Epidemiol. Infect. (2002), **128**, 205–211. © 2002 Cambridge University Press
DOI: 10.1017/S0950268801006574 Printed in the United Kingdom

Clinical effectiveness of conventional influenza vaccination in asthmatic children

A. J. SMITS, E. HAK*, W. A. B. STALMAN, G. A. VAN ESSEN, A. W. HOES AND TH. J. M. VERHEIJ

University Medical Center Utrecht, Julius Center for General Practice and Patient Oriented Research, Location Stratenum, P.O. Box 85060, 3508 AB Utrecht, the Netherlands.

(*Accepted 19 October 2001*)

SUMMARY

Influenza immunization rates among young asthmatics remain unsatisfactory due to persistent concern about the impact of influenza and the benefits of the vaccine. We assessed the effectiveness of the conventional inactivated trivalent sub-unit influenza vaccine in reducing acute respiratory disease in asthmatic children. We conducted a two-season retrospective cohort study covering the 1995–6 and 1996–7 influenza outbreaks in 22 computerized primary care practices in the Netherlands. In total, 349 patients aged between 0 and 12 years meeting clinical asthma-criteria were included; 14 children were lost to follow-up in the second season. The occurrence of physician-diagnosed acute respiratory disease episodes including influenza-like illness, pneumonia, bronchitis, bronchiolitis, asthma exacerbation and acute otitis media in vaccinated and unvaccinated children were compared after adjustments for age, prior health care and medication use. The occurrence of acute respiratory disease in unvaccinated children was 28% and 24% in the 1995–6 and 1996–7 season, respectively, and was highest in children under 6 years of age (43%). The overall pooled clinical vaccine effectiveness was 27% (95% confidence interval −7 to 51%, $P = 0{\cdot}11$) after adjustments. A statistically higher vaccine protectiveness of 55% (95% CI 20–75%, $P = 0{\cdot}01$) was observed among asthmatics under 6 years of age compared with −5% in older children (95% CI −81 to 39%). The occurrence of acute respiratory disease among asthmatic children during influenza epidemics is very high, notably in the youngest. Influenza vaccination may reduce morbidity in asthmatic infants and pre-school children. However, larger, preferably experimental, studies are needed to establish the benefits of vaccination, notably in older asthmatic children.

INTRODUCTION

Asthma is one of the commonest chronic conditions in childhood with a prevalence of approximately 7% [1]. An important causal agent in asthma exacerbation is influenza, especially during epidemics [2, 3]. Influenza has a major impact on children's well-being and need for medical treatment [4–6] and predisposes to complications such as pneumonia [7] and acute otitis media [7–10]. Annual influenza vaccination is therefore recommended worldwide for this population at risk [11].

Despite this recommendation, the low costs of the vaccine and the absence of systemic side-effects [2, 12] immunization rates remain low [11]. This seems mainly attributable to both the physician's and patient's doubt about the clinical protectiveness of the vaccine [13, 14]. So far, only indirect protectiveness against serologically proven influenza infection has been demonstrated in children (42–95% relative risk reduction) [8, 15]. Furthermore, few studies have provided evidence of a reduction in acute otitis media

* Author for correspondence.

rates and febrile illness episodes following influenza vaccination [8–10, 15]. The vaccine's clinical protectiveness against acute respiratory disease (including influenza-like illness, pneumonia, bronchitis, bronchiolitis, asthma exacerbation and acute otitis media) in asthmatic children has not been demonstrated [2, 16, 17]. We therefore evaluated, in a primary care-based, two-season study, whether influenza vaccination is effective in reducing the occurrence of acute respiratory disease in asthmatic children. In addition, we assessed whether the impact of influenza-associated morbidity and the effectiveness of influenza vaccination are different in infants and pre-school children as compared with schoolchildren.

METHODS

Design

Our study was designed as a retrospective cohort study. We defined a cohort of young asthmatics originating from a primary care database in 1995. This cohort was followed up during two consecutive years and influenza seasons (1995–6 and 1996–7).

