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Economic benefits of inactivated influenza vaccines in the prevention of seasonal influenza in children

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Abbreviations: ACIP, Advisory Committee on Immunization Practices; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; RT-PCR, reverse-transcription polymerase chain reaction

The aim of this study was to systematically review published studies that evaluated the efficiency of inactivated influenza vaccination in preventing seasonal influenza in children. The vaccine evaluated was the influenza-inactivated vaccine in 10 studies and the virosomal inactivated vaccine in three studies. The results show that yearly vaccination of children with the inactivated influenza vaccine saves money from the societal and family perspectives but not from the public or private provider perspective. When vaccination does not save money, the cost-effectiveness ratios were very acceptable. It can be concluded, that inactivated influenza vaccination of children is a very efficient intervention.

Introduction

Research carried out over the last 20 years has shown that the global health burden of influenza in small children, in terms of incidence and hospitalizations, is substantial, even greater than in the elderly.[1] In addition, it has been shown that schoolchildren are the fundamental nucleus of community transmission of influenza, especially in the initial stages of an epidemic outbreak.[2]

In June 2002, the Advisory Committee on Immunization Practices (ACIP) of the CDC and the American Academy of Pediatrics recommended annual influenza vaccination of children aged 6 to 24 months.[3] In 2006, they extended the recommendation to all children aged 6 to 59 months.[4] In 2008, the recommendation was extended to children > 18 years of age.[5] In 2010, the ACIP recommended universal yearly vaccination of the whole population of the United States.[6] This recommendation has been maintained for the 2012-2013 influenza season.[7]

Some countries have followed the United States strategy. These include Canada[8] and some European countries (Austria, Estonia, Finland, Lithuania, Rumania, Slovakia and Slovenia),[9,10] although there are some variations in the pediatrics age groups that should be vaccinated.

Traditional inactivated influenza vaccines provide little immunogenicity in small children and children aged < 8 years require two doses to obtain good levels of immunogenicity, especially the first time the vaccine is administered.[11]

Systematic reviews and meta-analyses of studies of protective efficacy (controlled clinical trials) or effectiveness (observational epidemiological studies) with two doses of classic inactivated vaccine have found protective levels against laboratory-confirmed influenza of around 60% in children aged > 2 years.[12-14] Vaccination protection is higher in vaccines with increased immunogenicity (88.7% for the virosomal vaccine and 86% for the MF59 vaccine).[15,16]

When making decisions on the introduction of a new pediatric vaccination program by the public health system, or the use of a vaccine in private practice, the health authorities in the first case, and the parents in the second case, must consider two questions related to the efficiency of the vaccination.[17] Does the vaccination save money? If not, how much does it cost to prevent a case, a hospital admission or a death due to the target disease of the vaccination? The answer to the first question lies in cost-benefit analysis, and the answer to the second in cost-effectiveness analysis.[17]

The aim of this study was to systematically review published studies that evaluated the efficiency of inactivated influenza vaccination in preventing seasonal influenza in children.

Results

The vaccine evaluated was the classic inactivated vaccine in 10 studies[18-27] and the virosomal inactivated vaccine in three studies[28-30] (the study by Weyker[22] does not mention the vaccine evaluated: however, as the study subject is the vaccination of children aged 6 months to 18 years, it may be deduced that the vaccine considered is the classic inactivated vaccine, because the

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intranasal attenuated vaccine is not indicated in children aged < 2 years).

The estimated vaccine efficacy varied according to the study and the end point considered, but ranged between 50% and 60%[18-25,29,30] in the prevention of clinical influenza, with the exception of the studies by Marchetti[26] and Esposito[28] in which the estimate was lower. In the studies by Esposito[28] and Pisu,[21] the efficacy was estimated by means of a controlled clinical trial and in the studies by Navas[29] and Salleras[30] by means of a prospective cohort study. The end points included were clinical in all studies included. In the studies by Esposito,[28] Navas[29] and Salleras[30] various end points were evaluated (acute respiratory processes avoided, antibiotic and antipyretic prescriptions avoided, lost days of schooling avoided in the study by Esposito,[28] and acute febrile respiratory illnesses, pediatric visits, prescription of antibiotics and antipyretics, maternal work absenteeism to care for the sick child in the study by Navas[29] from the social perspective, and the same factors plus school absenteeism in the study by Salleras et al. from the family perspective).[30] The remaining studies were modeled according to disease incidence, mortality rates and reported vaccine efficacies.

