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The effect of smoking on influenza, influenza vaccination efficacy and on the antibody response to influenza vaccination

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Abstract

We examined the relation between cigarette smoking and (1) the occurrence of influenza, (2) the efficacy of influenza vaccination and (3) the antibody response to influenza vaccination in fifteen family practices in South-Limburg, the Netherlands, during the influenza season 1991–1992. Data were used from a randomized double-blind placebo-controlled trial into the efficacy of influenza vaccination in which smoking status was measured 10 weeks after the start of the trial. A total of 1838 subjects aged 60 years or older, of whom 1531 subjects (321 smokers, 1152 non-smokers and 58 cigar/pipe smokers) who returned the smoking questionnaire and were not previously vaccinated, were used in the analyses. The main outcome measures were serological influenza (fourfold increase of antibody titre between 3 weeks and 5 months after vaccination); clinical influenza as determined by criteria of the Dutch Sentinel Stations from self reported symptoms in postal questionnaires 10 weeks and 5 months after vaccination; increases after vaccination and decreases after 5 months in logarithmic titres of antibody against the vaccine strains. No relation between smoking and either serological or clinical influenza was found, although the risk for serological influenza was slightly (not significantly) elevated in smokers compared to non-smokers. A statistical interaction was found between smoking and vaccination when serological influenza was the outcome measure indicating that the efficacy of vaccination was greater in smokers than in non-smokers (comparison of model with and without interaction; likelihood ratio test, $p < 0.0001$). This finding is supported by a greater titre rise 3 weeks after vaccination for two out of four strains, but not by the antibody response after vaccination in previous studies on influenza and other infectious diseases. Also, this possible difference of immunogenicity is not reflected in a better protection for clinical influenza. The rise in antibody titre 3 weeks after vaccination was higher in smokers for A/Singapore/6/86 and B/Beijing/11/87, but not for the other two strains. Decline in titres after 5 months was similar for smokers and non-smokers. We conclude that smoking has no clinical or preventive significance for risk of influenza in the elderly. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Smoking; Influenza; Vaccination; Antibody response; Randomized controlled trial

1. Introduction

Some studies found smokers to be more susceptible to influenza compared to non-smokers [1–3]. These studies were held among healthy young men [1, 2] and among a general population with a mean age of 44 years [3, 4]. Since 95% of the deaths due to influenza occur among people aged 60 years and older [5], we focused on the effect of smoking on influenza and on the efficacy of influenza vaccination in this age group.

Morbidity after influenza vaccination in the elderly was significantly reduced in cohort studies and in a randomized controlled trial [6, 7]. It is unknown if smoking in this group influences the efficacy of influenza vaccination.

The antibody response that follows immunization with influenza vaccine is similar in smokers and non-smokers during the first three months [8], but shows a greater decline in antibody titres after one year in smokers [3, 9]. The impaired persistence of serum antibody in smokers after immunization with influenza vaccine could influence the efficacy of the vaccine in preventing influenza.

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The objective of this study is to examine the relation between cigarette smoking and (1) the occurrence of influenza, (2) the efficacy of influenza vaccination and (3) the antibody response to influenza vaccination. The data for this study were derived from a randomized double-blind placebo-controlled trial evaluating the efficacy of influenza vaccination in elderly individuals [7]. We analyzed the effect of smoking on influenza risk, the effect of smoking on vaccine efficacy with clinical as well as serological outcomes and the effect of smoking on the antibody response to vaccination after 3 weeks (rate of increase) and 5 months (rate of decline).

2. Methods

2.1. Patients

In the winter of 1991–1992 a randomized clinical trial of the efficacy of influenza vaccination in the elderly was conducted, involving 31 general practitioners in 15 practices in South-Limburg, the Netherlands. Persons aged 60 or more were invited to participate if they did not belong to those high-risk groups in which vaccination was recommended (in the Netherlands age was no criterion for recommendation at that time) [10]. A total of 1838 patients agreed to participate. This group contained 490 patients with heart conditions, lung conditions, or diabetes mellitus who were not considered to belong to the high-risk groups by their general practitioner. The analysis was restricted to subjects not previously vaccinated. Details about the recruiting of patients have been described previously [7].

