

The Efficacy of Influenza Vaccination in Elderly Individuals

A Randomized Double-blind Placebo-Controlled Trial

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Objective.—To determine the efficacy of influenza vaccination in elderly people.

Design.—Randomized double-blind placebo-controlled trial.

Setting.—Fifteen family practices in the Netherlands during influenza season 1991-1992.

Participants.—A total of 1838 subjects aged 60 years or older, not known as belonging to those high-risk groups in which vaccination was previously given.

Intervention.—Purified split-virion vaccine containing A/Singapore/6/86(H1N1), A/Beijing/353/89(H3N2), B/Beijing/1/87, and B/Panama/45/90 (n=927) or intramuscular placebo containing physiological saline solution (n=911).

Main Outcome Measures.—Patients presenting with influenzalike illness up to 5 months after vaccination; self-reported influenza in postal questionnaires 10 weeks and 5 months after vaccination; serological influenza (fourfold increase of antibody titer between 3 weeks and 5 months after vaccination).

Results.—The incidence of serological influenza was 4% in the vaccine group and 9% in the placebo group (relative risk [RR], 0.50; 95% confidence interval [CI], 0.35 to 0.61). The incidences of clinical influenza were 2% and 3%, respectively (RR, 0.53; 95% CI, 0.39 to 0.73). The effect was strongest for the combination of serological and clinical influenza (RR, 0.42; 95% CI, 0.23 to 0.74). The effect was less pronounced for self-reported influenza.

Conclusion.—In the elderly, influenza vaccination may halve the incidence of serological and clinical influenza (in periods of antigenic drift).

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BASED on studies among young healthy volunteers, influenza vaccination appears to have a protective effect of 40% to 70%.¹⁻³ Since 95% of the deaths due to influenza occur among people aged 60 years and older, it is important to know the efficacy of vaccination among the

elderly.⁴ Several studies have suggested that vaccination of elderly people results in a decrease in complication rate (up to 72%) and mortality (up to 87%).⁵⁻⁸ However, these studies were primarily retrospective. Only a few prospective studies have been performed among the elderly⁹⁻¹²; none were randomized and blinded.

For editorial comment see p 1700.

We conducted a randomized double-blind placebo-controlled trial of the efficacy of influenza vaccination in elderly individuals, using both clinical and serological outcome parameters.

METHODS

Patients

The study was conducted in the winter of 1991-1992 and involved 34 family physicians in 15 practices in the southern region of the Netherlands. All persons aged 60 years or older (n=9907), not known as belonging to those high-risk groups in which vaccination had previously been given, were invited to enter the trial.

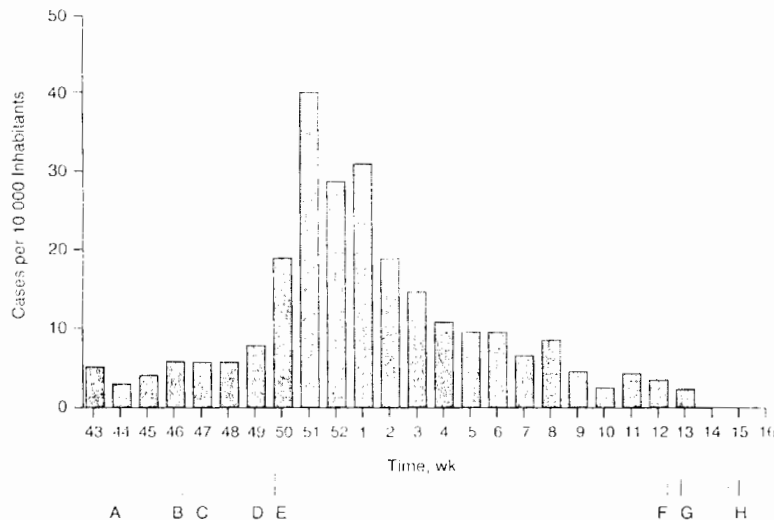
According to the Dutch Health Council,¹³ high-risk groups are patients with heart or lung conditions, diabetes mellitus, chronic renal insufficiency, and chronic staphylococcal infections. Of the people invited to enroll in the trial, 1838 (19%) agreed. The following reasons were given for nonparticipation: not understanding the letter of invitation; hesitation about participating in an investigation; fear of receiving an injection and having blood samples taken; and being pressed for time. Of those who enrolled, 238 indicated that they had been vaccinated against influenza in 1989 and/or in 1990. A history of cardiological, pulmonary, or metabolic problems were reported in 490 participants. (The family physicians appear to have had different interpretations of what it means to be at high risk for influenza.) To assess the influence of risk status on the effect of vaccination, the participants were divided into the following categories: cardiac disease, pulmonary disease, diabetes mellitus, and other conditions or healthy.

