Population-wide benefits of routine vaccination of children against influenza
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study considered the use of routine childhood immunisation against influenza for children aged 6 months to 18 years. Four different strategies were compared with the current level of vaccination (5%), namely the vaccination of 20, 40, 60 and 80% of the target population.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The population was a hypothetical cohort designed to represent a generic cross-section of the general population in terms of selected demographic factors deemed important to disease transmission. The age distribution of the population and the composition of households approximated those of the general population.

Setting
The setting was the community. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence was derived from studies published between 1980 and 2002. The cost data were taken from sources dating from 1996 to 2001. The price year was 2000.

Source of effectiveness data
The evidence was derived from a review or synthesis of published studies, augmented with estimates based on experts’ opinion.

Modelling
A stochastic simulation epidemic model was used for the analysis. The model allowed the transmission of influenza, clinical illness, and the economic costs to be considered. Individuals in the model were designated high risk or healthy. This was achieved by using the estimated percentage of persons in their age group who were at high risk of influenza-related complications. The four separate age cohorts considered were 0 - 4 years, 5 - 18 years, 19 - 64 years and 65+ years.

Outcomes assessed in the review
The parameters used in the model for the four different age and two different health status cohorts included the rates of
influenza illness and death, and medical care use for influenza illness. Other parameters were the average length of latent period and of infectivity, the probability of illness given influenza infection, and disease transmission between children and adults. Vaccine efficacy parameters included the protective efficacy of the influenza vaccine (i.e. efficacy for susceptibility) and the efficacy for infectiousness (i.e. in reducing direct transmission of disease from vaccinees to others).

**Study designs and other criteria for inclusion in the review**
No inclusion criteria for a review of any of the parameters were reported. However, the studies used by the authors included an analysis of individual primary studies of different designs.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
The authors reported approximately 40 studies as sources of effectiveness evidence.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The model parameters for each age cohort and health status cohort were presented in full in the paper. The model inputs reported below are for the 0 - 4 year age cohort. Selected model parameters included:

- the rate of influenza-related illness, 17 for both healthy and high risk;
- death, 0.0017 (healthy) and 0.0019 (high risk);
- hospitalisation, 0.275 (healthy) and 1.762 (high risk);
- outpatient visit, 58.8 (healthy) and 88.2 (high risk); and
- over-the-counter medication, 40.9 (healthy) and 10.0 (high risk).

The average length of latent period was 1.9 days, and of contamination 4.1 days. The probability of illness given influenza infection was 0.67.

Some parameters were not explicitly reported in the paper but were included in the model with references. These included disease transmission between children and adults.
The protective efficacy of the influenza vaccine was 70% among children and younger adults, and 50% among older adults. The efficacy for infectiousness (i.e. in reducing direct transmission of disease from those vaccinated to others) was assumed to be 80%.

Methods used to derive estimates of effectiveness
Several published parameters were augmented with authors' assumptions.

Estimates of effectiveness and key assumptions
Age-specific vaccine coverage levels were assumed to be 5% for the young (age 6 months to 4 years) and older children and, in all analyses, 23% for younger adults and 68% for older adults. Vaccine coverage was assumed to be twice as high among high-risk versus healthy children, and 1.5 times higher among high-risk versus healthy younger adults. In addition, asymptomatic persons were assumed to be half as infectious as symptomatic persons.

Measure of benefits used in the economic analysis
No summary measure of benefit was used in the economic evaluation. The costs and effects were left disaggregated and the study was, in effect, a cost-consequences analysis.

Direct costs
Estimates of direct medical costs included hospitalisation and associated physician visits (including admission, daily and discharge visits), outpatient visits for pneumonia and influenza, acute bronchitis, chronic respiratory disease and over-the-counter medication (related drug claims were also considered). The costs of vaccination were not included. All direct costs were estimated from published sources. The values were stepped down to costs using hospital-specific cost-to-charge ratios. Future costs were discounted at an annual rate of 3%. The costs from previous years were converted to year 2000 dollars using the medical care component of the Consumer Price Index. Estimates of the quantities and the costs were based on actual data and were derived using modelling. The price year was 2000.

Statistical analysis of costs
Although 1,000 stochastic simulations were performed for each scenario to explore uncertainty in the results, and the resource use was incorporated, it was unclear if a probability distribution or range was cited for the stochastic analysis of costs. As such, it appears that the unit costs seem to have been incorporated as a deterministic parameter.

