Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease

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Although pneumococcal vaccine has been recommended for patients with chronic obstructive pulmonary disease (COPD), its efficacy in this population has not been shown. A double-blind randomized controlled trial of 14-valent pneumococcal vaccine was carried out in 189 men and women aged 40 to 89 years with a clinical diagnosis of COPD and a forced expiratory volume in 1 second of less than 1.5 L. Of the 189, 92 received the vaccine and 97 received saline placebo. In a randomly chosen subsample of those who received the vaccine the mean titres of specific IgG antibody to selected pneumococcal polysaccharide serotypes increased two- to threefold by 4 weeks after vaccination. Over a 2-year period the rates of death, hospital admissions and emergency visits and the mean length of hospital stay were not significantly different in the two groups. Although a protective effect of 14-valent pneumococcal vaccine could not be shown, the small size of the sample and the relatively low follow-up rates preclude firm conclusions about efficacy from these data alone. The elevated antibody levels before vaccination in some of the patients, suggesting prior infection with *Diplococcus pneumoniae*, may partly explain the findings.

On a recommandé, sans que l'efficacité en ait été prouvée, le vaccin pneumococcique aux malades souffrant de pneumopathie obstructive chronique (POC). Nous avons fait l'essai comparatif à double insu, sur des sujets choisis au hasard, d'un vaccin 14-valent. Il s'agit de 189 hommes et femmes âgés de 40 à 89 ans chez qui ont avait porté un diagnostic clinique de POC confirmé par un volume expiratoire maximum seconde inférieur à 1,5 L. On donne le vaccin à 92 d'entre eux et un placébo sous forme de soluté salé à 97. Dans un sous-échantillon des vaccinés, choisi au hasard, on observe au bout de 4 semaines une multiplication par deux ou trois de la concentration moyenne des IgG contre des sérotypes polysaccharidiens pneumococciques choisis. Au bout de 2 ans d'observation, les deux groupes ne diffèrent pas de façon significative quant aux taux de mortalité, de visites en service d'urgences et d'hospitalisation; dans ce dernier cas la durée moyenne du séjour ne diffère pas non plus. Vu la taille modeste de l'échantillon et le nombre relativement petit des sujets qui ont été suivis, on ne peut porter, à partir de notre travail, un jugement de valeur sur ce vaccin. Les taux élevés d'anticorps observés chez quelques sujets dès avant la vaccination, qui font penser à l'infection pneumococcique antérieure, expliquent peut-être en partie nos résultats négatifs.

For a number of years the Centers for Disease Control, Atlanta, have recommended the use of polyvalent pneumococcal vaccine in patients with chronic obstructive pulmonary disease (COPD) because such patients were presumed to be at increased risk for pneumococcal pneumonia.[1] However, demonstrating the efficacy of pneumococcal vaccine in any population other than the original group of South African gold miners[2] has been difficult because of low infection rates and the difficulty of proving pneumococcal infection.[3-5]

In two recent reviews on the use of pneumococcal vaccine in patients with chronic lung dis-

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ease, opposing recommendations were made on the basis of the available data.[6,7] These reviews underline the added difficulties in establishing the role of pneumococcal vaccine in COPD, in which the incidence of pneumococcal infection may be relatively high, as suggested by one community-based study,[8] or relatively low because of previously acquired immunity.[9] Furthermore, only a small proportion of cases of exacerbation of COPD may be attributable to *Diplococcus pneumoniae*,[10,11] and baseline antibody titres may already be at a level considered protective.[9]

In an attempt to demonstrate a protective role of polyvalent pneumococcal vaccine in severe COPD, we undertook a prospective double-blind randomized controlled trial in a stable ambulatory population attending a chest clinic. The rarity of bacteriologic proof of pneumococcal infection influenced us to emphasize nonspecific outcomes, including any cardiopulmonary illness and death from all causes.