Studies based on controlled clinical trials[21,28] and observational cohort studies[29,30] use data from a single influenza season. Given the wide variability in the incidence of seasonal influenza from one season to another, these studies might have over- or underestimated the incidence rates. In addition, the concordance between influenza-causing strains and vaccine strains could vary from one year to another, and this could influence vaccine efficacy if only data from one year are considered.

One study analyzed the costs and benefits of individual (medical consults) or group (school) vaccination.[18] Another study compared the efficiency of vaccinating only within the working day (8-17 hours) with the use of a more-flexible timetable.[19] Vaccinations in groups or using a more-flexible timetable were much more efficient than their counterparts.

Two analyses of cost-effectiveness were carried out using cost-utility analysis (cost per quality-adjusted life year gained).[26,29]

Indirect protection was estimated in five studies. However, only one of these used a dynamic model.[22] The remaining studies used a static model[18,19,25,26,29] (reduction in incidence in family contacts) and did not consider all the possible indirect effects of vaccination (reduction in cases of influenza in school and leisure contacts, reductions in contacts of secondary cases, etc).

An analysis of the 13 studies retained (**Table 1**) in the systematic review shows that most studies made from the social perspective save money. From the provider perspective, almost all studies did not save money, but the cost-effectiveness ratios were reasonable, meaning that the intervention was cost-effective.

Our group made an economic evaluation of vaccination with the virosomal influenza vaccine in children from the perspective of the society, the provider and the family (**Table 2**).[29,30] The studies from the perspective of the society and public provider were made in high and low risk children aged 3 to 14 years and the study from the family perspective in low risk healthy children. The results showed that vaccination saved money from the social and family perspective. From the provider perspective, vaccination did not save money, but the cost-effectiveness ratios were very low.

Discussion

Every year, 15-20% of children contract influenza during the influenza season, giving rise to substantial costs in pediatric visits and antibiotic consumption and significant school and work absenteeism.[1]

The results of this systematic review show that yearly vaccination of children with the inactivated influenza vaccine saves money from the social and family perspective but not from the public or private provider perspective. When vaccination does not save money, the cost-effectiveness ratios were acceptable. In any of the cases, inactivated influenza vaccination of children is a very efficient intervention.

These results are similar to those of the excellent reviews carried out by Savidan (2008),[31] Nichol (2010)[32] and Newall (2012).[33]

The possible indirect economic benefits of pediatric vaccination in preventing cases of influenza in unvaccinated parents were not considered in some studies, including those by our group. Although a controlled clinical trial evaluating vaccine efficacy in children attending day-care centers[21] found no reduction in the costs of acute febrile respiratory processes in the families of vaccinated children, other studies[34-37] have shown that pediatric vaccination reduces the incidence of influenza-like syndrome and work absenteeism in the households of vaccinated children. A systematic review by Jordan et al.[38] concluded that the evidence suggests that vaccinating healthy children against influenza can potentially reduce the impact of influenza epidemics, although methodological differences between studies mean that no conclusions can be drawn on the size of the reduction. A recently published cluster randomized trial in rural Canadian communities of Canada[39] found that pediatric vaccination in schools reduced laboratory-confirmed (RT-PCR) cases of influenza in unvaccinated persons by 61%. The protection conferred in all study participants (vaccinated communities compared with unvaccinated communities) was similar (59%). The vaccination coverage achieved in children from vaccinated communities was 83%. Cluster randomization is the ideal design to evaluate the indirect protection conferred by a vaccine.[40,41] These results suggest that, in future studies, indirect protection should be estimated at 61% when vaccination coverage is > 80%. The inclusion of the potential benefits in studies that did not consider indirect protection would have increased vaccination efficiency considerably.