Intervention

The vaccine used was the purified split-virus vaccine produced by Evans Medical Ltd (Langhurst, Horsham, England). This vaccine was composed in

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Weekly influenza incidence in the Netherlands during the 1991-1992 influenza season (data from the Dutch Institute for Research on Primary Health Care), with research period (A to H) and time of vaccination and collecting blood samples. Period A to B indicates collecting first blood sample and vaccination; C to D, collecting second blood sample; E to F, collecting fourth and fifth blood samples, if applicable; and G to H, collecting third blood sample.

accordance with the advice of the World Health Organization and the Dutch Health Council. Each dose (0.5 mL) contained A/Singapore/6/86(H1N1), A/Beijing/353/89(H3N2), B/Beijing/1/87, and B/Panama/45/90, all with 15 µg of hemagglutinin. Physiological saline solution was used as placebo.

Between November 1 and 15, 1991, 9 mL of venous blood designated S1 was taken from all participants before vaccine or placebo was injected according to a stratified randomization scheme. Four strata, one for each of the disease categories just mentioned, were used for randomization. Patients were randomized to vaccine or placebo within the strata in the following manner (visually identical vaccine and placebo syringes were randomized and numbered in four strata). At the vaccination session, participants presented their identification numbers, which had been previously distributed. The name and number were checked against the list of participants, enabling us to identify the stratum to which the participant belonged. Then the participant received an injection with the next consecutively numbered syringe within the stratum in question. The number of the syringe was linked to the name of the participant. Two vaccination teams were involved, each consisting of one family physician not belonging to the participating practices, one assistant to take the blood sample, and one assistant to administer the vaccine. The participants were vaccinated in their own family physician's practice.

Three weeks later, a second blood

sample (S2) was taken. A third blood sample (S3) was taken 5 months after S1 (Figure). The serum from these blood samples was frozen at -20°C and sent to the National Influenza Center in Rotterdam for further analysis at the end of the study.

Follow-up

The participating physicians were asked to register the relevant symptoms of those patients presenting with an influenzalike illness. If possible, a blood sample was taken during this consultation and 3 weeks afterward (S4 and S5), to confirm an interim increase of the level of antibodies against influenza. Serum samples were treated in the same way as the samples S1, S2, and S3.

A questionnaire regarding possible influenza episodes and the symptoms experienced was sent to all participants after 10 weeks (first observation period) and after 23 weeks (second observation period) (Figure). Participants were asked to fill out and return these questionnaires. Questionnaires were analyzed by researchers blinded as to vaccination status.

Laboratory Measurements

The antibody titer in the serum samples was measured by means of the hemagglutinin inhibition test. Influenza virus strains for titrations were propagated in embryonated 12-day-old chicken eggs. Strains of or analogous to the vaccine were used for the titrations. Because of the low avidity of influenza B viruses, the allantoic fluid of the eggs

inoculated with these viruses was treated with ether¹⁴ and was used in the serological tests. The hemagglutinin inhibition titers before and after vaccination were independently and simultaneously measured by two technicians according to standard methods.¹⁵ The titers were expressed as the reciprocal values of the dilution, of which 50% of hemagglutinin inhibition occurred after addition of three units of hemagglutinin from the antigen.

Diagnostic Criteria

The average logarithmic titer value for the serum was calculated from the serum levels independently measured by two technicians. Titers less than 9 were arbitrarily regarded as 5.

Antibody titer after vaccination can be affected by the level of antibodies before vaccination.^{15,17} For this reason, the influence of the logarithmic titer of S1 on S2 was calculated using bivariate regression analysis, and S2 was corrected for this influence. The formula used was the following:

$$S2(\text{corr } 1) = S2 - C(S1 - \log 10),$$

in which $S2(\text{corr } 1)$ is the S2 level corrected for S1, C is the regression coefficient of the bivariate regression model, and $S1$ and $S2$ are the logarithms of the respective titers.