Methods

The charts of all patients seen in the outpatient clinic of the Montreal Chest Hospital between January and June 1981 were reviewed. Patients in whom COPD (including chronic bronchitis and emphysema but not asthma, cystic fibrosis or bronchiectasis) had been diagnosed by their physicians and who had a forced expiratory volume in 1 second (FEV_1) of less than 1.5 L were invited to participate in a double-blind trial of a vaccine that might help prevent pneumonia. A total of 129 patients who had previously received pneumococcal vaccine were excluded. Consent was obtained in the manner approved by the Human Investigations Committee of the hospital.

After stratification by age and FEV_1 within the two sexes, the participants were randomly assigned to receive either influenza vaccine in one arm and 14-valent pneumococcal polysaccharide vaccine (Merck Sharp & Dohme Canada, Kirkland, PQ) in the other or influenza vaccine in one arm and saline placebo in the other during October or November 1981. At 6-month intervals for 2 years they or, in the case of death, surviving relatives were interviewed and the charts reviewed to determine the number of deaths, hospital admissions and emergency visits to the clinic or emergency department. Diagnosis, length of hospital stay and, when available, follow-up FEV_1 and forced vital capacity (FVC) were also recorded for each event.

An upper respiratory tract infection was considered to be present when the patient complained of sore throat, runny nose, fever and increased cough without an increase in the quantity or a change in the colour of the sputum. A lower respiratory tract infection was defined as a combination of fever, increased cough and a change in the colour or an increase in the quantity of the sputum. Pneumonia was diagnosed when the patient had symptoms of a lower respiratory tract infection and evidence of a new infiltrate on a chest roentgenogram.

At 1 and 2 years the patients received appropriate updated influenza vaccination unless they had had a reaction the previous year or declined vaccination. Other than these vaccinations and the interviews, no intervention was made in the regular clinic or hospital care given to the patients by their physicians.

Sputum from a random sample of approximately 10% of the participants was cultured and examined specifically for *D. pneumoniae* colonization before vaccination. When sputum was unavailable a nasopharyngeal swab was cultured. A venous blood sample was collected at the same time and 4 weeks later. These samples were used to determine the titres of IgG antibody to pneumococcal polysaccharide serotypes 1, 2, 6A, 8, 9N, 12F, 19F and 23F. The titres were measured by means of an enzyme-linked immunosorbent assay (ELISA), as described elsewhere,[12] by a technician who did not know the vaccination status of the patients. Serum pairs were assayed simultaneously.

Differences in death rates between the two groups were analysed by means of the log-rank method for survival curves, estimated with the life-table method.[13] Rates of nonelective admissions and emergency visits per person-year of observation were compared with two-way analysis of variance, between-group and between-interval differences being examined.

Results

A total of 189 patients were entered into the trial, 92 in the experimental group and 97 in the control group. The two groups were similar in sex distribution and in age, FEV_1 and FVC at the outset of the trial (Table I). At 2 years, follow-up studies of lung function in 60% of each group showed marginal declines in FEV_1 and FVC. Sputum culture at the outset of the study yielded *D. pneumoniae* in only 1 of 21 cases.

During the study only one documented case of pneumococcal sepsis occurred, in a patient who received pneumococcal vaccine and had pneumonia. The pneumococcal serotype was not determined. There were no adverse reactions to pneumococcal vaccine.

Table II shows the mean titres of IgG antibody to pneumococcal polysaccharide before and 4 weeks after vaccination. The titres in the experimental group had increased two- to threefold at 4 weeks. The control group showed rises in all the titres as well, which suggests either fluctuation in the titres or antigenic exposure that occurred naturally. In general the titres in both groups tended to be greater than those in healthy adults given pneumococcal vaccine.[12]

A total of 23 patients (12%) could not be

traced for follow-up and were not included in the analysis of death rates. At each follow-up interview some patients refused to answer questions and were not included in the analysis of hospital admissions and emergency visits. Including deaths, the follow-up rates at 6, 12, 18 and 24 months were thus 97%, 85%, 79% and 59% respectively. Therefore, for comparison of the two groups the results are reported as rates per person-year of observation.

