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Stimulation of nonspecific immunity to reduce the risk of recurrent infections in children attending day-care centers

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A randomized, double blind, placebo-controlled clinical trial was performed in 423 children attending day-care centers to assess whether stimulating nonspecific immunity would reduce the incidence of recurrent infections. The drug used for the trial (Imocur®) is an extract obtained from eight different species of bacteria. At the end of the total follow-up period (3 months with treatment and 4.5 months without), the risk for ≥4 episodes of upper respiratory infections was not significantly lower in the treated group than in the placebo group (26.7% *vs.* 33.8%, relative risk, 0.79; 95% confidence interval, 0.59 to 1.06). In an exploratory analysis limited to the 3-month treatment period, however, we observed a 48% reduction in the risk of presenting ≥3 episodes of upper respiratory infections: 9.5% *vs.* 18.3%, respectively, in the treatment group and the placebo group (relative risk, 0.52; 95% confidence interval, 0.31 to 0.86). Similar results were found for the risk of ≥1 episode of gastroenteritis. We also observed a strong correlation between the drug efficacy and age; this observation is coherent with the underlying pathophysiologic model in which the immune system matures with age.

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INTRODUCTION

Close physical contact between children in day-care centers favors the transmission of infectious diseases.[1, 2] This situation represents a considerable health problem[3] and also has important economic consequences arising from the cost of the care provided and the time off work taken by parents to care for their sick children at home. Single episodes of upper respiratory tract infection and otitis media generally have a good prognosis, but evidence suggests that recurrence of these events (especially for otitis media) may adversely affect language and neurocognitive development[4, 5] and can lead to numerous medical and surgical treatments.[6] Wald et al.[7] found that the risk of experiencing six or more infections in 1 year was much higher in group day care (73%) than home care (29%) and we also showed that the risk of recurrent infections was 2 to 4 times higher in day-care centers than in family day care, depending on the type of infection.[8]

In most European countries prophylaxis of recurrent upper respiratory infections includes the use of immunostimulating agents made from a complex mixture of bacterial extracts (in contrast to purified preparations, such as glycans, also derived from bacteria).[9] An example of this latter class is Imocur®, also known as Broncho-Vaxom® or OM-85 BV, which is an extract obtained by submitting eight types of bacteria † to progressive alkaline lysis. The resulting preparation is then purified by means of clarification and filtration procedures. OM-85 BV was developed in Switzerland and in the 20 years since its release in 1972, it has been marketed in more than 30 countries in Europe, the Middle East and South America but not in North America. The drug is used in children with recurrent upper respiratory infections and is administered once

†*Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes*, viridans streptococci, *Moraxella catarrhalis*.

a day by mouth for 10 consecutive days in 3 consecutive months.

The mechanism of action of the drug is not completely understood, particularly because OM-85 BV is not a pure substance. OM-85 BV appears to stimulate nonspecific immunity rather than to provoke a specific response to its bacterial extracts; *in vitro* studies have demonstrated increased production of tumor necrosis factor alpha and interleukin 2 by macrophages, as well as an increase in the overall metabolic rate of the macrophages.[10-13] Activation of macrophages results in a two-pronged assault on invading organisms by enhancing the specific response of T lymphocytes and B lymphocytes and by increasing the phagocytic activity. This activation of macrophages may maintain the immune system in a "state of alert" that allows a rapid response to any invading organism, possibly rapid enough to prevent clinical illness.

Several double blind, randomized clinical trials have shown the efficacy of this product as a prophylaxis for children with a previous history of frequent respiratory infections.[14-16] The efficacy of OM-85 BV in breaking the cycle of recurrent infections was demonstrated recently by Paupe[17] in a double blind trial of OM-85 BV *vs.* placebo in 116 children ages 6 months to 19 years who had a recent history of at least 3 episodes of upper respiratory infections in a 6-month period. At the end of a 6-month follow-up period (3 months with treatment, 3 months without), 39% of children treated with OM-85 BV had no infections compared with 16% of the placebo group; concomitantly, fewer children in the treated group were prescribed antibiotics (24% *vs.* 44% in the placebo group).

Considering the high risk of repeated infections in day-care centers,[7, 8] the large variety of microorganisms involved and the fact that most of them cannot currently be prevented by vaccines, we hypothesized that stimulation of nonspecific immunity might be effective in this setting. We also hypothesized that the drug-induced nonspecific immune response might also provide protection against gastroenteritis, another highly prevalent condition in day-care centers. To our knowledge this is the first randomized clinical trial aimed at evaluating the efficacy of an immunostimulating agent for the prevention of recurrent infections in children attending day-care centers.

METHODS

Children were selected from 46 day-care centers in the Rhône region (Lyon) of France. We excluded children younger than 6 months of age (still protected by maternal antibodies), those unlikely to complete follow-up (e.g. planning to leave the day-care facility before the end of the study) and those with severe concomitant illnesses. Any child having received a drug modifying the immune system (i.e. immunosuppressant, immunostimulant, gamma-globulin, or long term use (≥2 weeks) of systemic corticosteroid) in the 6 months preceding the study was also excluded.