Setting

Twenty-two general practitioners in five primary care centres participated in the study. The practices covered a representative sample of approximately 40 000 patients. Practices are members of the Utrecht University General Practice Network [18] and are situated in urban as well as rural areas in the central part of the Netherlands. All physicians used computerized medical records to register patient contacts. Diagnoses were coded according to the International Classification of Primary Care (ICHPPC-2) and therapeutic agents according to the Anatomical Therapeutic Classification (ATC) [19–21]. All physicians regularly received extensive training in uniform registration of respiratory tract diseases. Anonymous use of patient information for scientific research derived from the database has been approved by the medical ethical committee of the University Medical Center Utrecht.

Subjects

First, a pre-selection of potential study subjects was performed using a 'computerized influenza prevention module' [22]. This module identified patients in high-risk categories for influenza infection on the basis of disease tags, ICPC- and ATC-codes. Potential study subjects were selected by their physicians on the basis of asthma criteria defined in the guidelines of the Dutch College of General Practitioners [23].

These criteria stated that in a patient under 6 years of age (probable) asthma was a clinical diagnosis based on symptoms and signs only. Required criteria were: recurrent episodes of coughing and/or congestion (> 5 times a year, > 10 days an episode) or wheezing associated with a viral infection *and* one of the following:

- improvement of complaints following a bronchodilator or
- indications of allergic stimuli causing airway symptoms or
- constitutional eczema or
- increase of wheezing and/or dyspnoea with age or
- asthma, hay-fever or eczema in a first-degree sibling.

In children aged 6–12 years, the same criteria were required in addition to pulmonary function measurements. Asthma was confirmed when forced expiratory volume or peak flow measurement indicated a reversible bronchial obstruction and/or when day–night variability (amplitude/mean $> 31\%$) was present.

We admitted 370 young asthmatics aged 0–12 years meeting the above-mentioned criteria in November 1995. To ensure current asthma activity, we excluded 21 children that did not contact their physician in the year preceding the inclusion date. Fourteen subjects were lost to follow-up in the second season and consequently excluded in the 1996–7 season

Intervention

Influenza vaccination was offered to patients in accordance with guidelines of the Dutch College of General Practitioners [24]. Annually, the parents of indicated patients received a personal postal invitation. Mass vaccination of children and parents who responded took place each year in the first 2 weeks of November. Children under 6 years of age received another dose 4 weeks after the first, if they had not received a vaccine in prior years. Each year the trivalent sub-unit vaccine was composed of strains recommended by the World Health Organization.

Influenza seasons

Influenza monitoring was performed by the Dutch National Influenza Centre in collaboration with the Dutch Sentinel Practice Network [25, 26]. We defined influenza seasons as the period in which the incidence

of influenza-like-illness reported by the sentinel practices was above 4 per 10000 inhabitants per week. The first season started in week 46 (1995) and ended in week 10 (1996). Peak incidence reached 39 per 10000 inhabitants per week. Most of the circulating viruses were of type influenza A/H3N2/Netherlands/218/95. There was good matching between the vaccine (with A/Johannesburg/33/94 strains) and the predominant influenza strain in this season, and circulating viruses were antigenic similar to those in the preceding two seasons (1992–3 and 1993–4). The second season started in week 48 (1996) and ended in week 11 (1997). Its peak incidence reached 29 per 10000 inhabitants per week. Due to antigenic drift this season's predominant strain (influenza A/Netherlands/172/96 and influenza A/Netherlands/286/97) was substantially different from earlier years, and a smaller type B wave followed. These strains, however, appeared to be well covered by that year's vaccine.

Data collection

All data were extracted anonymously from electronic patient records and classified by a physician (AJS). At the inclusion date general demographic characteristics such as sex, year of birth, region and health insurance were registered. The following prognostic indicators were determined in the 12 months prior to vaccination for every season: number of physician contacts, number of contacts associated with lower airway complaints, number of referrals (paediatrician, pulmonologist or ear, nose and throat-physician), antibiotic prescriptions, use of bronchodilators, antihistamines, cromoglicates, inhalation and oral corticosteroids and atopy. Each year vaccination status was assessed by search in free text and/or ICPC-code R44.1.

