345–9.

58. Bradley MD, Sheldon TA, Watt IS. Influenza vaccine and older people: an evidence-based policy? *Br J Gen Pract* 1997;**47**:271–2.

59. Fleming DM. The impact of three influenza epidemics on primary care in England and Wales. *Pharmacoeconomics* 1996;**9** Suppl 3:38–45.

60. Ashley J, Smith T, Dunnell K. Deaths in Great Britain associated with the influenza epidemic of 1989/90. *Popul Trends* 1991;**65**:16–20.

61. Perrotta DM, Decker M, Glezen WP. Acute respiratory disease hospitalisations as a measure of impact of epidemic influenza. *Am J Epidemiol* 1985;**122**:468–76.

62. Glezen WP, Decker M, Joseph SW, Mercready RG Jr. Acute respiratory disease associated with influenza epidemics in Houston, 1981–1983. *J Infect Dis* 1987;**155**:1119–26.

63. Curwen M, Dunnell K, Ashley J. Hidden influenza deaths. *BMJ* 1990;**300**:896.

64. Sprenger MJ, Mulder PG, Beyer WE, Van Strik R, Masurel N. Impact of influenza on mortality in relation to age and underlying disease, 1967–1989. *Int J Epidemiol* 1993;**22**:334–40.

65. McBean AM, Babish JD, Warren JL. The impact and cost of influenza in the elderly. *Arch Intern Med* 1993;**153**:2105–11.

66. Barker WH, Borisute H, Cox C. A study of the impact of influenza on the functional status of frail older people. *Arch Intern Med* 1998;**158**:645–50.

67. Bortz W. Disuse and aging. *JAMA* 1982;**250**:1203–8.

68. Fedson DS, Hirota Y, Shin HK, Cambillard PE, Kiely J, Ambrosch F, *et al*. Influenza vaccination in 22 developed countries: an update to 1995. *Vaccine* 1997;**15**:1506–11.

69. Neuzil KM, Reed GW, Mitchel EF Jr, Griffin MR. Influenza-associated morbidity and mortality in young and middle-aged women. *JAMA* 1999;**281**:901–7.

70. Glezen WP. Influenza control-unfinished business. *JAMA* 1999;**281**:944–5.

71. Nguyen-Van-Tam JS, Nicholson KG. Influenza immunization; vaccine offer, request and uptake in high-risk patients during the 1991/2 season. *Epidemiol Infect* 1993;**111**:347–55.

72. Kouides RW, Bennett NM, Lewis B, Cappuccio JD, Barker WH, LaForce FM. Performance-based physician reimbursement and influenza immunisation rates in the elderly. The Primary Care Physicians of Monroe County. *Am J Prev Med* 1998;**14**:89–95.

73. Nexoe J, Kragstrup J, Sogaard J. Decision on influenza vaccination among the elderly. A questionnaire study based on the Health Belief Model and the Multidimensional Locus of Control Theory. *Scand J Prim Health Care* 1999;**17**:105–10.

74. King S. Vaccination policies: individual rights v community health. We can't afford to be half hearted about vaccination programmes. *BMJ* 1999; **319**:1448–9.

75. Office of Technology Assessment, US Congress. Cost-effectiveness of influenza vaccination. Washington, DC: Government Printing Office; 1981.

76. CDC. Final results: Medicare influenza vaccine demonstration-selected states, 1988-1992. *Morb Mortal Wkly Rep* 1993;**42**:601–4.

77. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med* 1994;**331**: 778–84.

78. Foster DA, Talsma A, Furumoto-Dawson A, Ohmit SE, Margulies JR, Arden NH, *et al*. Influenza vaccine effectiveness in preventing hospitalisation for pneumonia in the elderly. *Am J Epidemiol* 1992; **136**:296–307.

79. Mullooly JP, Bennett MD, Hornbrook MC, Barker WH, Williams WW, Patriarca PA, *et al*. Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organisation. *Ann Intern Med* 1994;**121**:947–52.

80. Helliwell B, Drummond MF. The costs and benefits of preventing influenza in Ontario's elderly. *Can J Public Health* 1988;**79**:175–80.

