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A double blind multicentre trial with BRONCHO-VAXOM in adults

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Objective

Evaluation of the long-term effectiveness of BRONCHO-VAXOM *Adults* in the treatment of acute and chronic respiratory diseases over a three-month period.

Period of the study

1 October 1981-30 July 1982

Number of doctors

31

Total number of patients

230 adults

Patient selection criteria

Patients suffering from chronic obstructive diseases of the respiratory tract, who had been treated for acute respiratory infections, or in whom at least one infection of the respiratory tract had occurred during the months of autumn and winter of the previous year.

Patient exclusion criteria

Any who had been treated with an immunostimulant during the previous year.

Distribution into groups

Double blind, randomised: BRONCHO-VAXOM *Adults* against a placebo.

MATERIALS AND METHODS

Patients

The study included 230 adults, with a median age of 48 (17-82) years in the BRONCHO-VAXOM group and 51 (14-79) years in the placebo group (Table 1). There were 117 men and 102 women (Table 2).

Regimen

The duration of the study was six months. The treatment consisted in taking one capsule daily of BRONCHO-VAXOM *Adults* or of a placebo each morning before breakfast for ten consecutive days during the first three months of the study; the following three months served as a supplementary observation period. For more than 90% of the patients, the treatment began during the month of November or December (Table 3).

An infection was present at the beginning of the treatment in 66 (58%) of the patients in the BRONCHO-VAXOM group and in 65 (61%) of the placebo group (Table 8). Bronchitis was diagnosed in more than half of the patients. Other diagnoses were as follows: respiratory tract infection (influenza, common cold), pharyngitis, sinusitis, rhinitis, tonsillitis and bronchial asthma (Table 9). During the six-month observation period, the number, the type and the degree of severity of the infections, as well as the duration of antibacterial therapy needed and the appearance of possible side-effects were recorded.

The doctors also provided information regarding the degree of patients' compliance and later evaluated whether, in their opinion and in that of the patient, the treatment could be considered successful.

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The two groups, BRONCHO-VAXOM and placebo, were homogeneous from the point of view of their age and sex distribution, the time the treatment was initiated, the duration of the observation period, the degree of compliance, the type of diagnosis and the presence of an infection at the beginning of the treatment (Tables 1, 2, 3, 4, 8, 9).

RESULTS

119 patients were treated with BRONCHO-VAXOM and 111 with the placebo. The treatment was interrupted in five patients receiving BRONCHO-VAXOM and in one patient receiving the placebo because of side-effects (Table 5). Three patients of the placebo group were excluded because of poor compliance (Table 4). One death was recorded in each group, with no relationship to the product administered (myocardial infarction, asthmatic crisis, Tables 6, 7). A biometric evaluation could thus be performed in 113 patients on BRONCHO-VAXOM and 106 on the placebo.

Frequency of infections

Infections appeared during the first month of treatment in 67 patients treated with BRONCHO-VAXOM and 66 patients treated with the placebo.
During the first month of treatment, 47 patients from the BRONCHO-VAXOM group suffered from a single infection, 12 from 2 infections, 6 from 3 infections, 1 from 4 and another from 5. In the placebo group, 49 patients suffered from 1 infection, 11 from 2 infections, 4 from 3 and 2 from 5 infections. The infection frequency diminished constantly in both groups, although it was more pronounced in the BRONCHO-VAXOM group than in the placebo group over the next two months of treatment and the following three months of observation. Multiple infections, in particular, diminished from the third month of treatment in the BRONCHO-VAXOM group, while they remained constant in the placebo group (Fig. 1).
The number of BRONCHO-VAXOM patients in whom no new infection appeared during the supplementary observation period in comparison to the first treatment month was larger than those under the placebo, with 71, 86 and 86 patients compared to 60, 65 and 59 respectively for the placebo group (Table 11). The frequency of infections was globally reduced under BRONCHO-VAXOM, while it remained stationary or even increased under placebo during the months of treatment and supplementary observation. The differences between the BRONCHO-VAXOM group and the placebo group were statistically significant when observations of the 5th and 6th months were compared with those of the first month of treatment ($p<0,05$ and $p<0,01$ respectively; Uleman's test, Table 11).