A titer of 38 or greater and a fourfold titer increase in S3 relative to S2 were considered as meeting the criteria of influenza infection.¹⁸ The same procedure was used to determine whether a fourfold titer increase had occurred in S5 relative to S4.

An antibody titer of 100 or greater for A strains and 200 or greater for B strains was considered to be a protective titer.¹⁹

The family physicians were asked to apply the *International Classification of Health Problems in Primary Care (ICHPHC-2-Defined)*²⁰ criteria to patients presenting with influenzalike symptoms. Inclusion according to the *ICHPHC-2-Defined* criteria requires one of the following: (1) viral culture or serological evidence of influenza virus infection, (2) influenza epidemic plus four of the criteria in 3, or (3) six of the following: sudden onset, cough, rigors or chills, fever, prostration and weakness, myalgia, widespread aches and pains, no significant physical signs other than erythema of nasal mucous membrane and throat, and influenza in close contacts.

The criteria of the Dutch Sentinel Stations and the *ICHPHC-2-Defined* were used to evaluate the questionnaire filled out by the participants.^{20,21} The criteria of the Dutch Sentinel Stations include an acute onset, fever of at least 38°C measured rectally, and at least one of

Table 1.—Characteristics of the Study Subjects

Subgroup	Vaccine Group, No. (%) (n=927)	Placebo Group, No. (%) (n=911)
Risk status		
Cardiac disease	125 (13.5)	124 (13.6)
Pulmonary disease	105 (11.3)	95 (10.4)
Diabetes mellitus	21 (2.3)	20 (2.2)
Other/healthy	676 (72.9)	672 (73.8)
Total	927 (100)	911 (100)
Sex		
Male	420 (45.3)	449 (49.3)
Female	507 (54.7)	462 (50.7)
Total	927 (100)	911 (100)
Age, y		
60-64	368 (39.7)	396 (43.5)
65-69	281 (30.3)	249 (27.3)
70-74	176 (19.0)	177 (19.4)
75-79	66 (7.1)	61 (6.7)
80-84	29 (3.1)	19 (2.1)
85-91	7 (0.8)	9 (1.0)
Total	927 (100)	911 (100)
Previously vaccinated		
Yes	118 (12.7)	120 (13.2)
No	809 (87.3)	791 (86.8)
Total	927 (100)	911 (100)
Protective titer at first blood sample obtained		
A Singapore (886H1N1) ^a	29 (3.1)	23 (2.5)
B Beijing/354/90 (BNI) ^b	21 (2.3)	28 (3.1)
B Panama/4/90	23 (2.5)	60 (6.6)
B Beijing/14/7	95 (10.3)	88 (9.7)

Table 2.—Number of Drop-outs After Randomization

Reason	Vaccine Group, n	Placebo Group, n
Death	6	3
Unavailability of blood samples	1	2
Unavailability of laboratory data	5	3
Resignation	3	1
Already vaccinated by family physician	1	0
Missing laboratory data	12	13
Total	25	22

^aEight myocardial infarctions and one ruptured aortic aneurysm.

the following symptoms: coughing, coryza, sore throat, frontal headache, retrosternal pain, or myalgia.

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.

Data Analysis

The efficacy of vaccination against influenza was expressed in terms of the relative risk (RR) and was tested by χ^2 tests. The 95% confidence interval (CI) was computed following the Rothman method.³²

A logistic regression model was used to analyze the modifying effect of age, sex, previous vaccination status, and disease category on the efficacy of vaccination (a likelihood ratio was used to evaluate the interaction of these variables with the current vaccination status using the χ^2 test with an $\alpha=0.05$).³³

The analyses were conducted on a

Table 3.—Efficacy of Vaccination in Participants With Influenza or Influenzalike Illness Diagnosed According to Different Criteria

Influenza or Influenzalike Illness According to	Vaccine Group, No. (%) (n=927)	Placebo Group, No. (%) (n=911)	Relative Risk (95% CI)*	Logistic Regression, Odds Ratio (95% CI)†‡
Serology†	41 (4)	80 (9)	0.50 (0.35-0.61)	0.48 (0.33-0.71)
Family physician	17 (2)	31 (3)	0.53 (0.39-0.73)	0.52 (0.29-0.95)
Sentinel Stations‡	62 (7)	89 (10)	0.69 (0.50-0.87)	0.64 (0.46-0.91)
ICHPPC-2-Defined‡	108 (12)	129 (14)	0.83 (0.65-1.05)	0.78 (0.59-1.02)

*CI indicates confidence interval.