Outcome measures

Our combined outcome measure was the occurrence of one or more episodes of acute lower respiratory tract disease defined as physician-diagnosed influenza-like illness, pneumonia, bronchitis, bronchiolitis, asthma exacerbation or acute otitis media during the influenza seasons. All episodes were confirmed in free text and/or by ICPC-codes (R02-R05, R25, R29, R78, R80, R81, R83, R91, R96, R99, or H71). Except for acute otitis media episodes, other upper respiratory tract infections were not included in our primary outcome measure. Only lower respiratory tract infections and acute otitis media have traditionally been shown to be associated with influenza and are most likely to be reduced by vaccination.

Statistical analysis

With EPI-Info, version 6 (CDC, Atlanta, GA, USA) we estimated that a minimal cohort size of 330 children would give us an 80% chance of detecting a reduction of at least 50% [15, 27, 28] in outcome events among recipients of the vaccine. We assumed for this calculation an immunization rate of 45%, an event rate of 25% in unvaccinated persons and a two-sided alfa level of 5%. Statistical analysis was performed using SPSS for Windows, version 8.0 (SPSS Inc., Chicago, IL, USA). We dichotomized age into less than 6 and 6 years or older. This cut-off was chosen because of differences in clinical diagnosis of asthma and hypothesized differences in risk for complications of influenza between age groups. All analyses were performed for the two influenza seasons separately and for both seasons combined.

Uni- and multivariable logistic regression modelling was used to obtain crude and adjusted odds ratios and their 95% confidence intervals (CI) of vaccine effectiveness. In the first stage of constructing the multivariate model we defined vaccination status as the exposure term and acute respiratory disease as the dependent variable. We then added each potentially confounding variable independently to the model to assess its effect on the estimated vaccine effectiveness. In the final model we only included those variables that materially altered the effect estimate of influenza vaccine exposure. This model was used to obtain adjusted odds ratios in the complete cohort as well as in subgroups. Effect modification by age category and season was statistically tested by adding this variable and its first-order interaction term to the final model. We used the adjusted odds ratios as an approximation of the relative risk and calculated the adjusted effectiveness as follows: $(1-\text{adjusted odds ratio}) \times 100\%$. We used mixed effects regression modelling with MIXOR, version 2 (D Hedeker, RD Gibbons, IL, Chicago, USA) to take into account a possible child effect in the pooled analysis [29]. Point estimates and standard errors did not change substantially compared with the conventional logistic regression modelling.

RESULTS

Vaccination rates increased from 41% in the first season to 45% in the second (Table 1). Vaccinees were

Table 1. *Seasonal baseline characteristics**

Characteristic	1995/6 season ($n = 349$)		1996/7 season ($n = 335$)		Both seasons ($n = 684$)	
	Vaccinated ($n = 144$)	Not vaccinated ($n = 205$)	Vaccinated ($n = 149$)	Not vaccinated ($n = 186$)	Vaccinated ($n = 293$)	Not vaccinated ($n = 391$)
Male sex	55	66	54	69	55	67
Age (years) mean (S.D.)	6·6 (3·1)	6·0 (3·3)	7·7 (3·1)	7·0 (3·2)	7·1 (3·1)	6·5 (3·3)
Number of GP visits, mean (S.D.)	7·1 (5·9)	6·1 (4·9)	6·5 (5·0)	4·2 (4·2)	6·8 (5·4)	5·2 (4·6)
Number of specialist visits, mean (S.D.)	0·3 (0·7)	0·2 (0·4)	0·3 (0·6)	0·1 (0·5)	0·3 (0·6)	0·2 (0·5)
Pulmonary medication use	84	76	77	56	80	67
Oral prednisone use	5	1	3	3	4	2

* Data are presented as percentages except where noted otherwise.