Degree of severity of infections

During the first month of treatment, the degree of severity of the infections was classified as mild in 8 cases, moderate in 38 cases and marked in 52 cases in the BRONCHO-VAXOM group. In the placebo group, the degree of severity was classified as mild in 10 cases, moderate in 36 cases and marked in 47 cases.
In comparison with the placebo, the severity of infections was clearly reduced and in an increasing manner from the second month of treatment with BRONCHO-VAXOM. Thus, by the 6th month, only 8 infections were classified as mild, 9 as moderate and 2 as marked under BRONCHO-VAXOM by comparison with 10 mild, 42 moderate and 8 marked under the placebo (Fig. 2). Multiplication of the number of infections by their degree of severity (mild = 1, moderate = 2, marked = 3) during the course of each month gave significant differences for the 4th and 5th months of observation ($p<0,05$) and highly significant differences for the 6th month ($p<0,001$; Uleman's asymptotic test) in favour of BRONCHO-VAXOM (Table 10).

Duration of antibacterial treatment

During the first month of treatment, the 113 patients in the BRONCHO-VAXOM group received an antibacterial treatment during 400 days for infections of the respiratory tract by comparison with 365 days in the 106 patients in the placebo group. Distinctly less antibacterial medication was necessary for patients on BRONCHO-VAXOM during the second month of treatment and, in particular, for the 5th and 6th months of the supplementary observation period (Fig. 3 and 4).

Overall evaluation of the therapeutic success by the doctor and the patient

The doctors recorded a definite therapeutic response in 52 (46%) of the patients on BRONCHO-VAXOM and 24 (23%) of those on the placebo and a possible improvement in 42 (37%) of the patients on BRONCHO-VAXOM and 32 (30%) on the placebo. On the other hand, the doctors estimated that the effect was questionable in 13 (12%) of the BRONCHO-VAXOM cases and in 21 (20%) of the placebo cases. In only 6 (5%) of the cases treated with BRONCHO-VAXOM could it be said that there was no therapeutic success, the corresponding number was 29 (27%) for the placebo cases. The difference between the two groups was highly statistically significant ($p<0{,}001$; Ulemans's test).
Self-evaluation of the treatment by the patients gave similar results. Of the patients receiving BRONCHO-VAXOM, 65 (58%) indicated a distinct improvement as compared with 33 (31%) receiving the placebo. As in the case with the doctors, 6 (5%) of the patients on BRONCHO-VAXOM and 28 (27%) of those on the placebo did not judge themselves to have benefited from the treatment (Table 12, Figure 5).

Tolerance

The doctors noted that BRONCHO-VAXOM was well tolerated in 111 (93%) of the cases and the placebo in 98 (88%) of the cases. Side-effects were reported for 7 (6%) of the patients on BRONCHO-VAXOM and 12 (11%) of those on the placebo. The treatment was interrupted in 5 (4%) of the patients on BRONCHO-VAXOM and in one patient on the placebo. The regimen was continued for most of the patients who reported side-effects whenever it could be shown by a third party examining the randomisation code, that the patients were receiving the placebo (Table 5). In no case was it possible to establish a clear relationship with BRONCHO-VAXOM (Table 6). Similar side-effects were, however, noted more frequently in the placebo group (Table 7).

Table 1: *Demographic data: age*
Results for 230 adult patients (119 BRONCHO-VAXOM; 111 placebo)

Age	≤30 years	31-45 years	46-60 years	≥61 years	Total	Drop out +incomplete data
BV	21 (18%)	26 (22%)	30 (25%)	32 (27%)	119 (100%)	10 (8%)
P	12 (11%)	26 (23%)	39 (35%)	25 (23%)	111 (100%)	9 (8%)

The age distribution showed *no* significant difference according to the χ^2-test.

	BRONCHO-VAXOM:	Placebo:
Minimum:	17 years	14 years
Maximum:	82 years	79 years
Median:	48 years	51 years

Table 2: *Demographic data: sex*

Sex	Male	Female	Total	Drop out
BV	64	49	119	6
P	53	53	111	5

The two groups showed *no* significant difference according to the χ^2-test (Yates).