81. Schoenbaum SC, McNeil BJ, Kavet J. The swine-influenza decision. *N Engl J Med* 1976;**295**:759–65.

82. Diguiseppi C. Why everyone over 65 deserves influenza vaccine. *BMJ* 1996;**313**:1162.

83. Nicholson KG. Socioeconomics of influenza and influenza vaccination in Europe. *Pharmacoeconomics* 1996;**9** Suppl 3:75–8.

84. Szucs TD. What do we not know? What work is required? *Pharmacoeconomics* 1996;**9** Suppl 3:79–81.

85. Malek M. Economic evaluation of influenza vaccination and economic modelling. *Pharmacoeconomics* 1996;**9** Suppl 3:73–4.

86. Cornford CS, Morgan M. Elderly people's beliefs about influenza vaccination. *Br J Gen Pract* 1999;**49**:281–4.

87. Gosney M. Factors affecting influenza vaccination rates in older people admitted to hospital with acute medical problems. *J Adv Nurs* 2000;**32**:892–7.

88. Findlay PF, Gibbons YM, Primrose WR, Ellis G, Downie G. Influenza and pneumococcal vaccination: patient perceptions. *Postgrad Med J* 2000;**76**:215–17.

89. van Essen GA, Kuyvenhoven MM, de Melker RA. Why do healthy elderly people fail to comply with influenza vaccination? *Age Ageing* 1997;**26**:275–9.

90. Gupta A, Makinde K, Morris G, Thomas P, Hasan M. Influenza immunisation coverage in older hospitalised patients during winter 1998–99 in Carmarthenshire, UK. *Age Ageing* 2000;**29**:211–13.

91. Petty DR, Zermansky AG, Raynor DK, Vail A, Lowe CJ, Freemantle N, *et al*. "No thank you": why elderly patients declined to participate in a research study. *Pharm World Sci* 2001;**23**:22–7.

92. Beyer WE, Palache AM, Kerstens R, Masurel N. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. *Eur J Clin Microbiol Infect Dis* 1996;**15**:65–70.

93. Potter J, Stott DJ, Roberts MA, Elder AG, O'Donnell B, Knight PV, *et al*. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis* 1997;**175**:1–6.

94. O'Reilly D, Gormley G, Gilliland A, Cuene-Grandidier H, Rafferty C, Reilly P, *et al*. Influenza vaccinations in Northern Ireland: are older patients missing out? *Age Ageing* 2002;**31**:385–90.

Appendix 1

FLU IMMUNISATION TRIAL

My reasons for not wishing to be involved in the 1999 flu immunisation research project are as follows (please tick as appropriate):

I was concerned about side effects following the vaccination	Yes ☐	No ☐
I was unable to attend any of the vaccination sessions (e.g. on holiday)	Yes ☐	No ☐
I was unable to get to the GP Surgery	Yes ☐	No ☐
I do not feel that I require a flu vaccination	Yes ☐	No ☐
I had already received the vaccination from my GP Surgery	Yes ☐	No ☐
I would rather my own GP gave me the flu vaccination	Yes ☐	No ☐
For health reasons, I could not participate in the trial	Yes ☐	No ☐
I have previously had a bad reaction to the flu vaccination If 'yes' please state what:	Yes ☐	No ☐

.....

I am already involved in a clinical trial If 'yes' please state which trial:	Yes ☐	No ☐

.....

I objected to the word "Geriatric" being used in the trial	Yes ☐	No ☐
I do not want to be involved with a research project	Yes ☐	No ☐

Any other reason

.....

Appendix 2

THE UNIVERSITY
of LIVERPOOL

DEPARTMENT OF GERIATRIC MEDICINE

SIDE-EFFECTS QUESTIONNAIRE

Please could you fill in the following questionnaire THREE DAYS after your injection to outline the nature of any side effects which may have resulted from the vaccination.

Please tick in the relevant box(s) to indicate whether you suffered any of the following problems following vaccination. Please return the form irrespective of whether you report side effects or not. A response of no side effects is as important as a response outlining side effects.

Did you have any of the following symptoms?