Indirect Costs
Productivity costs were considered in the analysis. These included work loss due to influenza-related morbidity and the value of lost future earnings, plus fringe benefits for children and adults dying from influenza. The authors mentioned that a day's wages was used in calculating indirect productivity costs, and these were estimated using data from the US Bureau of Labour Statistics. Assumptions about quantities were reported. The costs from previous years were converted to year 2000 dollars using the medical care component of the Consumer Price Index. All the costs were discounted at a real annual rate of 3%.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was carried out and variability in the data was investigated. The method used to select the ranges was not reported. Sensitivity analyses were performed for age-specific rates of influenza illness, disease transmission probabilities, and other selected model parameters which were varied from 50 to 150% of their base-case values. These parameters included the rates and associated costs of influenza-related mortality, hospitalisation and outpatient visits,
and the value of work loss due to influenza-related morbidity. One thousand stochastic simulations were performed for each scenario to estimate the expected spread of influenza infection throughout the community. For each of these 1,000 simulations, an additional 25 stochastic simulations were performed (i.e. 25,000 in total) to estimate economic costs. Measures of interest were calculated by averaging the results across all simulations. Probability distributions were not reported in the stochastic simulation analysis. Another scenario using a higher overall attack rate was also evaluated.

Estimated benefits used in the economic analysis
At current rates of vaccination, the authors estimated that there was an average of 17.0 million cases of influenza illness among 0- to 18-year-olds in the USA annually, resulting in 340 deaths. Among adults, there were 14.3 million cases and 37,900 deaths.

With the 20% vaccination strategy for children aged 6 months to 18 years (or 14.9 million persons), the expected number of cases of illness would decline to 8.7 million among those aged 18 years or younger (49% reduction), and to 8.1 million among adults (43% reduction). Therefore, on a population-wide basis, it was estimated that this strategy would reduce the expected total number of cases of influenza illness to 16.8 million (46% reduction). Estimates of other measures of influenza-related burden would also be reduced. Total influenza-related outpatient visits would decline to 6.1 million, hospitalisations to 67,400 and deaths to 22,000.

With the vaccination of 80% of children, the expected number of cases of illness was estimated to decline to 0.8 million among those aged 18 or younger (95% reduction), and to 2.0 million among adults (86% reduction). The expected total number of cases accordingly would decline to 2.8 million (91% reduction) on a population-wide basis. The expected total annual number of outpatient visits would decline to 1.1 million, hospitalisations to 15,200 and deaths to 5,900.

Cost results
At current rates of vaccination, the direct costs in 0- to 18-year-olds were $0.7 billion and the indirect costs $2.2 billion. Among adults, the corresponding estimates were $1.5 billion in direct costs and $6.6 billion in indirect costs. Therefore, on a population-wide basis, these would have associated direct and indirect costs of $2.2 billion and $8.8 billion, respectively.

Vaccination of 20% of children aged 6 months to 18 years (or 14.9 million persons), would reduce the direct costs to $1.2 billion and indirect costs to $4.9 billion. On a population-wide basis, 20% coverage was estimated to confer cost-savings (excluding the cost of vaccination) totalling $443 per additional vaccinated child (direct cost-savings $89; indirect cost-savings $354).

The direct costs would decline to $0.3 billion and the indirect costs to $1.1 billion with the vaccination of 80% of children. At 80% coverage, the cost-savings per additional vaccinated child were estimated to total $174 (direct cost-savings $35; indirect cost-savings $139).

The cost-savings per additional vaccinee were found to be moderately sensitive to changes in rates of influenza-related mortality, hospitalisation and outpatient visits and their associated costs, as well as the value of work lost due to influenza-related morbidity.

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
The findings suggested that routine vaccination of children (aged 6 months to 18 years) against influenza would yield substantial public benefits and reduce medical care use and might, therefore, result in substantial savings in medical care costs. The vaccination of 20% of US children would reduce the total number of cases among persons aged 18 or younger by almost one-half, while 80% coverage would result in a 95% reduction in the number of cases among children. The burden of influenza would also be substantially reduced among adults (ranging from 43% with 20%
coverage to 86% with 80% coverage) since children are a major pathway by which infection is spread, especially within households.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was explicitly justified. The justification given for the strategies selected was based on published literature and standard clinical practice. You should judge whether these strategies are relevant in your setting, or whether other comparators from other vaccination strategies could have been relevant as well.