Table 2. *Attack rates of acute respiratory disease, crude and adjusted effectiveness by season and age category*

	Attack rate in non-vaccinees No. (%)	Attack rate in vaccinees No. (%)	Crude effectiveness % (95% CI)	Adjusted effectiveness* % (95% CI)	*P*-value
Both seasons					
All children	102 (26·1)	63 (21·5)	22 (−11, 46)	27 (−7, 51)	0·11
0 to 5 years	68 (43·3)	28 (28·6)	48 (10, 70)	55 (20, 75)	0·01
Not vaccinated: 157					
Vaccinated: 98					
6 to 13 years	34 (14·5)	35 (17·9)	−29 (−115, 23)	−5 (−81, 39)	0·85
Not vaccinated: 234					
Vaccinated: 195					
1995/6 season					
All children	57 (27·8)	40 (27·8)	0 (−61, 38)	−1 (−68, 39)	0·97
0 to 5 years	41 (43·6)	21 (36·2)	27 (−44, 63)	32 (−39, 67)	0·29
Not vaccinated: 94					
Vaccinated: 58					
6 to 13 years	16 (14·4)	19 (22·1)	−68 (−251, 19)	−52 (−225, 29)	0·28
Not vaccinated: 111					
Vaccinated: 86					
1996/7 season					
All children	45 (24·2)	23 (15·4)	43 (0, 77)	56 (18, 76)	0·01
0 to 5 years	27 (42·9)	7 (17·5)	72 (26, 89)	77 (35, 92)	0·01
Not vaccinated: 63					
Vaccinated: 40					
6 to 13 years	18 (14·6)	16 (14·7)	0 (−108, 52)	31 (−54, 69)	0·37
Not vaccinated: 123					
Vaccinated: 109					

* Adjusted effectiveness = (1 − adjusted OR) × 100%.

more likely to be girls, older, have a higher medical consumption (in primary as well as in secondary care) and use more pulmonary medication (any of four types) and prednisone than non-vaccinees. The mean age of the subgroup of children under 6 years was 3·2 (standard deviation [SD] 1·4) in season one and 3·5 (SD 1·1) years in season two. Corresponding figures for the older children were 8·6 (SD 1·9) and 9·0 (SD 1·9) years. Attack rates of acute respiratory disease in non-vaccinees, were 28% in the 1995–6 and 24% in the 1996–7 season, respectively, and 26% overall (Table 2). Acute respiratory disease was much more common among unvaccinated children under 6 years (43%) than among those 6 years or older (15%).

In multivariate modelling the child's age, number of physician contacts, number of referrals, use of

pulmonary medication and use of oral prednisone in the year preceding baseline confounded the association between vaccination status and the outcome and were therefore included in the final model. Although the point estimates of vaccine effectiveness differed substantially among the two seasons, differences were not statistically significant ($P > 0{\cdot}10$). Overall, the influenza vaccination was associated with a 27% reduction in the occurrence of acute respiratory disease (95% CI −7 to 51%, $P = 0{\cdot}11$, Table 2). We recorded a statistically significant reduction of acute respiratory disease of 56% (95% CI 18 to 76%, $P = 0{\cdot}01$) in the 1996–7 season only.

Overall, a statistically significant higher protectiveness ($P = 0{\cdot}02$ for interaction) was observed in children less than 6 years of age (55%, 95% CI 20 to 75%, $P = 0{\cdot}01$) than in older children (−5%, 95% CI −81 to 39%, $P = 0{\cdot}85$). In children under 6 years of age, the vaccine was associated with a 32% reduction (95% CI −39% to 67%) in the outcome in the 1995–96 season and a 77% (95% CI 35 to 92%) reduction of outcomes in the 1996–7 season.

DISCUSSION

Our study demonstrates that children with asthma experience significant respiratory morbidity during influenza epidemics. Almost a quarter of these children visited the primary care physician during the influenza epidemics. Importantly, such morbidity occurred in 4 out of 10 infants and pre-school children with asthma. Our data further suggest that the conventional influenza vaccine substantially reduced the occurrence of acute respiratory disease in this young high-risk group during the second influenza epidemic. Age seems therefore more important than the certainty or severity of the asthma-diagnosis.