These substantial indirect health and economic benefits should be taken into account in the decisions of health authorities, in the case of public vaccination programs, or by families in the case of private vaccinations. The possible indirect benefits of pediatric vaccination for the elderly population, in whom influenza may be severe and classic inactivated vaccines are less immunogenic and less efficacious than in adults, are especially important.[42]

The review by Newall et al.[33] recommends that forthcoming studies should consider vaccination efficacy against laboratory-confirmed influenza. The review also recommends dynamic

Table 1. Economic evaluation of paediatric influenza vaccination in the community setting

Author	Country	Year	Population	Perspective	Type of analysis	Conclusions
White et al.[18]	USA	1999	School age-children	Societal	CBA	COST-SAVING Net saving per child vaccinated - $ 3.99 for individual inactivated vaccination - $ 34.79 for vaccination in a group based setting (such as schools)
Cohen et al.[19]	USA	2000	Preschool children	Societal	CBA	COST-SAVING Net saving for vaccine recipient - $ 1.2 in vaccination during work office hours (8-17) - $ 21.88 in setting with flexible hours
Dayan et al.[20]	Argentina	2001	High risk children 6 months – 15 years	Societal	CEA	COST-SAVING $ 10.4 net saving for vaccinated child
Pisu et al.[21]	USA	2005	Day-care, 2-5 years	Societal Household	CBA	NOT COST-SAVING NOT COST-SAVING
Weycker et al.[22]	USA	2005	6 months to 18 years	Societal	CBA	LIKELY COST-SAVING
Meltzer et al.[23]	USA	2005	High-risk 6 m-14 y Healthy 6 m-14 y	Societal	CBA	COST-SAVING for high risk children Not uniformly cost-saving for non-healthy children
Salo et al.[24]	Finland	2006	Healthy children 6 months-13 years	Societal Provider	CBA	COST-SAVING COST-SAVING
Prosser et al.[25]	USA	2006	High risk 6 m-17 y Healthy 6 m-17 y	Societal Provider	CEA	COST-SAVING for high risk 6 months-2 years Cost-effective for healthy < 5 years old and all high risk children (< 30.000 US $)
Marchetti et al.[26]	Italy	2006	6-60 months	Societal Provider	CEA CEA	COST-SAVING NOT COST-SAVING
Skowronski et al.[27]	Canada	2006	6-23 months	Societal Provider	CEA CEA	NOT COST-SAVING NOT COST-SAVING
Esposito et al.[28]	Italy	2006	Healthy 2-5 years	Individual Society	CBA	COST-SAVING 150.90 US $ per child vaccinated
Navas et al.[29]	Spain	2007	3-14 years	Societal Provider	CBA CEA	COST-SAVING NOT COST-SAVING Cost-effective (€ 18.6 per quality adjusted live year gained)
Salleras et al.[30]	Spain	2009	3-14 years	Family	CBA	COST-SAVING

models that include all variables that could possibly influence the transmission of influenza. Lastly, the review recommends that the mean results from various influenza seasons should be used, in order to avoid over- or underestimating the incidence and complications of influenza.

It would also seem sensible for future economic evaluations to consider the protective value (efficacy/effectiveness) in the prevention of laboratory-confirmed influenza of the new vaccines with increases immunogenicity (88.7% for the virosomal vaccine[15] and 86% for the MF59 adjuvant vaccine, which is still not licensed for pediatric vaccination).[16]

Currently, in most European countries, there are no official recommendations for routine pediatric influenza vaccination. Vaccination is only recommended in children at high risk, similar to the recommendations for adults aged < 60 years. Economic evaluations from the family perspective should be carried out in these countries to aid informed decision making by private pediatricians and parents with respect to pediatric influenza vaccination.

Methods

Economic analysis. In the economic evaluation of vaccinations, as in other health interventions, the costs and benefits of the intervention are compared with no intervention (no vaccination).[17]

There are two main forms of economic evaluation: (1) cost-benefit analysis: costs and benefits are valued in monetary terms; (2) cost effectiveness analysis: costs are measured in monetary

Table 2. Economic evaluation of inactivated virosomal influenza vaccination in children

Author	Perspective of the study	Risk status	Cost-benefit analysis: Net present value	Cost-benefit analysis: Benefit-cost ratio	Cost-effectiveness analysis	
Navas et al.[29]	Society	HR+LR	Cost-saving	1.8		
Navas et al.[29]	Provider	HR+LR	Not cost-saving	-	- Cost per episode of acute febrile respiratory process avoided	5.0 euros
					- Cost per paediatric visit avoided	6.87 euros
					- Cost per episode of antibiotic consumption avoided	25.18 euros
					- Cost per quality adjusted life year saved	18.26 euros
Salleras et al.[30]	Family	LR	Cost-saving	2.15		