Children were recruited through group meetings with parents.[18] They were given 1 week to decide whether or not to participate and to sign an informed consent form. Children included in the study were allocated either to Imocur® or placebo groups by a double blind, centralized, randomization procedure according to a special program for remote data entry through Minitel® (a national telecommunication system network in France). Randomization was also stratified for day-care center (because of the high variability in the incidence of infection from one center to another) and blocked for every four children so as to favor a roughly equal number allocated to both groups in each center.

After randomization the parents were provided with a supply of the treatment allocated to their child, either the Imocur® (3.5 mg of bacterial extracts) or a physically similar placebo, to be taken by the mouth. On October 15, 1989, all children began their treatment for 10 consecutive days in each of 3 successive months (October, November and December, 1989). Follow-up began on the first day of treatment and was continued until May 31, 1990 (a total of 7.5 months), comprising a 3-month treatment period and a 4.5-month posttreatment follow-up that ended with the usual summer vacation.

All settings in this study were under the control of the French Public Health Services and had similar economic and social criteria for admission. Thus the populations were similar in all settings. All day-care settings were under the responsibility of a nursing director with specialization in pediatrics, who supervised the daily follow-up and recorded all infectious episodes. An infectious episode was defined as the acute occurrence of a new symptom lasting for at least 48 hours and resulting in a specific treatment (including nonpharmacologic treatment such as diet or cooling bath). Two episodes were counted as such only if they were separated by a symptom-free week. When a child was sick the event was reported by the nursing director and a questionnaire was given to the parents to record the symptoms, physician's diagnosis, treatment and final outcome. Two research assistants were responsible for data collection and quality control; they visited each nursing director once a week and data were entered daily using a computerized, interactive data quality control process that permitted the corrections of errors within a 2-week period after the end of an infectious event. Treatment side effects were monitored by spontaneous reporting during the study and by a questionnaire that was systematically completed at the end of the study to investigate the presence of digestive or respiratory problems.

The statistical analysis focused on the repetition of infectious events. Criteria for "repetition" were based on the distributions observed in other epidemiologic studies[8, 19] and were specified *a priori* in the protocol approved by the Claude Bernard Ethics Committee. The main study outcome was the occurrence of at least 4 episodes of upper respiratory infection. Each episode of upper respiratory infection was defined as a new illness characterized by either rhinitis plus fever, pharyngitis, laryngitis, cough, bronchiolitis or otitis media. Two secondary end points were also studied: the occurrence of ≥2 episodes of otitis media (as diagnosed by a physician), and ≥2 episodes of gastroenteritis (unusually loose or frequent stools, as determined by the care giver).

Two exploratory analyses also examined the variation of efficacy with the administration of the immunostimulating agent (i.e. during and after the treatment period) and the variation of efficacy with age. Because the treatment period was shorter the primary and secondary end points examined were, respectively, ≥3 episodes of upper respiratory infection, ≥1 episode of otitis and ≥1 episode of gastroenteritis.

The analysis was based on intention to treat using the SAS and BMDP statistical packages. The summarized results are presented as relative risks with their 95% confidence intervals. Systematic adjustment for potential confounders was also performed with a multivariate logistic model.

RESULTS

Of the 1222 children attending the selected day-care settings, 352 did not satisfy the inclusion criteria for the following reasons: 127 were too young; 96 were planning to leave the center before the end of the study; 140 were already receiving a similar drug; 14 were receiving gamma-globulin treatment; 3 children had a congenital cardiac condition; 2 had chronic pulmonary disease; and 5 had Down's syndrome. The parents of 427 of the 870 eligible children (49.5%) gave informed written consent, but as we had decided to include only centers with at least 4 participating children (i.e. one treatment block), 4 additional eligible children were also excluded, thus leaving 423. Randomization allocated 210 children to the treatment group and 213 to the placebo group. Table 1 shows the distribution of the variables that could confound the relationship between treatment and outcome.

Twenty-eight children (11 from the treated group and 17 from the placebo group), or 6.6%, did not complete the entire follow-up period. None of these children withdrew from the study for medical or drug-related reasons, however. The main reasons were either that the parents moved or that the mother stopped work. We were able to contact 18 of these families by telephone at the end of the study to obtain information concerning their child's health status. Thus the true number of children lost to follow-up was only 10 of 423 (2.3%).