Eleven patients in the control group and six in the experimental group died. The causes of death were respiratory failure in six cases, myocardial infarction in four cases and heart failure, lung cancer, other cancer, suicide and diabetes mellitus in one case each. The cause was unknown in two cases. Of the 12 deaths due to cardiopulmonary illness 7 were in the control group and 5 in the experimental group. Survival-curve estimates for the two groups were not significantly different (Fig. 1).

Tables III and IV show the numbers of, reasons for and rates of hospital admissions and emergency visits respectively. Two-way analysis of variance did not show any between-group differences for either admissions or visits. There was, however, a significant effect of time ($p = 0.02$) on the rate of emergency visits; it probably reflected the low rates in the final 6 months. This apparent fall in the rates occurred, however, in both groups. The mean length of hospital stay was not significantly different in the two groups.

Table I — Characteristics of patients with severe chronic obstructive pulmonary disease (COPD) who received or did not receive polyvalent pneumococcal vaccine

Characteristic	Mean (and standard deviation)	
	Control group (n = 97)	Experimental group (n = 92)
No. of men	69	66
Age, yr	67 (9)	66 (9)
Forced expiratory volume in 1 s, L	0.96 (0.30)	0.94 (0.26)
Forced vital capacity, L/s	2.13 (0.64)	2.18 (0.58)

Discussion

This study did not show any measurable benefit to patients with COPD of a single dose of 14-valent pneumococcal polysaccharide vaccine

Table II — Geometric mean titres of IgG antibody to selected pneumococcal polysaccharide serotypes before and 4 weeks after vaccination

Pneumococcal polysaccharide serotype	Normal values[12]		Control group (n = 10)		Experimental group (n = 11)	
	Before vaccination	After vaccination	Before vaccination	After vaccination	Before vaccination	After vaccination
1	1:28	1:178	1:85	1:129	1:146	1:357
2	1:67	1:234	1:106	1:163	1:122	1:333
6A	1:81	1:119	1:89	1:189	1:152	1:310
8	1:21	1:42	1:57	1:116	1:88	1:173
9N	1:97	1:301	1:82	1:261	1:172	1:475
12F	1:73	1:128	1:93	1:206	1:162	1:407
19F	1:86	1:171	1:90	1:304	1:141	1:439
23F	1:38	1:100	1:90	1:155	1:96	1:283

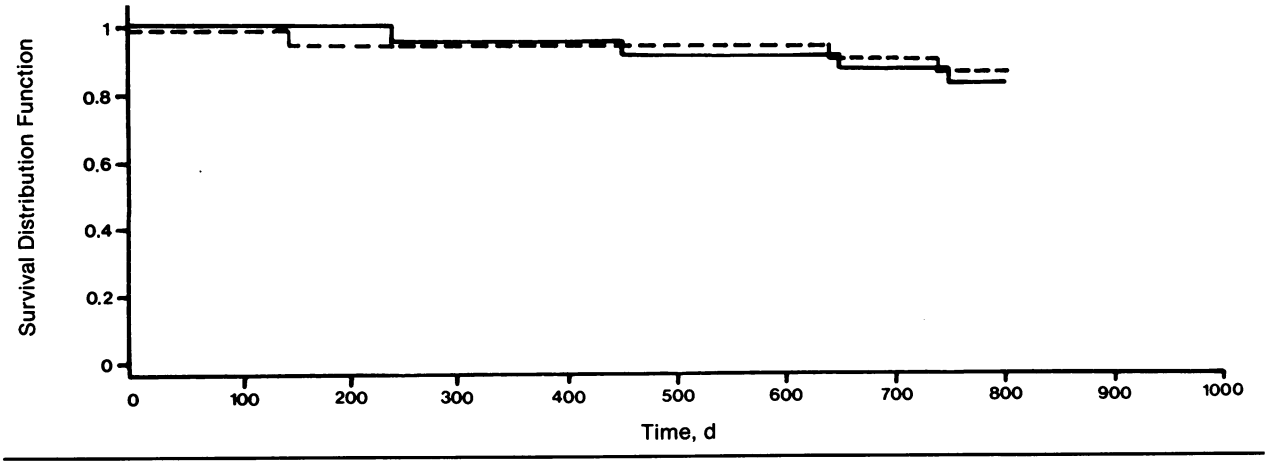

Fig. 1 — Survival-curve estimates for patients given polyvalent pneumococcal vaccine (broken line) and control group (solid line).

over 2 years of follow-up. Conversely, it did not show any harm from the vaccine.