The protocol was approved by the medical ethics committee of the University of Limburg and the University Hospital, Maastricht, the Netherlands. Informed consent was obtained and forms were signed by all participants.

2.2. Vaccination and blood samples

The research period covered five months (November 1991 until April 1992). Patients were vaccinated with 0.5 ml of purified split-virion vaccine ($n = 927$, A/Singapore/6/86 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90 and B/Beijing/1/87 (each strain with 15 μg of hemagglutinin)) or intramuscular placebo ($n = 911$, physiological saline solution) according to a randomization protocol. Between November 1 and 15, 1991, 9 ml of venous blood was taken from all participants (pre-titre) before vaccine or placebo was injected. Three weeks later a second blood sample was taken (post-titre). At the end of the follow up, 5 months

after vaccination, a final blood sample was taken (end-titre).

A total of 223 patients indicated to have been vaccinated previously in 1989 and/or 1990.

2.3. Smoking status

A questionnaire on smoking habits was sent to all participants 10 weeks after the start of the investigation. A total of 1756 subjects (96%) returned this questionnaire.

The information gathered about smoking status comprised current smoking status, past smoking status, smoking of cigars, pipe or cigarettes and the amount of cigarettes smoked every day (1–9 per day, 10–19 per day, 20+ per day). Never-smokers and ex-smokers were grouped as *non-smokers*, cigarette smokers as *smokers*, leaving a *rest* group. The rest group consisted of pipe and cigar smokers who did not smoke cigarettes currently or previously.

2.4. Antibody response and serological influenza

The antibody titres to the influenza strains in the vaccine were measured by means of the hemagglutinin inhibition test. The titres were expressed as the reciprocal values of dilution, of which 50% of hemagglutinin inhibition occurred after addition of 3 hemagglutinating units of antigen. Titres less than 9 were arbitrarily set to 5. The mean logarithmic titre value for the sera was calculated from the serum levels to ensure a normally distributed range of titre values used in the statistical analyses. The serum levels were independently measured by two analysts. This was done for all sera from all samples for each individual strain. Differences in logarithmic titres were calculated for smokers compared to non-smokers. Increases in logarithmic titre values were calculated from pre-titre to post-titre and post-titre to end-titre.

A titre of 38 or greater and a fourfold titre increase in end-titre relative to post-titre were taken as the criteria of serological influenza infection [11].

2.5. Clinical influenza

A questionnaire regarding possible influenza episodes and symptoms was sent to all participants 10 and 23 weeks after vaccination. Three criteria were used to diagnose clinical influenza: influenza according to the family physician, Dutch Sentinel Stations, and the International Classification of Health Problems in Primary Care (ICHPPC-2-defined). ICHPPC-2 defined influenza is the least rigid criterion and may cause a false-positive diagnosis of influenza for many patients [7]. Influenza according to the family physician could only be diagnosed if patients consulted the

physician during the follow-up period, possibly missing patients with influenza not visiting their physician. Criteria to diagnose clinical influenza were therefore restricted to criteria of the Dutch Sentinel Stations in this analysis.

These criteria include an acute onset of symptoms, fever of at least 38°C measured rectally and at least one of the following symptoms: coughing, coryza, sore throat, frontal headache, retrosternal pain or myalgia [12].

2.6. Control variables

A series of control variables was available to see if alternative explanations might exist for the relations of interest. These variables were age, sex, risk group, protective titre before vaccination and current vaccination status. Risk groups were categorized as heart conditions, lung conditions, diabetes mellitus and a group not having those conditions. A titre of 100 or greater for A strains and 200 or greater for B strains was considered to be a protective titre [13].

2.7. Statistical analysis

The group used for analysis consisted of 1756 – 225 (previously vaccinated) = 1531 subjects. In testing a possible relation between smoking and influenza stratification by current vaccination status was applied. Data were analyzed separately for the vaccine and the placebo group. The relation between smoking and influenza and the efficacy of vaccination in smokers and non-smokers was analyzed, using the odds ratio and the risk difference. Confidence limits for the risk difference were calculated using the formula for cumulative incidence data described by Rothman [14]. Logistic regression was used to correct for age, sex and risk group in the relation between smoking and influenza and for age, sex, risk group and protective titre before vaccination in the analyses of vaccination efficacy in the two smoking groups. A trend in the incidence of influenza over the smoking categories, non-smoker, 1–9 a day (light smoker), 10–19 a day (moderate smoker) and 20 or more a day (heavy smoker), was evaluated using regression analysis with controlling for age, sex and risk group.

