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Multicentre double blind clinical trial with BRONCHO-VAXOM in children

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Objective

The evaluation of the effectiveness of BRONCHO-VAXOM *Children* in the treatment of acute respiratory tract infections in children, and in the reduction of the frequency and the degree of severity of recurrences.

Period of the study

1 October 1981 - 30 July 1982

Number of doctors

27

Total number of patients

164 children

Inclusion criteria

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

Exclusion criteria

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

Distribution of groups

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

MATERIALS AND METHODS

Patient population

The study included 164 infants distributed over three age groups (Table 1):
≤ 4 years: 42% of patients in the BRONCHO-VAXOM group, and
40% of the patients in the placebo group.
5-10 years: 38% of the patients in the BRONCHO-VAXOM group and
43% of the patients in the placebo group
≥11 years: 13% of the patients in the BRONCHO-VAXOM group, and
8% of the patients in the placebo group.
73 of them were males and 80 females (taking into account the 11 cases of drop outs or with incomplete data which were excluded).

Trial design

The duration of the study was six months. The treatment consisted of taking one capsule of BRONCHO-VAXOM or of the placebo daily in the 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 started in the months of November or December 1981 (Table 3).
At the start of the treatment, an infection was present in 63 (76%) of the patients in the BRONCHO-VAXOM group and 53 (74%) of the placebo group (Table 7).

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Respiratory tract infections (among others: colds, influenza) were diagnosed in 39% of the BRONCHO-VAXOM group and 33% of the placebo group. Other diagnoses were: bronchitis (in 28% of the patients on BRONCHO-VAXOM and 35% of those on the placebo), pharyngitis, tonsillitis, rhinitis, otitis, sinusitis and bronchial asthma (Table 8).
During the course of the six-month observation period, the number, the type, and the degree of severity of the infections, as well as the duration of any necessary antibacterial therapy and the appearance of any possible side-effects were recorded.
The doctors also provided information in regard to the patients' degree of compliance and later evaluated whether, in their opinion and that of the patients or their parents, the treatment could be considered as a success.
The two groups, BRONCHO-VAXOM and the placebo, were equally represented by age and sex distribution, time the treatment began, observation period, degree of compliance, diagnosis and the presence of an infection at the start of the treatment (Tables 1, 2, 3, 4, 7, 8).

RESULTS

87 patients were treated with BRONCHO-VAXOM and 77 with the placebo. The treatment was interrupted in two patients in the BRONCHO-VAXOM group and one patient in the placebo group because of side-effects (Tables 5 and 6). Two patients from the BRONCHO-VAXOM group and four from the placebo group were excluded from the trial because of poor compliance (Table 4).
A biometric evaluation could thus be undertaken in 83 patients on BRONCHO-VAXOM and 72 on the placebo.

Frequency of infections

Infections appeared during the first month of treatment in 63 patients treated with BRONCHO-VAXOM and 53 patients treated with the placebo.
During the first month of treatment, in the BRONCHO-VAXOM group, 43 patients suffered from a single infection, 14 from 2 infections and 2 from 3 infections. In the placebo group, 33 patients suffered from a single infection, 16 from 2 infections and 4 from 3 infections. The frequency of infection diminished in a constant manner for both groups, although more strongly under BRONCHO-VAXOM by comparison with the placebo, for the following two months of treatment and the next three months of observation. In the patients of the BRONCHO-VAXOM group, the incidence of multiple infections was particularly reduced from the third month of treatment, whilst it remained unchanged in the patients of the placebo group (Fig. 1).
The numbers of BRONCHO-VAXOM patients who had suffered an infection during the first month of treatment and in whom no new infection appeared during each month of the three-month supplementary observation period, were 43, 41 and 47. These were larger than the number of equivalent patients on the placebo, in whom 32, 35 and 21 patients did not develop new infections at the corresponding times. The frequency of infections was reduced overall on BRONCHO-VAXOM, whilst it remained unchanged or even increased on the placebo during the course of the treatment and supplementary observation months. The differences between BRONCHO-VAXOM and the placebo were statistically significant when the 6th observation month was compared to the first treatment month ($p<0,01$, Uleman's test, Table 10).