• Soreness around the injection site	Right arm	Yes [ ]	No [ ]
	Left arm	Yes [ ]	No [ ]
• High temperature/sweats		Yes [ ]	No [ ]
• Aching arms/legs or joints		Yes [ ]	No [ ]
• Itchy rash		Yes [ ]	No [ ]
• Feeling tired & lethargic		Yes [ ]	No [ ]
• Runny nose		Yes [ ]	No [ ]
• Cough		Yes [ ]	No [ ]
• Headache		Yes [ ]	No [ ]
• Sore throat		Yes [ ]	No [ ]

THANK YOU FOR YOUR PARTICIPATION

Appendix 3

SELF-REPORTED ILLNESS QUESTIONNAIRE

If you suffer from any of the symptoms listed below please tick the relevant date boxes on the calendar to indicate the length of your illness. If you have to see your own doctor or attend hospital with a flu-like illness or chest infection, please could you indicate this in the relevant date box(es) below.

OCTOBER

SYMPTOM	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sudden onset of flu-like illness																															
Cough																															
High temperature/fever																															
Aching arms/legs or joints																															
Illness confined me to bed																															
Tired & lethargic																															
Runny nose																															
Headache																															
Sore throat																															
Please list any medication taken for these illnesses																															

NOVEMBER

SYMPTOM	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Sudden onset of flu-like illness																														
Cough																														
High temperature/fever																														
Aching arms/legs or joints																														
Illness confined me to bed																														
Tired & lethargic																														
Runny nose																														
Headache																														
Sore throat																														
Please list any medication taken for these illnesses																														

SELF-REPORTED ILLNESS QUESTIONNAIRE – Part 2

If you suffer from any of the symptoms listed below please tick the relevant date boxes on the calendar to indicate the length of your illness.
If you have to see your own doctor or attend hospital with a flu-like illness or chest infection, please could you indicate this in the relevant date box(es) below.

DECEMBER

SYMPTOM	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sudden onset of flu-like illness																															
Cough																															
High temperature/fever																															
Aching arms/legs or joints																															
Illness confined me to bed																															
Tired & lethargic																															
Runny nose																															
Headache																															
Sore throat																															
Please list any medication taken for these illnesses																															

JANUARY

SYMPTOM	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sudden onset of flu-like illness																															
Cough																															
High temperature/fever																															
Aching arms/legs or joints																															
Illness confined me to bed																															
Tired & lethargic																															
Runny nose																															
Headache																															
Sore throat																															
Please list any medication taken for these illnesses																															

SELF-REPORTED ILLNESS QUESTIONNAIRE – Part 3

If you suffer from any of the symptoms listed below please tick the relevant date boxes on the calendar to indicate the length of your illness. If you have to see your own doctor or attend hospital with a flu-like illness or chest infection, please could you indicate this in the relevant date box(es) below.

FEBRUARY

SYMPTOM	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Sudden onset of flu-like illness																												
Cough																												
High temperature/fever																												
Aching arms/legs or joints																												
Illness confined me to bed																												
Tired & lethargic																												
Runny nose																												
Headache																												
Sore throat																												
Please list any medication taken for these illnesses																												

MARCH

SYMPTOM	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sudden onset of flu-like illness																															
Cough																															
High temperature/fever																															
Aching arms/legs or joints																															
Illness confined me to bed																															
Tired & lethargic																															
Runny nose																															
Headache																															
Sore throat																															
Please list any medication taken for these illnesses																															