To appreciate these findings, some potential limitations of our study need to be addressed. The size of the cohort was large enough to demonstrate an expected 50% reduction of outcomes resulting from the vaccine based on earlier observations. Sugaya et al. [15], for example, recorded a 49% reduction in febrile episodes in vaccinated asthmatic children aged 2–14 years, Khan et al. [28] demonstrated a vaccine efficacy for preventing school absenteeism due to respiratory illness of 56% in healthy children and Gross et al. [27] recorded a 50% reduction in influenza-related illness among the elderly in a large meta-analysis. In the 1996–7 season we were therefore able to demonstrate a statistically significant vaccine protectiveness of 56% overall and of 77% in the youngest asthmatics. However, vaccine protectiveness seemed less in the first season (1%). Although in that season a protectiveness of 32% was observed in the younger children, overall no protectiveness could be demonstrated mainly due to negative results in the older group (−52%). We believe that the effect estimate and its corresponding large confidence intervals in this older subgroup could at least partly be attributed to a lack of sufficient statistical power since the incidence of outcomes in unvaccinated older children was much lower than expected. Residual immunity resulting from exposure to similar influenza strains in previous seasons might also have led to a decreased contrast between unvaccinated and vaccinated children.

As no statistically significant modification of effectiveness across the two seasons was found and the circulating viruses and the vaccine composition differed substantially in both seasons, we pooled the data to enhance statistical power [30]. In vaccinated infants and pre-school children the occurrence of acute respiratory disease was halved ($P = 0{\cdot}01$), but among the older children no effectiveness was found ($P = 0{\cdot}85$). Despite the fact that the same children were counted twice in these pooled analysis and observations were therefore statistically dependent, results of mixed effect regression modelling were essentially the same.

Another explanation for finding no effect in the older children and a potential underestimation of the vaccine effectiveness in the younger group could have resulted from incomparability of prognosis among comparison groups. In general, vaccinated children had most probably more severe asthma than unvaccinated children and risk of significant respiratory disease resulting from infections is therefore higher in vaccinated children. We have tried to adjust for this so-called 'confounding by indication' by controlling for the various available prognostic indicators in the study design and data analysis [31]. Statistical adjustment led to a substantial increase in the point estimate of the vaccine's protectiveness in the older group. However, confounding by unmeasured factors might also have been responsible for detecting no statistically significant protectiveness.

Studying clinical instead of serological outcomes can lead to non-differential misclassification of outcome values and consequently to an underestimation of the vaccine's effectiveness. This effect has been demonstrated in a recent study by Heikkinen et al.

who reported a 83% reduction of influenza-associated acute otitis media by the vaccine, the reduction of acute otitis media overall being 36% [10, 32]. Obviously, the difference depends upon the influenza-attributable fraction of outcomes. We restricted our outcome measurements to the influenza epidemic periods when influenza viruses are mainly circulating and an important respiratory pathogen [2, 3, 25, 26]. The fact that the incidence rates of acute respiratory disease were reduced by vaccination support the contention that influenza played a major role in these episodes. An advantage of studying clinical instead of serological outcomes is that these data are more relevant from a patient's and physician's point-of-view.

Some might argue that prior influenza vaccination or inadequate dosage of vaccination might have influenced our effectiveness estimates. The information in medical records on vaccination status in 1994 and received number of vaccine doses was, however, incomplete and we could not collect valid data on these issues. We have examined a potential effect modification by prior vaccination status. Most of the vaccinees in 1996 also received the vaccine in 1995 (83%). We could not establish a statistically significant difference in effectiveness as compared with those few subjects who received the vaccine for the first time. This is in agreement with the findings of Beyer et al. who did not observe modified vaccine effectiveness resulting from prior immunization in a large meta-analysis [33].