Degree of severity of infections

During the first month of treatment, the degree of severity of infections in the BRONCHO-VAXOM group was classified as mild in 19 cases, moderate in 34 cases and marked in 28 cases. In the placebo group, the degree of severity was classified as mild in 20 cases, moderate in 29 cases and marked in 28 cases.
There was no difference between the two groups in regard to the frequency and the degree of severity of infections during the first month of treatment. In comparison with the placebo, the degrees of severity of infections then diminished in an increasing manner from the second month of treatment with BRONCHO-VAXOM. Thus, by the sixth month of observation, only 17 infections were classified as mild, 9 as moderate and 4 as marked in the BRONCHO-VAXOM group compared with 21 mild, 18 moderate and 10 marked in the placebo group (Fig. 2). The relative

incidences of infections, obtained by multiplying the number of infections by their degree of severity (mild = 1, moderate = 2, marked = 3), were noted for each observation month. The differences were highly significant in favour of BRONCHO-VAXOM by the sixth month ($p<0,001$, Uleman's asymptotic test, Table 9).

Duration of concomitant antibacterial treatment

During the first month of treatment, the 83 patients of the BRONCHO-VAXOM group received antibacterial treatment for respiratory tract infections for a total of 146 days as compared to 169 days for the 72 patients on the placebo. During the third treatment month and in particular during the supplementary observation period at the 4th, 5th and 6th months, a clearly smaller number of antibacterial medications was administered to the patients under BRONCHO-VAXOM (Fig. 3 and 4).

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

The doctors noted a positive response in 38 (46%) of the patients in the BRONCHO-VAXOM group and 19 (26,5%) of those in the placebo group.
On the other hand, for 25 (30%) BRONCHO-VAXOM patients and 26 (36%) placebo patients, a positive response was classified as possible. Furthermore the doctors considered the effect to be questionable in 9 (11%) of the patients in the BRONCHO-VAXOM group and 14 (19,5%) in the placebo group. No therapeutic success was noted in 11 (13%) of the patients treated with BRONCHO-VAXOM and in 13 (18%) of those on the placebo. The difference between the two groups was statistically significant ($p<0,05$, Uleman's test).
Evaluation of the treatment by the patients (or their parents) gave similar results. Of the patients in the BRONCHO-VAXOM group, 48 (58%) pointed out a clear improvement compared with 23 (32%) of those in the placebo group. As was the case with the doctors, 12 (14,5%) of the patients (or their parents) in the BRONCHO-VAXOM group and 16 (22%) of those in the placebo group noted no effect from the product (Table 11, fig. 5).

Tolerance

The doctors noted that BRONCHO-VAXOM was well tolerated in 83 (98%) of the cases and the placebo in 66 (91%) of the cases. 2 (2%) of the patients in the BRONCHO-VAXOM group and 7 (9%) of those in the placebo group reported side-effects. The treatment was interrupted in 2 (2%) of the patients in the BRONCHO-VAXOM group and in one patient in the placebo group. 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 link with BRONCHO-VAXOM (Table 6). Similar side-effects were, on the other hand, reported more often in the placebo group (Table 6).

Table 1: *Demographic data: age*
Results for 164 children (87 BRONCHO-VAXOM, 77 placebo)

Age / Product	≤4 years	5-10 years	≥11 years	Total	Drop out and incomplete data
BV	37 (42%)	33 (38%)	11 (13%)	87	6 (7%)
P	31 (40%)	33 (43%)	6 (8%)	77	7 (9%)

	BRONCHO-VAXOM	Placebo
Minimum:	1 year	1 year
Maximum:	19 years	18 years
Median:	5 years	5 years

The age distribution did *not* show any significant difference according to the χ^2 test.