Table 3: *Beginning of the treatment*

1981/82	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Drop out	Total
BV	1 (1%)	68 (60%)	35 (31%)	5 (4%)	2 (2%)	2 (2%)	6 –	119 (100%)
P	– –	58 (55%)	38 (36%)	8 (7,5%)	2 (1,5%)	– –	5 –	110 (100%)

Duration of observation

Month	6	5	4	3	2	1	Drop out	Total
BV	107	5	–	1	–	–	6	119
P	101	5	–	–	–	–	5	111

Table 4: *Compliance*

Parameter		BV	Placebo
Compliance:	good	110 (98%)	94 (89%)
	doubtful	2 (2%)	9 (8%)
	poor	–	3 (3%)
Total patients		112 (100%)	106 (100%)
Incomplete data or drop out		7	5
Overall total		119	111

Table 5: *Tolerance*

	BV	Placebo
Good tolerance	111 (93%)	98 (88%)
Side-effects without interruption of treatment	2 (2%)	11 (10%)
Side-effects with interruption of treatment	5 (4%)	1 (1%)
Drop out (see tables 6 and 7)	1 (1%)	1 (1%)
Total patients	119 (100%)	111 (100%)

(The different rates of interruption noted in the patients under placebo are obviously explained by the fact that after opening of the randomisation code, these patients continued in the trial, whereas those under BRONCHO-VAXOM interrupted it.)

Table 6: *Side-effects noted in the BRONCHO-VAXOM group (n = 119)*

Patient No.	Type of side-effect	Doctor's comments	Interruption of treatment
11	Nausea	The patient saw a relation between the treatment and the side-effect mentioned	Stopped after 1 month
14	Swelling and redness of the face	The side-effects mentioned were not objectivated	Stopped after 2 months
48	Fatigue	–	*No* interruption
56	The patient mentionned loss of hair	Subjective increase in the trouble, ineffectiveness	Stopped after 1 month
80	Conjunctivitis with blurred vision	Interruption after the second administration period because of a direct relation with the medication	Stopped after 2 months
94	(–)	Patient died after an asthmatic crisis	(–)
97	Cold	Aggravation of cold	Stopped after 4 months
112	Diarrhoea	2 days' diarrhoea upon first dose, doubtful side-effect	*No* interruption

Table 7: *Side-effects noted in the placebo group (n = 111)*

Patient No.	Type of side-effect	Doctor's comments	Interruption of treatment
10	Regulation of stools	According to the patient	*No* interruption
15	(–)	Patient died after a myocardial infarction	(–)
24	Urticaria	Unknown cause (randomisation code opened by a third party)	*No* interruption
41	Sneezing fits, tingling eyes, cold	–	*No* interruption
45	Headaches	–	*No* interruption
46	Thirst, sleeping difficulties	No improvement of the disorders	*No* interruption
59	Mild gastro-intestinal disorders initially	No disorders after 3 days	*No* interruption
61	On 2nd and 3rd days, mild gastrointestinal disorders	–	*No* interruption
83	Mild nausea	Mild nausea on the 1st day	*No* interruption
84	Extreme fatigue	Extreme fatigue mentioned after 2 months	Interruption after 2 months
87	Loss of hair, gastrointestinal disorders	The patient mentioned 3 days of gastrointestinal disorders, increase in hair loss after taking the 1st capsule	*No* interruption
103	Nausea	Sometimes a little nausea after taking the dose	*No* interruption
110	Headaches	Occasional headaches mainly when taken on an empty stomach	*No* interruption

Table 8: *Presence of an infection at the start of treatment*

Product	Yes	No	Total patients
BV	66 (58%)	47 (42%)	113 (100%)
P	65 (61%)	41 (39%)	106 (100%)

The distribution was *not* significantly different according to the χ^2-test.

Table 9: *Distribution of diagnoses*

Diagnoses	BV	(%)	P	(%)
Tonsillitis	14	4,2	14	3,3
Bronchial asthma	4	1,2	10	2,3
Bronchitis	170	51,3	217	50,9
Respiratory tract infections (influenza, cold)	40	12,1	32	7,5
Pharyngitis	37	11,2	60	14,0
Rhinitis	27	8,2	67	15,7
Sinusitis	33	10,0	24	5,6
Others (otitis, allergy, mumps)	6	1,8	3	0,7
Total diagnoses	331	100,0	427	100,0

As a single patient may have had several infections, the number of diagnoses is larger than that of the patients (n = 113, BRONCHO-VAXOM; n = 106, placebo). The χ^2-test is not applicable, as it presumes independent parameters.