Our study is unique in that it addressed the clinical effectiveness of influenza vaccination on the reduction of acute respiratory disease in asthmatic children. In a prior study by Sugaya et al. the vaccine provided a 49% reduction of influenza-related febrile illnesses in asthmatic children aged 2–14 years [15], a figure similar to our findings. They found, however, the vaccine to be more effective in children older than 7 years of age, but effect modification by age was not statistically confirmed. In 1974 Bell et al. observed a 66% reduction in hospitalization days due to influenza-like-illness and to influenza-like-illness and asthma, but not due to asthma alone [34]. Although both studies, like ours, included asthmatic children, there are some major differences. Neither study measured the effect of vaccination on acute respiratory disease, nor were they primary care-based, multi-season or did they adjust for potential confounders. So far, only protection against acute otitis media has been suggested in healthy children in three prospective, single-season trials, with an effectiveness of 30–40% [8–10].

In conclusion, the conventional influenza vaccine appears to offer protection against relevant morbidity in asthmatic infants and pre-school children in return for a safe and relatively cheap intervention. Expansion of the indication range to include children with 'probable asthma' and 'recurring airway diseases' under 6 years of age needs to be seriously considered. Larger, preferably experimental, studies are needed to establish whether older asthmatic children benefit from the vaccine as well.

ACKNOWLEDGEMENTS

We thank the physicians of the Utrecht University General Practices Network for their help with this study: Andriesse JA, Asbreuk HAM, Blankestijn JG, Blommestein JG, Bolderink JF, van den Broek MW, Daggelders GJA, de Groot MM, Hendrickx EFHM, Hirsch R, de Jong HHG, Juffermans JMA, Nicolai N, Pieters HM, Rijkens CD, Rutten FH, van der Snoek BE, Stalman WAB, Stoutenbeek IJ, Truijens L, de Wit NJ, van Zijl WLG. Statistical help by Dr J. Faber is gratefully acknowledged.

REFERENCES

1. American Lung Association. Trends in asthma morbidity and mortality. Epidemiology & Statistics Unit, November 1998.
2. Rothbarth PH, Kempen BM, Sprenger MJ. Sense and nonsense of influenza vaccination in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; **151**: 1682–6.
3. McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *J Pediatr* 1973; **82**: 578–90.
4. Neuzil KM, Mellen BG, Wright PF, Mitchel Jr EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; **342**: 225–31.
5. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; **342**: 232–9.
6. McIntosh K, Lieu T. Is it time to give influenza vaccine to healthy infants? *N Engl J Med* 2000; **342**: 275–6.
7. Connolly AM, Salmon RL, Lervy B, Williams DH. What are the complications of influenza and can they be prevented? Experience from the 1989 epidemic of H3N2 influenza A in general practice. *BMJ* 1993; **306**: 1452–4.
8. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent,