Table 2: *Demographic data: sex*

Sex	Male	Female	Total	Drop out and incomplete data
BV	39	43	87	5
P	34	37	77	6

The two groups did *not* show any significant difference according to the χ^2 test.

Table 3: *Beginning of the treatment*

1981/82	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Drop out	Total patients
BV	–	41 (49,5%)	36 (43%)	4 (5%)	2 (2,5%)	–	4	87
P	–	33 (46%)	35 (49%)	4 (5%)	–	–	5	77

Duration of observations

Month	6	5	4	3	2	1	Drop out	Total patients
BV	75	–	8	–	–	–	4	87
P	65	–	7	–	–	–	5	77

Table 4: *Compliance*

Parameter	BV	P
Compliance:		
good	83 (97%)	69 (90%)
doubtful	1 (1%)	4 (5%)
poor	2 (2%)	4 (5%)
Total patients	86 (100%)	77 (100%)
Incomplete data or drop out	1	–
Overall total	87	77

Table 5: *Tolerance*

	BV	P
Good tolerance	83 (98%)	66 (91%)
Drop out (see table 6)	2	4
Side-effects without interruption of treatment	–	6 (8%)
Side-effects with interruption of treatment	2 (2%)	1 (1%)
Total patients	87 (100%)	77 (100%)

(The different rates of interruption of treatment are obviously explained by the fact that after the opening of the randomisation code, the patients in the placebo group continued with the trial, whilst those in the BRONCHO-VAXOM group interrupted it.)

Table 6: *Reported side-effects*

BRONCHO-VAXOM group (n = 87)

Patient number	Type of side-effect	Doctor's comments	Interruption of treatment
27	Abdominal pains and diarrhoea	Immediately after the 1st capsule (the patient interrupted the treatment for personal reasons)	Interruption
69	Gastrointestinal distress	No relationship to BRONCHO-VAXOM	Interruption

Placebo group (n = 77)

1	Hyperkeratotic folliculitis on the forehead and neck	–	*No* interruption
2	Loss of hair	Questionable	*No* interruption
3	Facial folliculitis	In the first month	*No* interruption
6	Feeling of gastrointestinal pressure	Several times after the dose (10-15 minutes), no vomiting, spontaneous regression of the troubles	*No* interruption
14	Vomiting	–	*No* interruption
25	Uncontrollable cough of long duration	Developed into pertussis (mother refused permission to continue the treatment)	Interruption
56	Allergy	Red spots on the trunk	*No* interruption

Table 7: *Presence of infection at the start of treatment*

Product	Yes	No	Total patients
BV	63 (76%)	20 (24%)	83 (100%)
P	53 (74%)	19 (26%)	72 (100%)

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

Table 8: *Distribution of diagnoses*

Diagnoses	BV	%	P	%
Sore throat	18	5,9	23	7,6
Bronchial asthma	4	1,3	3	1,0
Bronchitis	87	28,4	105	34,6
Respiratory tract infections (cold, influenza)	119	38,9	100	32,9
Pharyngitis	40	13,1	36	11,8
Rhinitis	15	5,0	15	4,9
Sinusitis	5	1,6	7	2,3
Otitis	16	5,2	11	3,6
Others (periporitis, pyodermia)	2	0,6	4	1,3
Total diagnoses	306	100	304	100

As one patient might have had several infections, the number of diagnoses is higher than that of the patients (n = 83, BRONCHO-VAXOM group; n = 72, placebo group). The χ^2 test is not applicable, as it presumes independent parameters.

Table 9: *Number of infections × degree of severity (see Fig. 1 and 2)*

Number 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	20	19	32	32	36	36	44	32	51	42	57	28
1	13	10	14	10	18	15	15	9	17	13	13	18
2	26	18	22	23	18	14	19	14	10	10	8	15
3	9	11	6	5	6	2	3	13	4	4	2	8
4	5	5	2	1	2	2	2	1	0	1	3	1
5	2	1	4	0	2	0	0	3	1	1	0	1
6	7	5	3	1	0	3	0	0	0	1	0	1
≥7	1	3	0	0	1	0	0	0	0	0	0	0
Total patients	83	72	83	72	83	72	83	72	83	72	83	72
Significance	n.s.		n.s.		n.s.		n.s.		n.s.		p<0,001	

Highly significant reduction at the 6th observation month ($p<0{,}001$, Uleman's asymptotic test).