Table 10: *Number of infections × degree of severity (see Fig. 1 and 2)*

No. of infections×degree of severity	1st month		2nd month		3rd month		4th month		5th month		6th month	
	BV	P	BV	P	BV	P	BV	P	BV	P	BV	P
0	47	41	63	47	63	60	75	60	88	68	95	68
1	5	4	5	8	15	7	15	11	8	7	7	6
2	20	25	26	23	21	18	17	19	11	13	10	13
3	24	19	9	15	9	9	5	8	3	10	1	8
4	3	5	5	3	3	7	1	5	–	4	–	6
5	1	3	–	1	1	–	–	–	–	–	–	–
6	8	4	3	8	1	2	–	1	3	2	–	3
7	5	5	2	1	–	3	–	2	–	2	–	2
Total of patients	113	106	113	106	113	106	113	106	113	106	113	106
Significance	n.s.		n.s.		n.s.		p<0,05		p<0,05		p<0,001	

Significant reduction at the 4th and 5th months of observation (p<0,05) and *highly significant* at the 6th month (p<0,001; Uleman's asymptotic test).

Table 11: *Regression of infections*

Frequency of infections	4th month compared to 1st month Number of patients		5th month compared to 1st month Number of patients		6th month compared to 1st month Number of patients	
	BV	P	BV	P	BV	P
Without symptoms No infection after treatment	71 (63,5%)	60 (57%)	86 (77%)	65 (61,5%)	86 (80%)	59 (58%)
Number of infections *reduced*	10 (9%)	13 (12%)	7 (6%)	9 (8,5%)	5 (5%)	7 (7%)
Stationary	15 (13,5%)	17 (16%)	9 (8%)	17 (16%)	7 (6,5%)	23 (23%)
Increased	16 (14%)	16 (15%)	10 (9%)	15 (14%)	9 (8,5%)	12 (12%)
Observation period shorter than 6, 5 or 4 months resp.	1	–	1	–	6	5
Total number of patients	113	106	113	106	113	106
Significance	n.s.		p<0,05		p<0,01	

Table 12: *Evaluation of the effect of treatment by the doctor and the patient*

Parameter	DOCTOR Number of patients		PATIENT Number of patients	
	BV	P	BV	P
Evident effect	52	24	65	33
Possible effect	42	32	31	28
Questionable effect	13	21	13	17
No effect	6	29	6	28
Total patients	113	106	113	106
Significance (Uleman's asymptotic test)	p<0,001		p<0,001	

The difference between BRONCHO-VAXOM and the placebo was *highly significant* (p<0,001; Uleman's asymptotic test).