intranasal influenzavirus vaccine in children. *N Engl J Med* 1998; **338**: 1405–12.
9. Clements DA, Langdon L, Bland C, Walter E. Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care. *Arch Pediatr Adolesc Med* 1995; **149**: 1113–7.
10. Heikkinen T, Ruuskanen O, Waris M, Ziegler T, Arola M, Halonen P. Influenza vaccination in the prevention of acute otitis media in children. *Am J Dis Child* 1991; **145**: 445–8.
11. Hayden GF, Frayha H, Kattan H, Mogarri I. Structured guidelines for the use of influenza vaccine among children with chronic pulmonary disorders. *Pediatr Infect Dis J* 1995; **14**: 895–9.
12. Swierkosz EM, Newman FK, Anderson EL, Nugent SL, Mills GB, Belshe RB. Multidose, live attenuated, cold-recombinant, trivalent influenza vaccine in infants and young children. *J Infect Dis* 1994; **169**: 1121–4.
13. Meynaar IA, van't Wout JW, Vandenbroucke JP, van Furth R. Use of influenza vaccine in The Netherlands. *BMJ* 1991; **303**: 508.
14. van Essen GA, Kuyvenhoven MM, de Melker RA. Compliance with influenza vaccination. Its relation with epidemiologic and sociopsychological factors. *Arch Fam Med* 1997; **6**: 157–63.
15. Sugaya N, Nerome K, Ishida M, Matsumoto M, Mitamura K, Nirasawa M. Efficacy of inactivated vaccine in preventing antigenically drifted influenza type A and well-matched type B. *JAMA* 1994; **272**: 1122–6.
16. Cates CJ, Jefferson TO, Bara AI. Influenza vaccination in asthma; efficacy and side-effects (Cochrane Review). In: The Cochrane Library 1999; Issue 1: Oxford Update Software.
17. Neijens HJ, Rothbarth PH, Sprenger MJ. Indications for influenza vaccination in children with lung disorders. Dutch Association for Pediatric Medicine. *Ned Tijdschr Geneeskd* 1997; **141**: 2213–7.
18. Stalman WAB. The Utrecht network of general practitioners. In: *Management of sinusitis-like complaints in general practice* [dissertation]. Utrecht: Drukkerij Elinkwijk BV, 1997: 45–53.
19. Classification committee of WONCA. *ICHPPC-2 defined. International classification of health problems in primary care*. Oxford: Oxford University Press, 1983.
20. Lamberts H, Wood M. *ICPC, International classification of primary care*. Oxford: Oxford University Press, 1987.
21. WHO Collaborating Centre for Drug Statistics Methodology. *Anatomical Therapeutic Chemical (ATC) classification index*. Oslo, 1996.
22. Hak E, Hermens RP, van Essen GA, Kuyvenhoven MM, de Melker RA. Population-based prevention of influenza in Dutch general practice. *Br J Gen Pract* 1997; **47**: 363–6.
23. Dirksen WJ, Geijer RMM, Haan MD, Koning GD, Flikweert S, Kolnaar BGM. NHG guidelines Asthma in children. *Huisarts Wet* 1998; **41**: 130–43.
24. Van Essen GA, Sorgedrager YCG, Salemink GW, Govaert ThME, Van den Hoogen JPH, Van der Laan JR. NHG guidelines influenza and influenza vaccination. *Huisarts Wet* 1993; **36**: 342–6.
25. Claas EC, de Jong JC, Bartelds AI, Rimmelzwaan GF, van Wijngaarden JK, Osterhaus AD. Influenza in the 1995/'96 season; vaccine composition for the 1996/'97 season. *Ned Tijdschr Geneeskd* 1996; **140**: 2047–50.
26. Rimmelzwaan GF, de Jong JC, Bartelds AI, Claas EC, van Wijngaarden JK, Osterhaus AD. Influenza in the 1996/'97 season; vaccine composition for the 1997/'98 season. *Ned Tijdschr Geneeskd* 1997; **141**: 1743–7.
27. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly people. A meta-analysis and review of the literature. *Ann Intern Med* 1995; **123**: 518–27.
28. Khan AS, Polezhaev F, Vasiljeva R, et al. Comparison of US inactivated split-virus and Russian live attenuated, cold adapted trivalent influenza vaccines in Russian schoolchildren. *J Infect Dis* 1996; **173**: 453–6.
29. Braun H, Prescott R. Applied mixed models in medicine. New York: John Wiley and Sons, 1999: 360.
30. 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.
31. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. *BMJ* 1997; **315**: 1151–4.
32. Weller SC, Mann NC. Influenza vaccination and acute otitis media in children. *Am J Dis Child* 1992; **146**: 1018–9.
33. Beyer WE, De Bruijn IA, Palache AM, Westendorp RG, Osterhaus AD. Protection against influenza after annually repeated vaccination: a meta-analysis of serologic and field studies. *Arch Intern Med* 1999; **159**: 182–8.
34. Bell TD, Chai H, Berlow B, Daniels G. Immunization with killed influenza virus in children with chronic asthma. *Chest* 1978; **73**: 140–5.