The difference in vaccine efficacy between smokers and non-smokers was tested in a logistic regression analysis by evaluating interaction between vaccination and smoking, controlling for age, sex, risk group. This was done using the likelihood ratio test as described by Kleinbaum [15].

Antibody response was expressed as the mean change of the individual titre after vaccination (post-titre–pre-titre) and as the decline after 5 months (end-titre–post-titre). In analyzing the decline after 5

months subjects who had serological influenza (4 fold titre increase) were excluded. Differences in increases and declines between smokers and non-smokers were tested by *t*-test for independent groups and ANOVA for each strain controlling for age, sex and risk group.

3. Results

Table 1 shows the characteristics of the study subjects, which consisted of 321 smokers, 1152 non-smokers and 58 pipe and/or cigar smokers (rest). The smokers and non-smokers groups were similar with regard to current vaccination status, risk group and protective titre before vaccination. Younger subjects and male subjects were overrepresented among smokers. Serological data were incomplete for 31 participants in the trial population. Subjects with incomplete samples were retained in the analyses whenever possible.

Table 2 shows the effect of smoking on serological and clinical influenza in previously unvaccinated subjects and categorized by current vaccination status. No statistical significant differences were found. In the placebo group, a higher rate of serological influenza was found in smokers compared to non-smokers. However this difference was not statistically significant and was not confirmed in the vaccine group (even the reverse was true). The rate of clinical influenza did not differ for smokers compared to non-smokers.

The relation between smoking and influenza was further analyzed by using a classification of non-smokers, light smokers (1–9 cigarettes per day), moderate smokers (10–19 per day) and heavy smokers (20 or more per day). The rate of serological influenza in the vaccine group was 6% in non-smokers, 3% in light smokers, 3% in moderate smokers and 0% in heavy smokers (trend $p = 0.10$). In the placebo group serological influenza increased from 9% in non-smokers to 11% in light smokers, 13% in moderate smokers and 15% in heavy smokers (trend $p = 0.13$). No trends were found for clinical influenza.

Table 3 shows the efficacy of vaccination in smokers and in non-smokers. The data do not confirm the hypothesis that smoking attenuates vaccine efficacy. Rather the reverse was true when serological influenza was the outcome measure. Vaccinated smokers were more protected against serological influenza (corrected OR = 0.17) than were vaccinated non-smokers (corrected OR = 0.71). This difference in efficacy between smokers and non-smokers was statistically significant (likelihood ratio test $p < 0.0001$; corrected for age, sex and risk group). When clinical influenza was the outcome measure no difference in efficacy of vaccination was found between smokers and non-smokers

Table 1
Characteristics of the study subjects ($n = 1531$)

Subgroup	Smoker ($n = 321$)		Nonsmoker ($n = 1152$)		Rest ($n = 58$)		Total ($n = 1531$)
	n	%	n	%	n	%	n
Current vaccination status							
Vaccine	153	47.7	590	51.2	28	48.3	771
Placebo	168	52.3	562	48.8	30	51.7	760
Sex							
Male	194	60.4	476	41.3	53	91.4	723
Female	127	39.6	676	58.7	5	8.6	808
Age							
60–64	170	53.0	482	41.8	16	27.6	668
65–69	100	31.1	326	28.3	19	32.7	445
70–74	42	13.1	231	20.0	11	19.0	284
75–79	9	2.8	71	6.2	8	13.8	88
80–84	0	0.0	31	2.7	3	5.2	34
85–91	0	0.0	11	1.0	1	1.7	12
Diagnosis							
Heart	37	11.5	156	13.5	13	22.4	206
Lung	44	13.7	87	7.6	5	8.6	136
Diabetes mellitus	6	1.9	22	1.9	1	1.7	29
Rest	234	72.9	887	77.0	39	67.3	1160
Number with protective titre at pre-titre against ^a							
A/Singapore/6/86 (H1N1)	3	0.9	6	0.5	2	3.4	11
A/Beijing/353/89 (H3N2)	6	3.3	11	1.0	1	1.7	18
B/Panama/45/90	17	5.3	39	3.4	2	3.4	58
B/Beijing/11/87	23	7.2	71	6.2	3	5.2	97

^a Combinations do not add up to n because subjects without a protective titre are not given.