Fig. 1: Number of infections per month

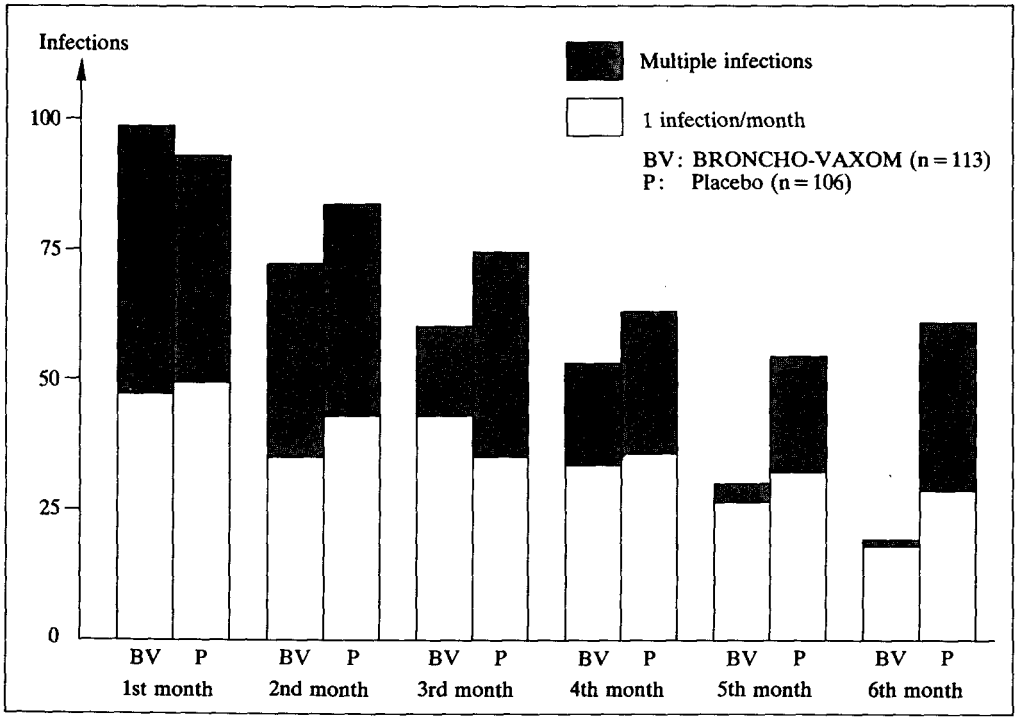


Fig. 2: Degree of severity of infections under BRONCHO-VAXOM in comparison with the placebo

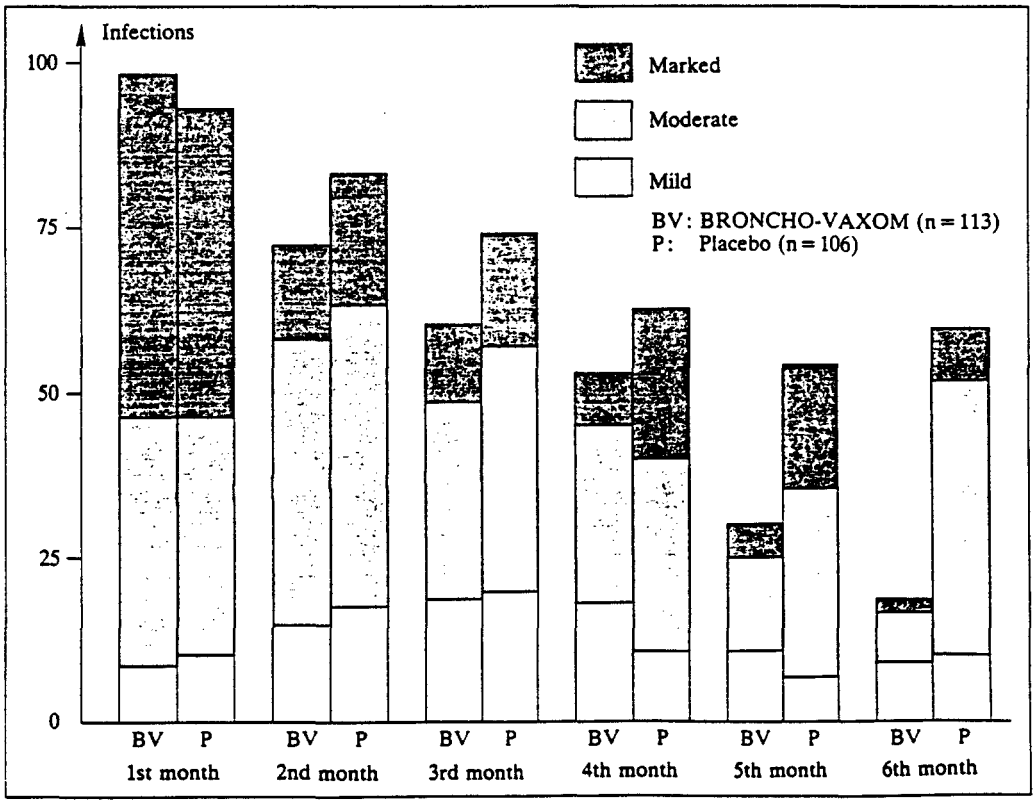


Fig. 3: Duration of antibacterial treatment (days relative to the total number patients) under BRONCHO-VAXOM or the placebo