Table 10: *Regression of infections*

Infection frequency	4th month compared to 1st		5th month compared to 1st		6th month compared to 1st	
	BV	P	BV	P	BV	P
Without symptoms No infection after treatment	43	32	41	35	47	21
Number of infections *reduced*	10	12	9	7	4	17
Stationary	28	20	18	14	20	18
Increased	2	8	7	9	4	9
Observation period shorter than 6, 5 and 4 months respectively			8	7	8	7
Total number of patients	83	72	83	72	83	72
Significance	n.s.		n.s.		$p<0,01$	

Table 11: *Evaluation of the effect by the doctor and the patient*

Parameter	Doctor		Patient	
	Number of patients		Number of patients	
	BV	P	BV	P
Evident effect	38	19	48	23
Possible effect	25	26	12	25
Questionable effect	9	14	11	6
No effect	11	13	12	16
Incomplete data				2
Total patients	83	72	83	72
Significance (Uleman's asymptotic test)	$p<0,05$		$p<0,05$	

The difference between BRONCHO-VAXOM and the placebo is *significant* ($p<0,05$, Uleman's asymptotic test).

Fig. 1: Number of patients suffering from infections

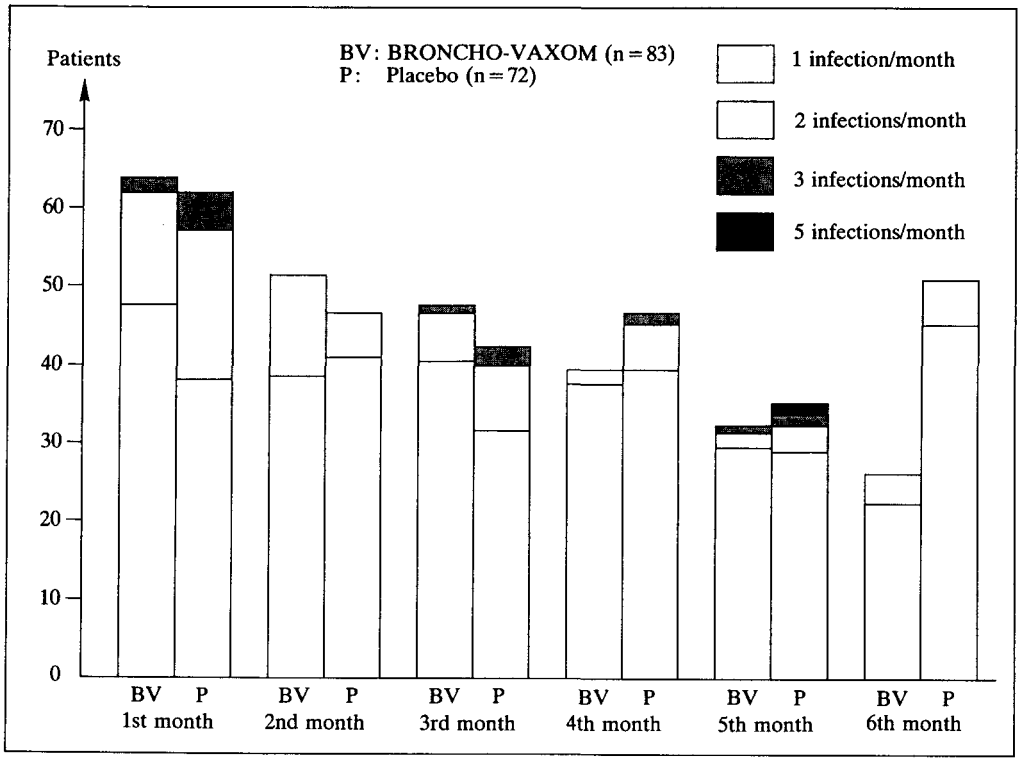


Fig. 2: Decrease in degree of severity of infections

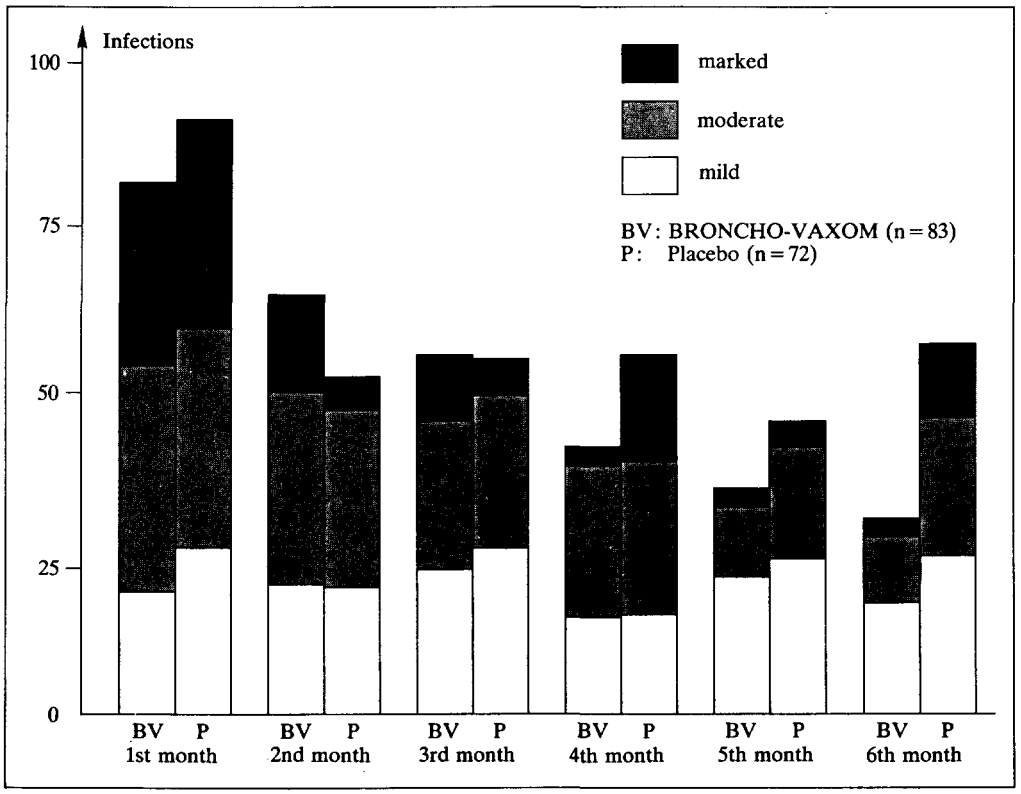


Fig. 3: Duration of antibacterial treatment (days in relation to the total number of patients)