†Controlled for age, sex, previous vaccination status, and disease category (cardiac disease, pulmonary disease, diabetes mellitus, and other conditions or healthy).

‡Dropouts in Serology subgroup were 25 vaccine and 22 placebo; in Sentinel Stations, eight vaccine and two placebo; and in International Classification of Health Problems in Primary Care (ICHPPC-2-Defined) criteria,³⁰ eight vaccine and two placebo.

VAX mainframe computer, using the BMDP program,³¹ 1990 version.

RESULTS

The composition of the trial population is shown in Table 1. The vaccine and placebo groups were similar with regard to age, sex, risk groups, previous vaccination in 1989 and 1990, and protective antibody titer before vaccination. Serological data were incomplete for 47 participants, partly due to participants unavailable for follow-up and missing blood samples (Table 2). Morbidity and mortality of the dropouts did not occur after symptoms resembling influenza. Subjects with incomplete samples were retained in the analyses whenever possible. The participants returned 1806 questionnaires (98%) at the end of the first observation period and 1756 (96%) at the end of the second period.

Table 3 shows the efficacy of vaccination. Serological influenza and influenzalike illness according to the family physician and Sentinel Stations had a statistically significant lower incidence in the vaccine group than in the placebo group. The effect on influenzalike illness according to the ICHPPC-2-Defined criteria was smaller and not statistically significant. However, when we evaluated the effect of vaccination in the period of week 49 in 1991 to week 6 in 1992, the period with epidemic elevation (Figure), a significant effect was noted also for influenzalike illness according to the ICHPPC-2-Defined criteria (RR, 0.74; 95% CI, 0.24 to 1.00). In the same period, the RR was 0.39 (95% CI, 0.22 to 0.68) for serological influenza, 0.40 (95% CI, 0.19 to 0.87) for influenzalike illness according to the family physician, and 0.41 (95% CI, 0.28 to 0.61) for influenzalike illness according to the Sentinel Stations.

Table 4 shows the results after stratification for risk status, sex, age, and previous vaccination status. The incidence of influenza or influenzalike illness was approximately the same for the various subgroups as for the entire

trial population. With the exception of participants aged 70 years and older, vaccinated participants consistently had a clearly lower incidence of influenza or influenzalike illness than did nonvaccinated participants. In the 70 years and older age category, little difference was found in the incidence of influenza and influenzalike illness between vaccinated and nonvaccinated participants. The CIs were wider likely because of fewer subjects per group.

The odds ratios found in the logistic regression analysis adjusted for age, sex, previous influenza vaccination, and disease status were similar to the unadjusted RRs. An exception was the effect of influenza vaccination on influenzalike illness according to the family physician; with an increase in age, the effect of vaccination disappeared (with age as the continuous variable in this model, $P<0.01$; with age as dichotomous variable, 60 to 69 years and 70 years or older, $P=18$). Since this regression analysis was simultaneously corrected for other variables, this influence cannot be explained by, for example, the number of earlier vaccinations, which increase with age.

In the previously vaccinated participants (n=238) who were now revaccinated, serological influenza only occurred in 0.9%, compared with 5.1% in those not previously vaccinated ($P=.04$) (Table 4). In the logistic regression analysis, the modifying effect of previous vaccination on the serological efficacy of current vaccination was of borderline statistical significance ($P=.07$). For clinical influenza, a difference in influenza rate was not observed.

Table 5 shows the RRs of vaccinated participants compared with the nonvaccinated regarding possible combinations of clinical and serological influenza. It indicates that the diagnosis of influenza on purely clinical grounds was not confirmed serologically in most cases. The efficacy of vaccination was highest for a diagnosis of influenza confirmed both clinically and serologically (RR, 0.42; 95% CI, 0.23 to 0.74).