Appendix 4

EQ-5D health questionnaire

DESCRIBING YOUR OWN HEALTH TODAY

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

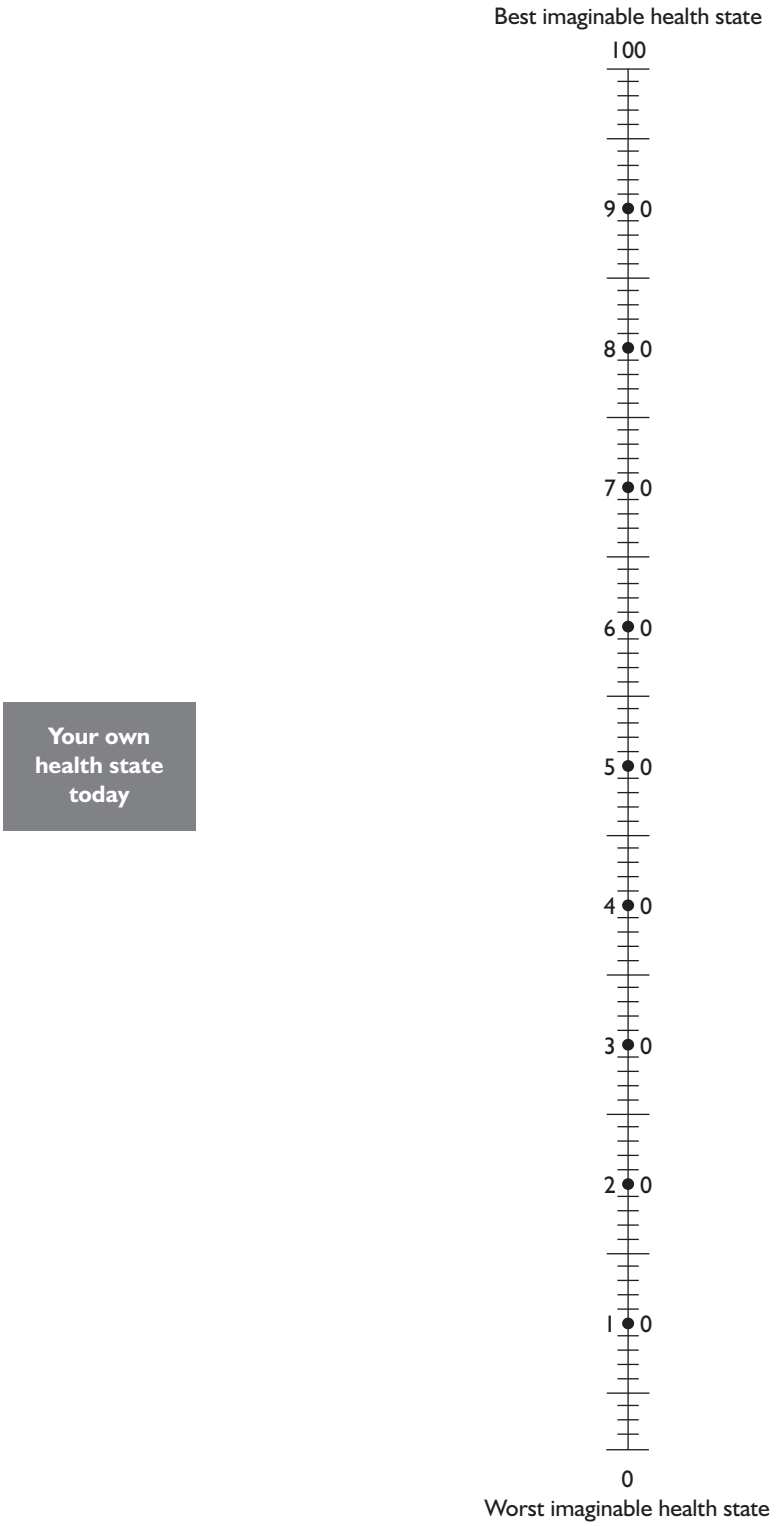
Compared with my general level of health a year ago, my health state today is

Better ☐
About the same ☐
Worse ☐

VALUING YOUR OWN HEALTH TODAY

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



Appendix 5

HOSPITAL ANXIETY AND DEPRESSION QUESTIONNIARE

Please place a cross in the box which best matches your reponse.