(likelihood ratio test $p = 0.46$; corrected for age, sex and risk group).

Table 4 shows the mean logarithmic titre change, from pre-titre to post-titre and from post-titre to end-titre, in the vaccine group for smokers compared with non-smokers. No great differences were found in pre-titres for smokers compared to non-smokers (adjusted for age, sex and risk group). The rise in titre after vaccination was statistically significantly higher in smokers for A/Singapore/6/86 and B/Beijing/11/87, but not for A/Beijing/353/89 and B/Panama/45/90. For all strains the post to end-titre decline was marginally higher in smokers. The end-titre was still slightly higher in smokers compared to non-smokers for B/Panama/45/90 and B/Beijing/11/87 and statistically significantly higher for A/Singapore/6/86 ($P = 0.04$, adjusted for age, sex and risk group).

4. Discussion

In this study smokers did not have a greater incidence of serological or clinical influenza compared to non-smokers. Odds ratios for smoking and serological influenza were estimated from the serological data

depicted in the studies of Finklea et al. [1], Kark et al. [2], and MacKenzie et al. [3]. These ORs were 1.3, 1.4 and 1.9, respectively, and are comparable to the odds ratio of 1.61 found in our study in the group receiving no real vaccination (placebo group). These results are consistent with the idea that the OR for the relation between smoking and influenza is somewhere between 1 and 2, indicating that the effect is small. In our study no trend among the different smoking categories was found with serological or clinical influenza as outcome variables. Smoking had no effect on clinical influenza in our study. However, Finklea et al. and Kark et al. did find a relationship between smoking and clinical influenza (odds ratios of about 1.5, $p < 0.05$ and 2.42, $p < 0.0001$ respectively).

An effect of smoking on influenza would be more plausible if smoking influences the susceptibility to other viral infections as well. Cohen et al. found that smokers were at greater risk for getting common colds than non-smokers [16]. Smokers were more likely both to develop infection with rhinoviruses, respiratory syncytial virus, and coronavirus (OR = 2.23; 95% CI = 1.03, 4.82) and to develop illness following infection with these viruses (OR = 1.83; 95% CI = 1.00, 3.36). In their review on cigarette smoking

Table 2

The effect of smoking on the incidence rate of influenza in people not previously vaccinated and stratified according to current vaccination status (rate as %)

Influenza according to	Vaccine or placebo	Number of people (rate)		Influenza in smokers compared to non-smokers		
		smoker (<i>n</i> = 321) ^a	non-smoker (<i>n</i> = 1152) ^b	rate difference (95% CI) ^{c,d}	odds ratio (95% CI) ^{c,e}	logistic regression odds ratio (95% CI) ^{c,f}
Serology	vaccine	4/151 (3%)	34/578 (6%)	–3% (–6%–2%)	0.44 (0.15–1.25)	0.51 (0.18–1.50)
	placebo	21/166 (13%)	44/552 (8%)	5% (–1%–11%)	1.67 (0.96–2.90)	1.61 (0.91–2.83)
Sentinel stations	vaccine	8/153 (5%)	37/590 (6%)	–1% (–5%–3%)	0.82 (0.38–1.80)	0.89 (0.39–2.00)
	placebo	16/168 (10%)	57/562 (10%)	0% (–5%–5%)	0.93 (0.52–1.67)	0.96 (0.53–1.75)

^a Includes 4 missing values for serological influenza.

^b Includes 22 missing values for serological influenza.

^c CI indicates confidence interval.

^d According to Ref [14].

^e Not corrected for covariables.

^f Corrected for age, sex and risk group, but not for protective titre before vaccination (possible intermediate factor).

and respiratory tract infection Marcy et al. showed that healthy smokers have a higher frequency of respiratory infections and an increased severity of symptoms when infected [17]. To summarize, studies on non-influenza respiratory infections consistently show smokers to be at an increased risk.