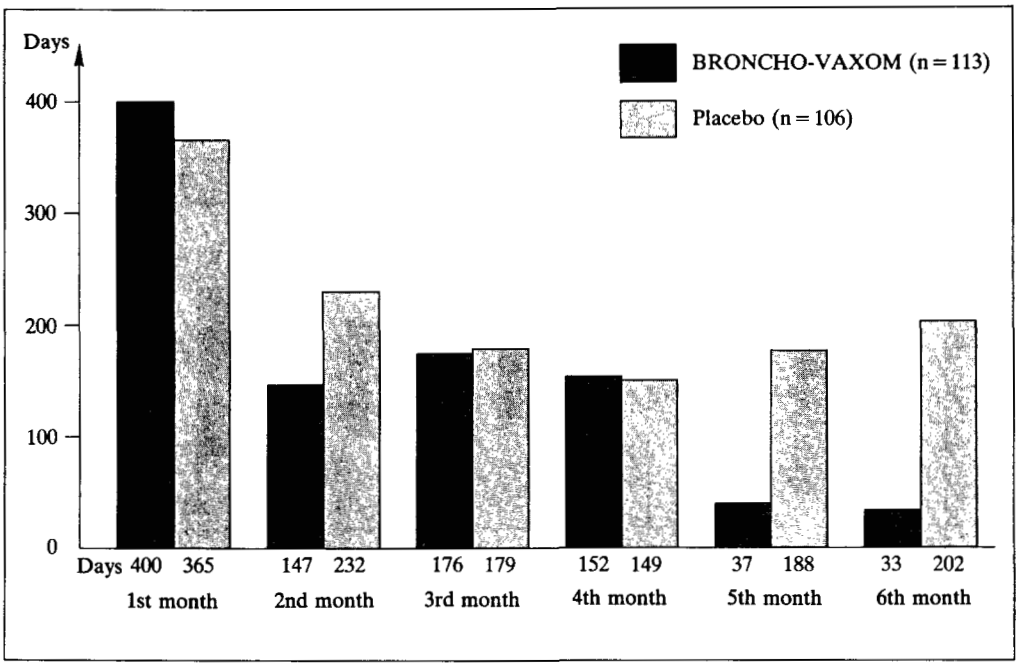
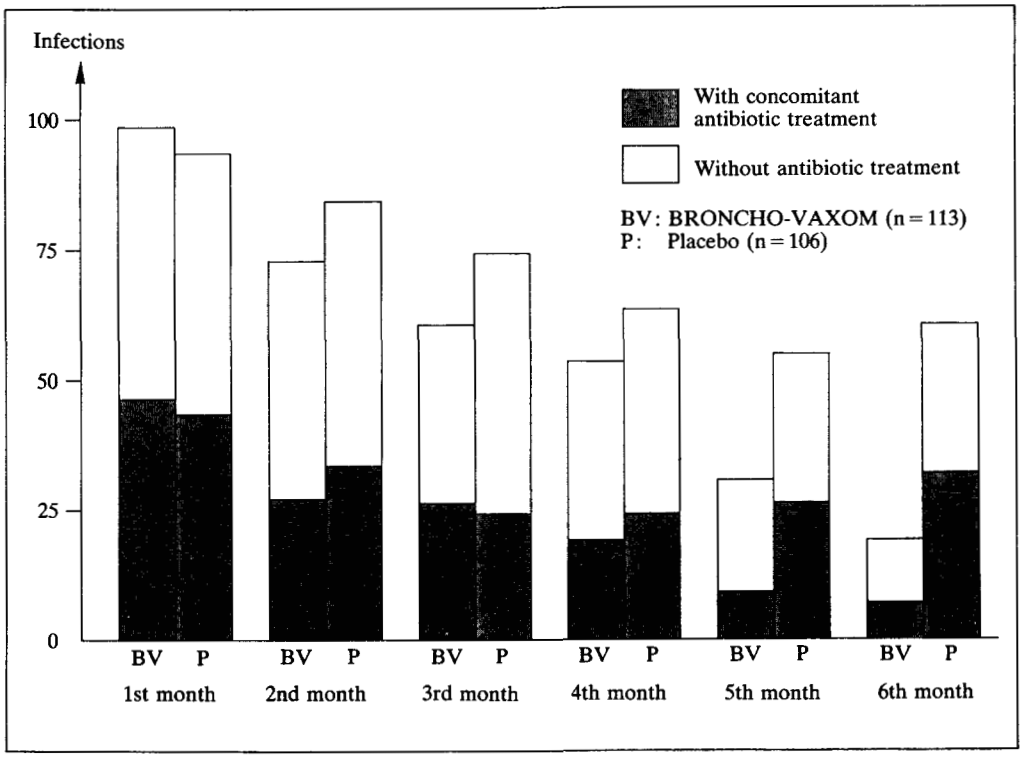