Navas et al.[31] Salleras et al.[32] HR, High risk; LR, Low risk.

terms and benefits are measured either in heath units or in health utilities. In this last case, the study is called a cost-utility analysis. In fact, cost utility analysis is a special form of cost-effectiveness analysis that includes the quality of life gained in the measurement.[17,43,44]

These studies can be made from different perspectives: the individual, the family, the society and the provider (payer). In public health, the evaluation of the efficiency of pediatric vaccination is made from the perspective of the society or the provider. In the first case, the direct (medical) costs and benefits and the indirect (social) costs and benefits, such as loss of maternal productivity to care for a sick child, are included. The provider's perspective only includes the direct costs and benefits. In private practice, the analysis is made from the perspective of the family, and includes the health costs and benefits, such as the costs of diagnosis and treatment of the disease and the social and economics costs incurred by the family, such as loss of maternal productivity to care for sick children and loss of schooling of sick children.

In studies of vaccination efficiency, the time horizon (estimated duration of protection of the vaccine) is very important. This is very short for the influenza vaccine (around 6 months). Vaccination is carried out in the Northern hemisphere in October-November, and the health and socioeconomic benefits are obtained during the influenza season (normally December-February).

Another important point is the discount or update. When the costs and benefits do not accrue in the same year, they are discounted to the base year using a discount rate calculated according to the increase in the cost of living or bank interest rates. The costs and benefits of influenza vaccination accrue in the same year, and therefore no discount is necessary.

Economic evaluation of vaccinations is carried out in two stages. In the first stage, the cost of vaccination and the disease is assessed. The cost of vaccination includes the cost of the vaccine, the cost of vaccine administration, the cost of treating the adverse effects of the vaccine and the cost of time lost and of transportation to the health center to be vaccinated. The cost of the disease (without and with vaccination), depending on the perspective, includes only direct costs (perspective of the provider) or direct and indirect costs (perspective of the patient, the family or the society). In the second stage, four basic parameters are calculated: (1) the economic benefits of vaccination, which are the savings in disease costs as a consequence of vaccination. This is calculated by subtracting the cost of the disease with vaccination from the cost of the disease without vaccination; (2) the net present value, which is the difference between the economic benefits of vaccination and the costs of vaccination; (3) the benefit-cost ratio, which is the ratio between the economic benefits of vaccination and the costs of vaccination and (4) the cost-effectiveness ratio, which is the ratio between the net present cost (the difference between the costs and benefits of vaccination) and the effectiveness of vaccination expressed in health units or in health utilities (cost-utility ratio).[44]

In benefit-cost ratio analysis, when the net present value is greater than zero and the benefit-cost ratio greater than 1, vaccination saves money. No further economic analysis is required. If net present value is lower than zero and the benefit-cost ratio lower than 1, vaccination does not save money. In this case, cost-effectiveness analysis should be carried out.[16]

Sensitivity analysis is used to investigate how the variation in the main variables that influence the costs and benefits of the vaccination affects the results of the economic evaluation. The main variables that usually influence the efficiency of a vaccination program are the disease burden, the protective efficacy of the vaccine, the cost of vaccination and the loss of productivity or schooling.[16,17]

Search strategy. We searched MEDLINE, EMBASE and SCOPUS databases up to 30 September 2012 for studies that included an economic evaluation of inactivated influenza vaccination in children aged < 18 years using the following key words: inactivated influenza vaccine or vaccination, children, infant, toddler, child; economic analysis, economic evaluation; cost-benefit; cost-effectiveness and cost-utility. Only papers written in English were considered. This research strategy identified 21 potentially relevant articles.

Papers that evaluated efficiency in both vaccinated children and adults were excluded as were papers that evaluated both inactivated and intranasal influenza vaccine and studies carried out in non-community settings. Reviews and general discussion articles were also excluded. Thirteen articles were thus retained in the final systematic review.[18-30]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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