Vaccination of smokers against influenza was serologically more efficacious compared to non-smokers in our study (see Table 3). As this was not expected and no other studies investigated the efficacy of influenza vaccination in smokers and non-smokers, we sought support for this finding in the antibody response after vaccination. A greater titre rise due to vaccination was observed in smokers compared to non-smokers for two out of four strains 3 weeks after vaccination. A greater antibody response was also found by Finklea et al. [9]. In their study pre-vaccination titres (that were lower for smokers than non-smokers) leveled up after vaccination. A possible explanation is that smokers develop a better immunological protection after

vaccination, resulting in a lower incidence of serological influenza compared to non-smokers. The clinical relevance of this finding appears to be low, because no difference in efficacy of vaccination was found for clinical influenza between smokers and non-smokers in our study. Also, MacKenzie et al. and Knowles et al. found no greater antibody response in smokers compared to non-smokers after vaccination with influenza vaccine [3, 8]. Instead, hepatitis B vaccination has been shown to be less immunogenic in smokers versus non-smokers in several studies [18–20]. For example, for subjects receiving hepatitis B vaccine at 0, 1 and 6 months (standard schedule) it was found that vaccinated smokers had lower antibody levels than non-smokers after 3, 7 and 13 months [18]. In summary, the tendency for smokers to have a higher antibody response than non-smokers found in our study is not found in other studies on influenza vaccination (except Finklea et al.) and hepatitis B vaccination. The greater protection against serological influenza in smokers

Table 3

The efficacy of vaccination in smoker and non-smoker for people not previously vaccinated (rate as %)

Influenza according to	Smoker or non-smoker	Number of people (rate)		Influenza, vaccine compared to placebo		
		vaccine (<i>n</i> = 743) ^a	placebo (<i>n</i> = 730) ^b	rate difference (95% CI) ^{c,d}	odds ratio (95% CI) ^{c,e}	logistic regression odds ratio (95% CI) ^{c,f}
Serology	smoker	4/151 (3%)	21/166 (13%)	–10% (–16%––4%)	0.19 (0.06–0.56)	0.17 (0.06–0.52) ^g
	non-smoker	34/578 (6%)	44/552 (8%)	–2% (–5%–1%)	0.72 (0.45–1.15)	0.71 (0.45–1.14) ^g
Sentinel stations	smoker	8/153 (5%)	16/168 (9%)	–4% (–10%–2%)	0.52 (0.22–1.26)	0.54 (0.22–1.33)
	non-smoker	37/590 (6%)	57/562 (10%)	–4% (–7%––1%)	0.59 (0.39–0.91)	0.58 (0.38–0.90)

^a Includes 14 missing values for serological influenza.

^b Includes 12 missing values for serological influenza.

^c CI indicates confidence interval.

^d According to Ref. [14].

^e Not corrected for covariables.

^f Corrected for age, sex, risk group and protective titre before vaccination.

^g Difference in efficacy between smoker and non-smoker was significant (likelihood ratio = 11.81; *p* < 0.005; corrected for age, sex and risk group).

Table 4
Mean logarithmic titre changes in the vaccine group for smoker compared with non-smoker

Strain	Smoking category	Pre-titre	Post-titre	Mean titre change	Difference in mean titre change (95% CI) ^a	Adjusted difference in mean titre change (95% CI) ^{a,b}
Change post-titre–pre-titre (151 smokers, 580 non-smokers)						
AS	smoker	0.80	1.92	+ 1.12	0.20 (0.07–0.34)	0.18 (0.04–0.32)
	non-smoker	0.78	1.70	+ 0.92		
AB	smoker	0.88	2.31	+ 1.43	0.03 (–0.11–0.17)	0.05 (–0.09–0.20)
	non-smoker	0.86	2.26	+ 1.40		
BP	smoker	1.25	2.57	+ 1.32	0.02 (–0.08–0.13)	0.03 (–0.07–0.14)
	non-smoker	1.16	2.46	+ 1.30		
BB	smoker	1.19	2.54	+ 1.35	0.12 (0.02–0.23)	0.12 (0.00–0.25)
	non-smoker	1.19	2.42	+ 1.23		
Change end-titre–post-titre (146 smokers, 544 non-smokers) ^c						
AS	smoker	1.96	1.70	–0.26	–0.04 (–0.10–0.02)	–0.05 (–0.11–0.01)
	non-smoker	1.72	1.50	–0.22		
AB	smoker	2.35	1.98	–0.37	–0.05 (–0.11–0.00)	–0.05 (–0.11–0.01)
	non-smoker	2.31	1.99	–0.32		
BP	smoker	2.57	2.36	–0.21	–0.02 (–0.06–0.03)	–0.02 (–0.07–0.03)
	non-smoker	2.47	2.28	–0.19		
BB	smoker	2.53	2.23	–0.30	–0.03 (–0.08–0.02)	–0.05 (–0.10–0.00)
	non-smoker	2.42	2.15	–0.27		