Table 4.—Efficacy of Influenza Vaccination Stratified According to Disease Status, Sex, Age, and Previous Vaccination Status

Subgroup*	Influenza or Influenzalike Illness According to							
	Serology (n=121)		Family Physician (n=48)		Sentinel Stations (n=151)		ICHPPC-2-Defined† (n=237)	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Patients at potential risk‡								
No. (%)	9 (3.7)	21 (9.0)	5 (2.0)	11 (5.0)	21 (8.4)	23 (9.7)	35 (14.0)	39 (16.4)
RR (95% CI)	0.41 (0.19-0.89)		0.43 (0.15-1.23)		0.87 (0.49-1.53)		0.85 (0.56-1.30)	
Other:healthy								
No. (%)	32 (4.8)	59 (9.0)	12 (1.8)	20 (3.0)	41 (6.1)	66 (9.8)	73 (10.9)	90 (13.4)
RR (95% CI)	0.55 (0.36-0.83)		0.60 (0.29-1.21)		0.62 (0.43-0.91)		0.81 (0.61-1.09)	
Men								
No. (%)	12 (2.9)	41 (9.3)	5 (1.2)	15 (3.3)	24 (5.7)	33 (7.4)	39 (9.3)	46 (10.3)
RR (95% CI)	0.32 (0.17-0.59)		0.36 (0.13-0.97)		0.78 (0.47-1.30)		0.91 (0.61-1.36)	
Women								
No. (%)	29 (5.8)	39 (8.7)	12 (2.4)	16 (3.5)	38 (7.6)	56 (12.1)	69 (13.8)	83 (17.8)
RR (95% CI)	0.68 (0.43-1.07)		0.68 (0.33-1.43)		0.62 (0.42-0.92)		0.77 (0.57-1.03)	
Age, y								
60-69								
No. (%)	27 (4.3)	62 (9.9)	9 (1.4)	22 (3.4)	47 (7.3)	73 (11.3)	84 (13.0)	105 (16.3)
RR (95% CI)	0.43 (0.28-0.67)		0.41 (0.19-0.88)		0.64 (0.45-0.91)		0.80 (0.61-1.04)	
≥70								
No. (%)	14 (5.2)	18 (6.8)	8 (2.9)	9 (3.4)	15 (5.5)	16 (6.0)	24 (8.7)	24 (9.1)
RR (95% CI)	0.77 (0.39-1.51)		0.85 (0.33-2.17)		0.90 (0.46-1.79)		0.96 (0.56-1.66)	
Previously vaccinated								
Yes								
No. (%)	1 (0.9)	9 (8.0)	3 (2.5)	11 (9.2)	11 (9.3)	15 (12.6)	16 (13.6)	23 (19.3)
RR (95% CI)	0.11 (0.01-0.83)		0.27 (0.08-0.95)		0.74 (0.36-1.54)		0.70 (0.39-1.26)	
No								
No. (%)	40 (5.1)	71 (9.1)	14 (1.7)	20 (2.5)	50 (6.3)	74 (9.4)	91 (11.4)	106 (13.4)
RR (95% CI)	0.56 (0.38-0.81)		0.69 (0.35-1.35)		0.67 (0.47-0.94)		0.85 (0.65-1.10)	

*Participants with incomplete data were not included. RR indicates relative risk; and CI, confidence interval.
 †ICHPPC-2-Defined indicates International Classification of Health Problems in Primary Care.²⁰
 ‡Cardiac or pulmonary disease or diabetes mellitus.

Table 5.—Relative Risks (RRs) and 95% Confidence Intervals (CIs) of Vaccinated Participants Compared With Nonvaccinated Participants in Relation to Serological Influenza and Clinical Influenza

Influenza		Vaccine Group, n (n=927)	Placebo Group, n (n=911)	RR (95% CI)
Clinical*	Serological			
No	No	753	694	...
Yes	No	107	115	0.92 (0.72-1.17)
No	Yes	25	42	0.59 (0.36-0.96)
Yes	Yes	16	38	0.42 (0.23-0.74)
Dropouts		26	22	...

*Clinical influenza if any of the criteria (family physician, Sentinel Stations, or International Classification of Health Problems in Primary Care²⁰ criteria) were met.