Validity of estimate of measure of effectiveness
The authors used data from published sources. The main sources of effectiveness evidence were studies of varied design. Despite this fact, it was unclear if a systematic review of the literature was undertaken. The authors reported the methods used to derive the estimates of effectiveness (probabilities of acquiring influenza infection and illness, and probabilities of disease transmission) and justified their choice of assumptions with reference to the medical literature. The estimates were investigated in sensitivity analyses, although the stochastic model was not described in detail. The study derived the burden of disease (cases of influenza and deaths) of current vaccination coverage (5%) and other alternative scenarios using modelling, and reported the results adequately. The lack of reporting on the search methods, inclusion criteria and pooling for the review of the effectiveness parameters made it difficult to ascertain if the best available evidence had been used to populate the model. However, the stochastic nature of the model will help to deal with some of the uncertainty in these parameters.

Validity of estimate of measure of benefit
The authors did not derive a measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

Validity of estimate of costs
The authors reported that the costs were estimated from a societal perspective, thus indirect costs were appropriately included. Although some costs might have been omitted from the analysis, these were unlikely to have affected the authors conclusions. The price values used were stepped down to costs using cost-to-charge ratios. Again, although a stochastic model was undertaken, the details were not reported in sufficient detail.

To estimate the total direct costs, the authors considered inpatient care, outpatient care and over-the-counter medication. Although they were taken from different sources and years, appropriately adjustments were performed and reported. The resource use quantities and prices were taken from published sources and derived from the model. Sensitivity analyses of the costs were conducted. Vaccination costs were not included, but can be explored in each setting to see how they relate to the direct and productivity (indirect) costs.

Other issues
The authors compared their findings with those from other studies which, in general, showed their findings to be in agreement. The issue of the generalisability to the USA was addressed explicitly in that the authors considered the age distribution and household structure of their model population approximated that of the USA. In addition, the model yielded estimates of the current clinical and economic burden of influenza which were consistent with published data, taking into account changes over time in the size of the US population and rates of vaccination. The authors appear to have presented their results somewhat selectively, although their conclusions reflected the scope of the analysis.

The authors explicitly stated some limitations of their study since their model, as all other models, simplified reality in a number of aspects. The population on which they based their simulations consisted of 10,000 persons. Influenza was introduced into the population only once, rather than multiple times over the course of an influenza season. All vaccinations were assumed to occur prior to the introduction of the virus. Reduced susceptibility due to prior influenza infection and/or prior vaccination was not considered on an individual basis. However, the authors stated that the impact of many of these simplifications on their findings was minimal, as they apply similarly to all vaccination
scenarios, and their effects might be largely negated when attention was focused on differences between scenarios. They also noted that their results reflected expected outcomes for an "average" influenza season. The benefits of vaccination might be lower in years with poor antigenic match between the vaccine and circulating viruses and/or substantially lower infection rates, and higher in years with good antigenic match and/or substantially higher rates of infection.

**Implications of the study**
Infection rates among children are generally the highest of any age group during typical influenza seasons. Children are the major pathway by which influenza is spread to others in the community. This study highlighted the public health importance of routine childhood vaccination against influenza. Vaccination would prevent substantial numbers of cases of illness by directly protecting those at highest risk of infection, and by reducing transmission of the disease to the rest of the population. Substantial reductions were also estimated to occur in influenza-related mortality and economic costs.

**Source of funding**
Funded by Wyeth Research, Collegeville (PA) and the National Institutes of Health.

**Bibliographic details**

**PubMedID**
15652671

**DOI**
10.1016/j.vaccine.2004.08.044

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adolescent; Adult; Age Factors; Algorithms; Child; Child, Preschool; Cost Savings; Cost of Illness; Costs and Cost Analysis; Hospitalization /economics /statistics & numerical data; Humans; Immunization Schedule; Infant; Influenza Vaccines /economics /therapeutic use; Influenza, Human /economics /immunology /prevention & control; Mass Vaccination /economics; Models, Economic; Models, Statistical; Population; Risk Assessment; United States /epidemiology

**AccessionNumber**
22005000188

**Date bibliographic record published**
28/02/2006

**Date abstract record published**
28/02/2006