Q1.
I feel tense and wound up:

- Most of the time ☐
- A lot of the time ☐
- Time to time, occasionally ☐
- Not at all ☐

Q2.
I still enjoy the things I used to enjoy:

- Definitely as much ☐
- Not quite as much ☐
- Only a little ☐
- Hardly at all ☐

Q3.
I get a sort of frightened feeling as if something awful is going to happen:

- Very definitely & quite badly ☐
- Yes but not too badly ☐
- A little, but it does not worry me ☐
- Not at all ☐

Q4.
I can laugh and see the funny side of things:

- As much as I always did ☐
- Not quite as much now ☐
- Definitely not so much now ☐
- Not at all ☐

Q5.
Worrying thoughts go through my mind:

- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not too often ☐
- Only occasionally ☐

Q6.
I feel cheerful:

- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

Q7.
I can sit at ease and feel relaxed:

- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

Q8.
I feel as if I am slowed down:

- Nearly all of the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

Q9.
I get a sort of frightening feeling like butterflies in my stomach:

- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

Q10.
I feel restless as if I have to be on the move:

- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

Q11.
I have lost interest in my appearance:

- Definitely ☐
- I don't take as much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

Q12.
I look forward with enjoyment to things:

- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

Q13.
I get sudden feelings of panic:

- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Hardly at all ☐

Q14.
I can enjoy a good book or radio or TV programme:

- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Appendix 6

Barthel index

THIS QUESTIONNAIRE IS CONFIDENTIAL AND ANONYMOUS. You are required to tick the box (under the 10 headings below) that best describes you. If you have any difficulty in answering the questions a member of staff will be available to assist you at your vaccination appointment.

1. FEEDING

Unable	–	Totally dependent	0	☐
Needs help	–	cutting, spreading butter but feeds self	5	☐
Independent	–	can eat normal food (not only soft food) provided by others but not cut up	10	☐

2. BATHING

Dependent			0	☐
Independent	–	can get in and out unsupervised and wash self. In shower, independent if unsupervised/unaided.	5	☐

3. GROOMING (personal care)

Needs help			0	☐
Independent	–	washes face, does hair, brushes teeth, shaves (implements can be provided by helper)	5	☐

4. DRESSING

Dependent			0	☐
Needs help	–	e.g. with buttons, zips etc. but can do about half task unaided	5	☐
Independent	–	can select and put on all clothes (including buttons, zips, laces etc.)	10	☐

5. BOWEL CONTROL (preceding week)

Incontinent			0	☐
Occasional accident	–	once a week or less often	5	☐
Continent			10	☐

6. BLADDER CONTROL

Incontinent	–	or catheterized and unable to manage catheter	0	☐
Occasional accident	–	less than once a day (24h)	5	☐
Continent	–	for over 7 days. If catheterized, can manage catheter alone	10	☐

7. TOILET USE

Dependent			0	☐
Needs some help	–	can wipe self plus can do some of other tasks required of independent person	5	☐
Independent	–	can reach toilet/commode, undress sufficiently, wipe self, dress and leave	10	☐

8. CHAIR/BED TRANSFER

Unable	–	no sitting balance, cannot sit, requires two people to lift	0	☐
Major help	–	can sit, requires one strong/skilled or two normal people to lift	5	☐
Minor help	–	one person can lift easily or needs any supervision for safety	10	☐
Independent	–		15	☐

9. MOBILITY

Immobile			0	☐
Wheelchair independent	–	can negotiate corners/doors unaided	5	☐
Walks with help	–	one untrained person providing physical help, supervision or moral support	10	☐
Independent	–	can walk 50 metres or around house. May use any aid, e.g. stick, except rolling walker	15	☐

10. STAIRS

Unable			0	☐
Needs help	–	verbal or physical help or carrying aid	5	☐
Independent	–	up and down, carrying any walking aid	10	☐

TOTAL SCORE ☐☐ (we will add this up for you)

Appendix 7

THE UNIVERSITY
of LIVERPOOL

DEPARTMENT OF GERIATRIC MEDICINE

TIME AND TRAVEL QUESTIONNAIRE

How did you get here today?

- Walk ☐
- Bus ☐
- Car ☐
- Taxi ☐
- Other *Please specify* _____

How many miles did you travel to reach the clinic both ways? ☐

How long did your journey take (one way) in minutes ☐

Did anyone bring you here today? ☐
(*e.g. friend or relative*)

If so did they incur any additional costs? ☐
(*e.g. time off work*)

Did you pay for your journey here today? Yes ☐ No ☐

If yes, how much did your journey cost? £ _____
(*fare both ways*)

THANK YOU FOR YOUR PARTICIPATION

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We look forward to hearing from you.

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