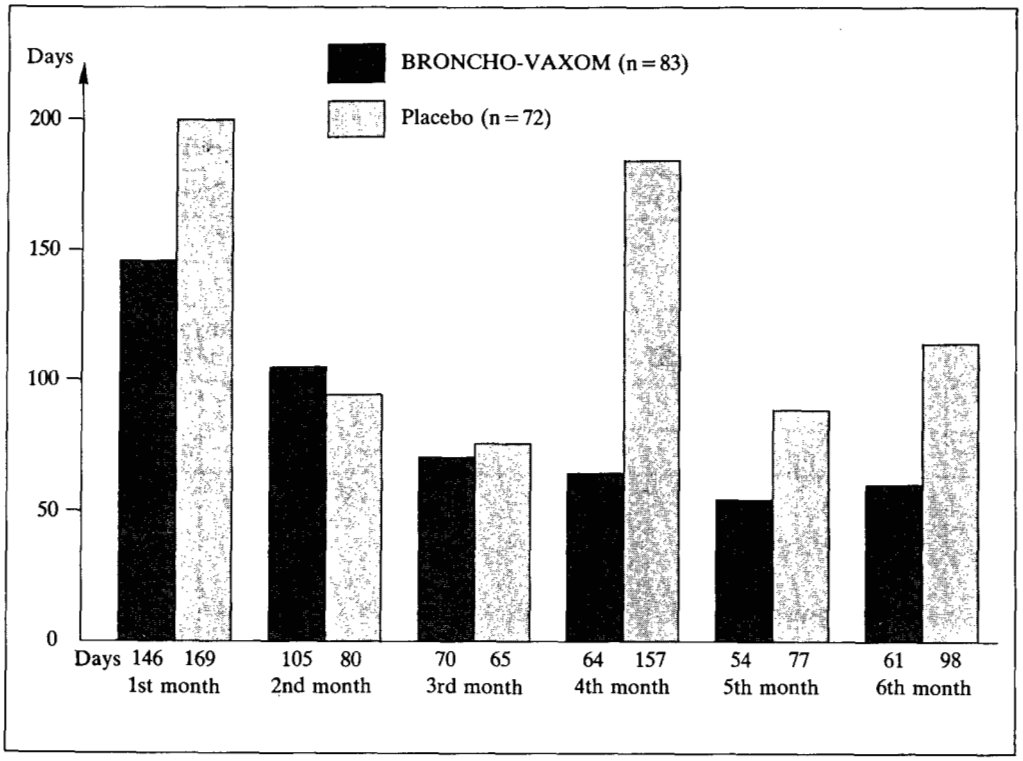
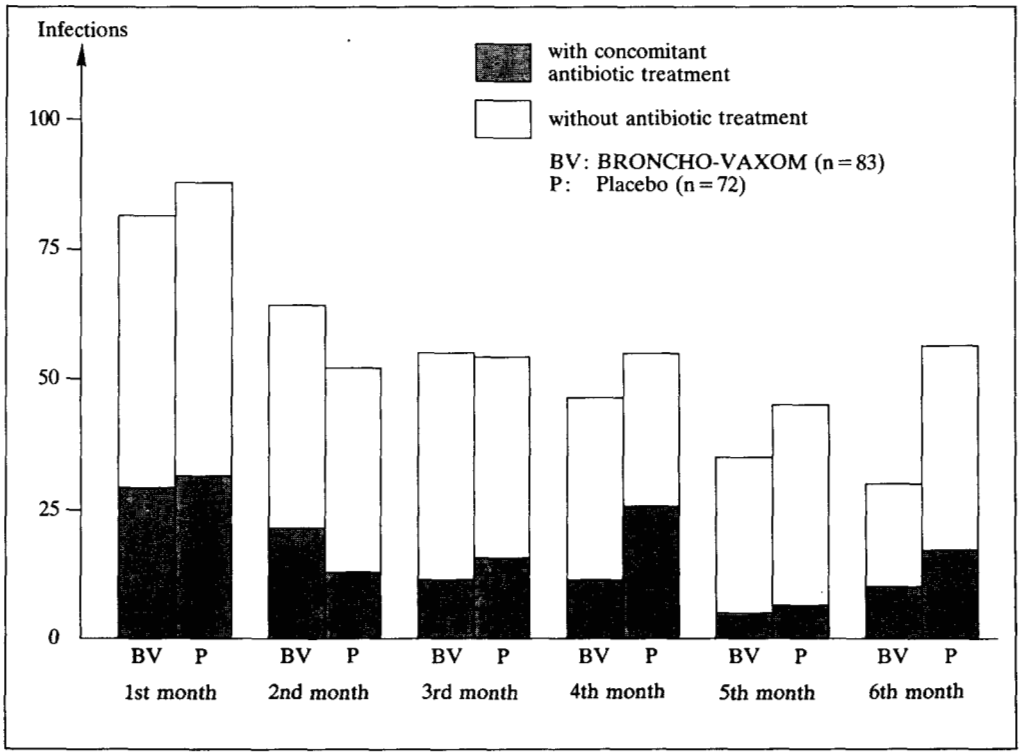
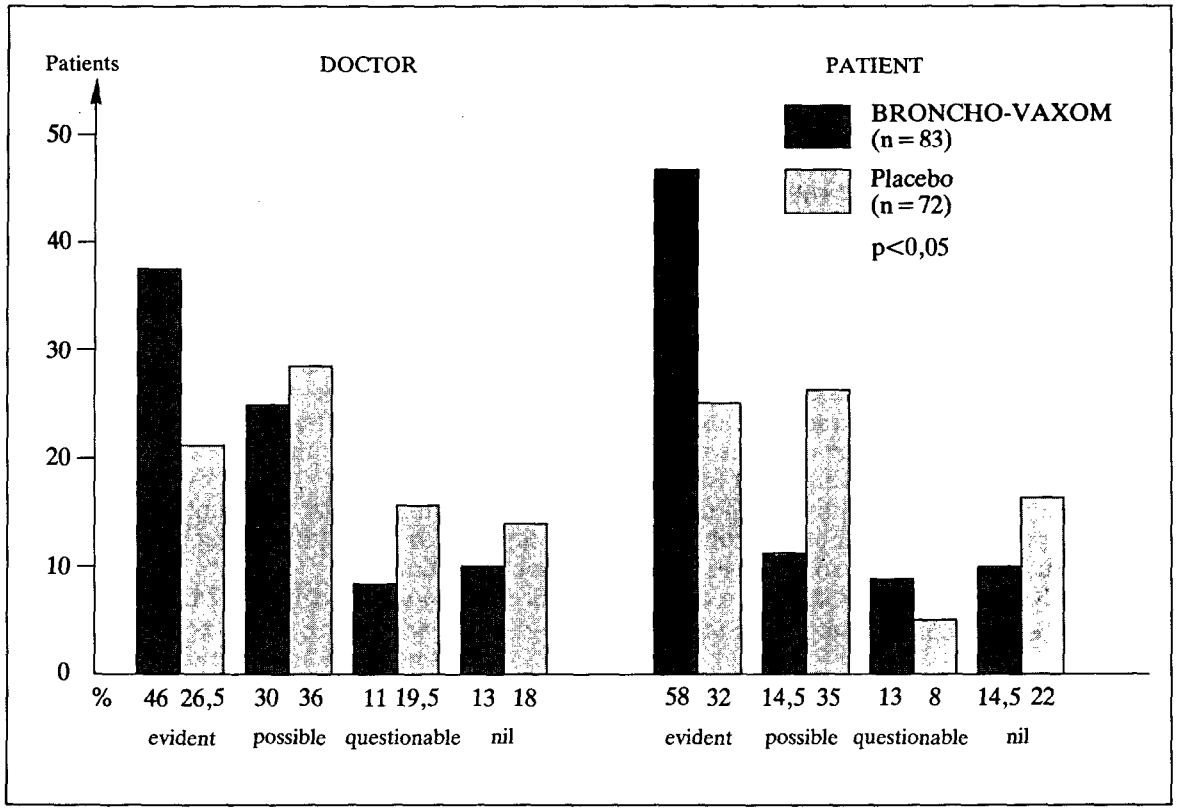


Fig. 4: Number of infections per month



Figs. 3 and 4: As these represent the total of the inter- and intra-individual data, a statistical analysis of the interference could not be performed.

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



The difference between BRONCHO-VAXOM and the placebo is *significant* ($p<0,05$, Uleman's symmetrical asymptotic test). (placebo group = 3% of incomplete data.)

Figs. 1, 2, 3, 4 and 5: In order to obtain statistically comparable values, the data from the placebo group have been multiplied by the coefficient 1,15.