Of the 121 participants with serological influenza, 67 showed no clinical symptoms. Fifty-five of these 67 had an increased antibody titer at S2. These titers were not high enough to prevent influenza infections serologically (≥ 100 and ≥ 200 , respectively), but apparently, they were sufficiently high to prevent a clinical manifestation of influenza infection.¹¹

COMMENT

The results of this study are consistent with a halving of the influenza risk by vaccination. However, the RR varied with the diagnostic criteria from 0.50 for serological influenza to 0.83 for clinical influenza, according to ICHPPC-2-Defined criteria. The latter criteria may be considered the most lax, so that many

patients may have had a false-positive diagnosis of influenza, resulting in a dilution of the observed effect of vaccination. Hence, the real effect may be nearer a risk reduction of 50%. If the most rigid criterion was used (clinical influenza, serologically confirmed) the risk reduction was 58% (RR, 0.42). If the risk period for the clinical diagnosis was limited to the epidemic period (and, consequently, the false-positive cases were reduced), the effect was significant even when the least rigid clinical criteria were used (RR, 0.74 for ICHPPC-2-Defined). This illustrates the importance of specification of the risk period when comparing different studies that express the results in terms of RR or risk reduction.^{1,25} The efficacy of vaccination may have been maximized by the good match

between the vaccine and the epidemic strains and the close proximity of vaccination to the influenza season. However, we have no reason to believe this match differed essentially from previous seasons.

The serological efficacy of the vaccine (67 participants with serological influenza showed no clinical symptoms) could be relevant in preventing "herd infections."

In our study, a protective response of the vaccine was primarily found for the A/Beijing strain. During the 1991-1992 season in the Netherlands, 65% of the isolated strains showed an antigen closely related to the vaccine virus A/Beijing/353/89(H3N2). Conclusions regarding the protective response of the other strains in the vaccine cannot be drawn due to the limited number of infections with these virus strains (A/Singapore/6/86[H1N1], B/Beijing/1/87, and B/Panama/45/90).

A number of studies suggest that the degree of serological protection is reduced by previous vaccination.^{15-19,26} This may be explained by the presence of an increased antibody titer against a certain strain before vaccination, influencing the production of new antibodies. Nevertheless, our study shows that previously vaccinated participants acquire influenza less often. The geometric mean

titer and protection rate, the most important parameters for estimation of immune response to vaccination,²⁷ are parameters of humoral immunity. There is also most likely a cellular immunity against the influenza virion, and both humoral and cellular immunities may be responsible for the efficacy of the vaccination.

Earlier studies show that the response to vaccination in elderly people is lower than in young people.^{5, 7, 28, 30} Nevertheless, a risk reduction of 50% in a population in which 95% of all fatalities related to influenza occur is a highly acceptable incentive for systematic vaccination in elderly people. However, our results suggest that the effect of vaccination may decrease after the age of 70 years. In our trial, the incidence of influenza was low and the number of participants aged 70 years and older was too small to detect a modifying effect of age with reasonable confidence. It is known that older people have a lower antibody titer response to vaccination than younger people, but other factors, such as cellular immunity, may influence resistance to influenza.

This study has potential limitations

regarding the external validity of the study population. First, the study population could have been selected in such a way that it overrepresents people who are the most susceptible for the preventive effect of vaccination. However, since little is known by medical researchers or the general public about this susceptibility, there would be no means for patients to select themselves on this basis (family physicians were not involved in this selection after the application of inclusion and exclusion criteria), and therefore bias is only hypothetical. Possible exceptions may be previous vaccination, previous chronic diseases, and, perhaps, age, and thus we have stratified the results for these factors (Table 5). Since these factors were not of primary interest beforehand, however, we did not make a power calculation to determine sample size to detect, for example, effect modification by age. The post hoc analysis suggests that the efficacy may be lower in those aged 70 years and older, and therefore further evaluation of this group would be interesting.

A second question might be whether the external validity could have been

affected by the number of people (8069; 81%) who declined to participate in this investigation. However, the reasons given for not participating are not likely to be related to the effectiveness of vaccination and are unlikely to affect the results since the subjects were randomized after enrollment.

Despite the exclusion of known high-risk patients there were still 490 participants with cardiological, pulmonary, or metabolic problems in the study population, but these participants likely had less severe disease. Thus, the results of this study may not be applied to a more ill population aged 60 years and older, although the most ill and highest risk patients could not ethically be randomized to placebo. In summary, the results of this study indicate that vaccination of individuals aged 60 years and older achieved up to a 50% reduction in influenza.

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