Our inability to demonstrate a protective effect of pneumococcal vaccine may reflect only a small sample, a low frequency of pneumococcal infection or both. A calculation of sample size based on an incidence of bacteremia of 2.2% (as reported for asplenic patients[14]), an α error of 0.05 and a β error of 0.2 indicated that approximately 1600 subjects may be needed to show an improvement of 50% in rates of pneumococcal sepsis. In our study, in which we hoped to include less specific but probably more frequent outcomes of pneumococcal infection than pneumococcal bacteremia, we may have observed too few subjects to be certain of a negative result. With the observed reduction of risk of about 40% in our study, at least 500 subjects per group would have been necessary to show a statistically significant difference. However, in a similar but much larger study, in 15 000 elderly people in institutions, a protective effect of the vaccine was also not shown.[4]

Moreover, in patients with COPD a lower rate of new infections may also be a factor. We found that the sputum of only 1 of 21 subjects yielded *D. pneumoniae* when cultured at the outset of the study. Assuming a constant rate of septicemia over 2 years we estimate the true incidence of pneumococcal sepsis in our population to be 0.66% (95% confidence limits 0.0% and 2.41%), compared with 2.2% in asplenic patients[14] and population-based rates of 7.5 cases per 100 000 person-years in West Virginia[8] and 8.5 cases per 100 000 person-years in South Carolina.[15]

The low infection rates may have been due to prior infections. We found that before vaccination our patients had elevated levels of antibody to the pneumococcal serotypes tested. Landesman and colleagues,[9] using radioimmunoassay for determining titres, reported similar findings in elderly patients with COPD. This could mean that such patients may already be protected from serious pneumococcal disease by naturally acquired antibodies.

Table III — Hospital admissions among the two groups

Time after vaccination, mo; group	Reason for admission					Rate of admissions for cardiopulmonary illness*
	Pneumonia	Exacerbation of COPD	Cardiac illness	Other	Total	
≤ 6						
Control (n = 94)	1	13	1	3	18	0.32
Experimental (n = 89)	2	7	1	4	14	0.23
7–12						
Control (n = 84)	1	14	1	6	22	0.38
Experimental (n = 76)	2	10	1	6	19	0.34
13–18						
Control (n = 79)	2	15	1	2	20	0.46
Experimental (n = 71)	5†	14	1	4	24	0.56
19–24						
Control (n = 60)	1	7	2	2	12	0.33
Experimental (n = 52)	0	6	1	2	9	0.23

*Number of admissions per person-year of observation.
†Includes the only documented case of pneumococcal sepsis.

Table IV — Emergency visits among the two groups

Time after vaccination, mo; group	Reason for visit					Rate of visits for respiratory illness*
	Upper respiratory tract infection	Lower respiratory tract infection	Pneumonia	Other	Total	
≤ 6						
Control (n = 94)	4	37	2	13	56	0.83
Experimental (n = 89)	9	35	3	11	58	0.85
7–12						
Control (n = 84)	0	20	11	15	46	0.74
Experimental (n = 76)	0	21	3	18	42	0.63
13–18						
Control (n = 79)	11	26	6	9	52	0.81
Experimental (n = 71)	8	19	11	26	64	0.85
19–24						
Control (n = 60)	2	13	1	11	27	0.47
Experimental (n = 52)	3	12	1	9	25	0.50

*Number of visits for lower respiratory tract infection or pneumonia per person-year of observation.