AS, A/Singapore/6/86 (H1N1); AB, A/Beijing/353/89 (H3N2); BP, B/Panama/45/90; BB, B/Beijing/11/87.

Geometric mean titre (GMT) = $10^{\log \text{titre}}$; change(GMT) = $10^{\log \text{changevalue}} \times 10^{\log \text{prevalue}} - 10^{\log \text{prevalue}}$.

^a CI indicates confidence interval.

^b Corrected for age, sex and risk group, but not for protective titre before vaccination (possible intermediate factor).

^c Subjects with serological influenza were excluded (= a titre at end-titre ≥ 4 times the titre at post-titre) causing a small difference to occur in the post-titre used in post-titre–pre-titre compared to the post-titre used in end-titre–post-titre.

compared to non-smokers found in our study is therefore hardly supported by other immunological data.

In our study the decline in titres 5 months after vaccination was similar for smokers and non-smokers, which is consistent with the finding of Knowles et al. after a 3 month follow-up [8]. However, MacKenzie et al. and Finklea et al. found a depressed persistence of hemagglutination-inhibiting antibody after 1 year in smokers compared to non-smokers [3, 9]. This raises the question if a depressed antibody titre in smokers compared to non-smokers after vaccination manifests itself only after several months. However, this question can not be decided with our data that covers a period of 5 months.

It is important to consider potential limitations regarding the internal validity of the design. A possible bias is that the measurement of the smoking status could be influenced by the outcome of clinical influenza, because smoking status was measured 10 weeks after the start of the investigation. However, the hypotheses about smoking were not known to the

patients during the data collection, making it unlikely that patients tried to report their smoking status differently in order to please the investigators or to try and explain why they got influenza. Selection biases are unlikely to occur because the data used in this study resulted from a randomized clinical trial. Beyer et al., Palache, Gross et al. and Poirier et al. pointed out some shortcomings in the research on influenza vaccination [6, 21–23]. In many studies on the efficacy of vaccination pre-vaccination titres, previous vaccination status, age, gender and the health status were not taken into account. In our study previously vaccinated patients were excluded, no differences were found in pre-titres for smokers and non-smokers and corrections were made for age, gender and health status. Also vaccine doses are relevant for the interpretation of the results [23]. These vaccine doses were the same for all subjects. The influenza activity in the influenza season 1991–1992 in the Netherlands was dominated by the strains A/Singapore/6/86 (H1N1) and A/Beijing/353/89 (H3N2) and therefore matched

at least two of the strains used in the vaccine for that season [24]. In summary, no real threats to the validity of our results are found.

No strong effects were found in this study. A slightly elevated, but not significant, risk for serological influenza in the placebo group was found in smokers compared to non-smokers. This was consistent with previous studies, but did not result in a clinical difference. Smokers were better protected than non-smokers against serological influenza after vaccination and titre rise due to vaccination was higher in smokers than non-smokers for some (but not all) strains. However, little support for this finding was found in the antibody response after vaccination in previous studies on influenza or other infectious diseases. Finally, smokers did not have a lower immune titre 5 months after vaccination compared to non-smokers. We conclude that smoking may enhance the immunological response to vaccination in smokers, resulting in a higher protection against serological influenza in smokers compared to non-smokers. Nevertheless, we found no clinically significant effect of smoking on risk of influenza and vaccine efficacy.

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