Fig. 4: Number of infections per month



Figs. 3 and 4: As this is a question of the sum of inter- and intra-individual data, the statistical evaluation of the interference had to be excluded.

Fig. 5: Evaluation of the therapeutic success by the *doctor* and the *patient*

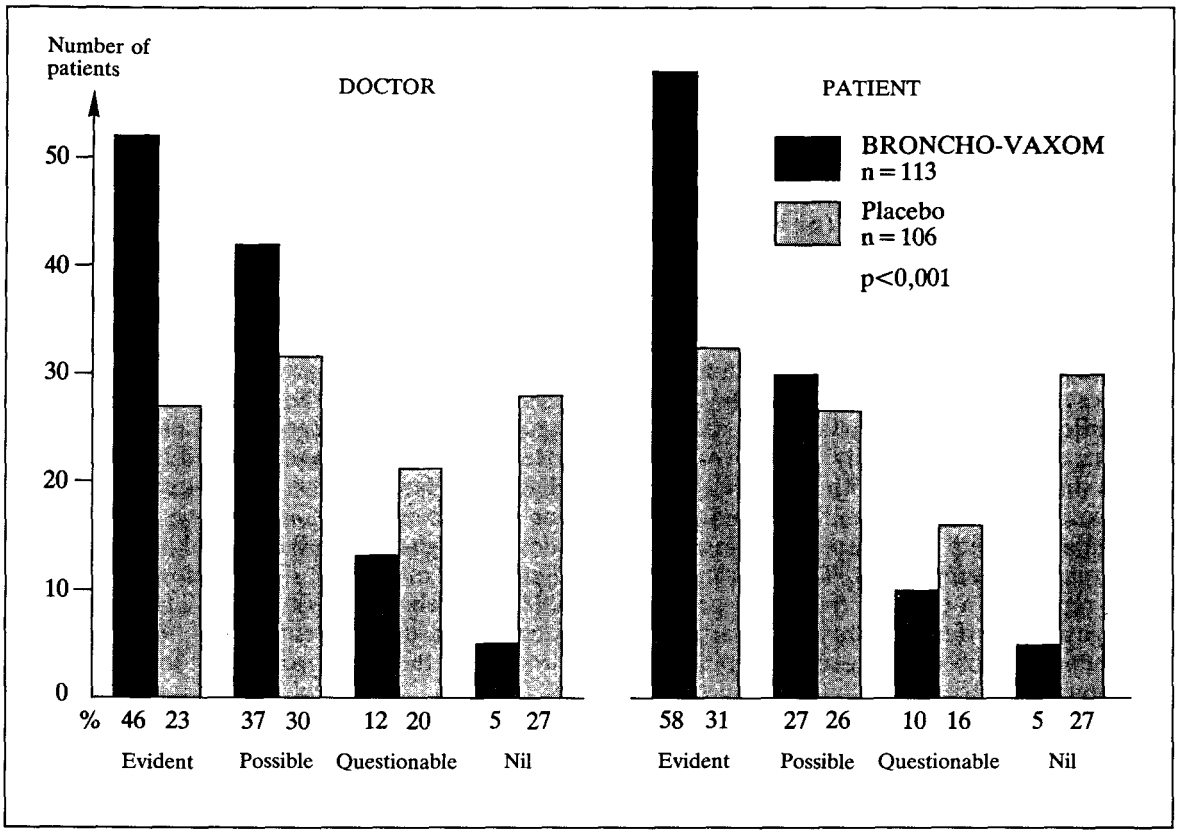


Fig. 5: The difference between BRONCHO-VAXOM and the placebo is *highly significant* ($p<0,001$, Uleman's asymptotic symmetrical test).