Our 2-year death rate of approximately 10% is probably lower than that reported for other groups with similar degrees of airflow obstruction.[16,17] For example, in a recent multicentre trial the 2-year death rate in patients with an FEV_1 less than 50% of that predicted was approximately 10% to 28%.[16] These differences may reflect the larger proportion of women in our study and the fact that patients with other major systemic disease were generally not followed at a subspecialty hospital.

Our results suggest that pneumococcal vaccine, by further raising already elevated antibody levels, can still be immunogenic in patients with COPD and that it does not have any harmful effects. However, the results also raise the question of the necessity of giving the vaccine to patients with COPD, many of whom are likely to have elevated antibody titres without vaccination.

It has been suggested that a randomized controlled trial to study the effectiveness of pneumococcal vaccine in patients with COPD will now never be carried out.[7,18] This is particularly likely because many patients have already been vaccinated on the basis of current recommendations. A selection bias may therefore always be introduced by their exclusion from any prospective trial. Such circumstances underscore the need for data collection from appropriate patient populations before widespread recommendations are made for any vaccine.

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References

1. Centers for Disease Control, Department of Health and Human Services: Update: pneumococcal polysaccharide vaccine usage — United States. Recommendations of the Immunization Practices Advisory Committee. *Ann Intern Med* 1984; 101: 348-350
2. Austrian R, Douglas RM, Schiffman G: Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Physicians* 1976; 89: 184-194
3. Patrick KM, Woolley FR: A cost-benefit analysis of immunization for pneumococcal pneumonia. *JAMA* 1981; 245: 473-477
4. Austrian R: *Surveillance of Pneumococcal Infection for Field Trials of Polyvalent Pneumococcal Vaccines* (rep DAB [VDP] 12-84), National Institutes of Health, Bethesda, Md, 1980: 1-84
5. Pneumococcal vaccine. *Med Lett Drugs Ther* 1978; 20: 13-14
6. Williams JH Jr, Moser KM: Pneumococcal vaccine and patients with chronic lung disease. *Ann Intern Med* 1986; 104: 106-109
7. La Force FM, Eickhoff TC: Pneumococcal vaccine: the evidence mounts [E]. Ibid: 110-112
8. Mufson MA, Gretchen O, Hughey D: Pneumococcal disease in a medium-sized community in the United States. *JAMA* 1982; 248: 1486-1489
9. Landesman SH, Smith PM, Schiffman G: Pneumococcal vaccine in elderly patients with COPD. *Chest* 1983; 84: 433-435
10. Reichek N, Lewin EB, Rhoden D et al: Antibody responses to bacterial antigens during exacerbations of chronic bronchitis. *Am Rev Respir Dis* 1970; 101: 238-244
11. Davis AL, Aranda C, Christianson L et al: Effects of 14-valent pneumococcal polysaccharide vaccine in patients with COPD. *Chest* 1984; 85 (suppl): 582-583
12. Ruben FL, Uhrin M: Specific immunoglobulin-class antibody responses in the elderly before and after 14-valent pneumococcal vaccine. *J Infect Dis* 1985; 151: 845-849
13. *SAS User's Guide: Statistics*, version 5, SAS Institute, Cary, NC, 1985: 529-557
14. Ruben FL, Norden CW, Korica Y: Pneumococcal bacteremia at a medical/surgical hospital for adults between 1975 and 1980. *Am J Med* 1984; 77: 1091-1094
15. Filice GA, Darby CP, Fraser DW: Pneumococcal bacteremia in Charleston County, South Carolina. *Am J Epidemiol* 1980; 112: 828-835
16. Anthonisen NR, Wright EC, Hodgkin JE and the IPPB Trial Group: Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14-20
17. Burrows B, Earle RH: Prediction of survival in patients with chronic airways obstruction. *Am Rev Respir Dis* 1969; 99: 865-871
18. Austrian R: A reassessment of pneumococcal vaccine [E]. *N Engl J Med* 1984; 310: 651-653

Medicine

The art has three factors, the disease, the patient, the physician. The physician is the servant of the art. The patient must co-operate with the physician in combating the disease.

— Hippocrates (460?-377? BC)