TABLE 1. Pretreatment characteristics of the placebo and treated groups

Characteristics	Placebo Group (n = 213)	Treated Group (n = 210)
Age (months)		
<12 (%)	37	28
12–<18 (%)	34	33
≥18 (%)	29	39
Male child (%)	56.3	50.0
Breast-fed ≥1 month	57.7	64.3
Child's case history (%)		
Wheezy bronchiolitis	31.9	33.3
Rhinitis with fever	74.2	80.0
Otitis media	48.8	49.2
Gastroenteritis	29.1	33.8
Previous hospitalization (%)	10.8	9.5
Family history (%)		
Otitis media		
Father	12.4	13.2
Mother	17.4	21.2
Asthma		
Father	5.1	8.2
Mother	6.3	6.4
Hay fever		
Father	19.9	17.2
Mother	9.2	16.2
No. of siblings (mean)	1.54	1.52
≥1 parent who smokes (%)	39.2	48.6
Living in a house (*vs.* apartment) (%)	14.2	10.4
Central heating (*vs.* other type) (%)	36.3	41.4
Followed by a pediatrician (%)	68.2	69.4

The results at the end of the total follow-up period (main analysis) are summarized in Table 2. We observed a small, nonsignificant reduction of 21% in the risk of recurrent infection; adjustment for potential confounders (i.e. age, gender, breast-feeding, history of maternal hay fever and presence of a smoker in the home) did not change these results.

In an exploratory analysis limited to the 3-month treatment period, however, we observed a 48% reduction in the risk of ≥3 episodes of upper respiratory infections: 9.5% *vs.* 18.3%, respectively, in the treatment and the placebo groups (relative risk, 0.52; 95% confidence interval, 0.31 to 0.86). Similar results were found for the risk of ≥1 episode of gastroenteritis: 20.5% in the treatment group *vs.* 32.9% in the placebo group (relative risk, 0.62; 95% confidence interval 0.45 to 0.87). Adjustment for potential confounders did not change these results. During this period we also found that age modified the effect of treatment, with a

TABLE 2. Results obtained during the total (7.5-month) follow-up period

Outcome Criteria	No. in Placebo Group (n = 213)	No. in Treated Group (n = 210)	Relative Risk
Main end point: ≥4 upper respiratory infections	72 (33.8)*	56 (26.7)*	0.79 (0.59–1.06)†
Secondary end points			
≥2 otitis media	41 (19.2)	29 (13.8)	0.72 (0.46–1.10)
≥2 gastroenteritis	33 (15.5)	25 (11.9)	0.77 (0.47–1.25)

* Numbers in parentheses, percent.
† Numbers in parentheses, 95% confidence interval.

positive association between child age and treatment efficacy. For the age groups 6 to 9 months (n = 78), >9 to 12 months (n = 59), >12 to 18 months (n = 142) and >18 months (n = 144), the relative risks (and 95% confidence intervals) comparing treatment and placebo were 0.86 (0.40 to 1.87), 0.68 (0.23 to 2.01), 0.66 (0.23 to 1.92), and 0.21 (0.06 to 0.71), respectively. The relationship between the improvement of drug efficacy and child age is presented in Figure 1; this trend is linear and the slope is statistically different from 0 (P = 0.024).

Through spontaneous reporting of side effects, we recorded 17 medical events for the treated group and 19 for the placebo group, with no obvious differences between the 2 groups (Table 3). The responses to the end-of-study questionnaire were very similar in the 2 groups, with no difference reaching statistical significance.

TABLE 3. Medical events recorded from spontaneous reporting by parents

Treated Group	Placebo Group
Crushed finger	Crushed finger
Intussusception	Tympanocentesis (n = 3)
Mycosis	Urinary infection
Inguinal hernia	Impetigo
Eczema (n = 3)	Adenoidectomy (n = 2)
Reaction to measles-mumps-rubella vaccine	Convulsion
	Bilateral inguinal hernia
Dermatitis, with reddening and fever	Surgical operation
Nappy rash, with infection	Eczema
Fall, broken finger	Urinary infection
Adenoidectomy (n = 2)	Vesicoureteric reflux
Hypospadias (operated)	Urticaria
Reaction to mosquito bite	Vaginal candidiasis
Convulsion	Fall
Burn	Fungal infection on buttocks
	Broken collarbone

DISCUSSION

The efficacy of Imocur® has previously been studied in children suffering from recurrent upper respiratory infections,[14–17] but our study is the first in which attention has focused on its efficacy in the primary prevention of recurrent infections for children attending day care. The double blind design, the small loss (6.6% withdrawal; 2.3% lost to follow-up) and the high quality of nursing directors (who received specific training for the study) provide added confidence in the results.

It is interesting to note the difference in the effect between the total follow-up period, where the clinical impact of the treatment was marginal and not statistically significant, and the treatment period, where (although based on an analysis not planned *a priori*) it was associated with a clinically important and statistically significant reduction in the risk of three or more episodes of upper respiratory infections. One possible explanation for this difference in efficacy for the two periods is that the immune system is stimulated only when the product is being taken and that the effect gradually diminishes during the post treatment period. The cumulative risk of having at least three episodes of upper respiratory infections in both groups is displayed graphically in Figure 2. It can be seen that the difference between the two groups increases progressively until the end of the treatment period, when the difference is highly significant; the difference in risk then remains constant (no further increases and no catch-up phenomena), but becomes

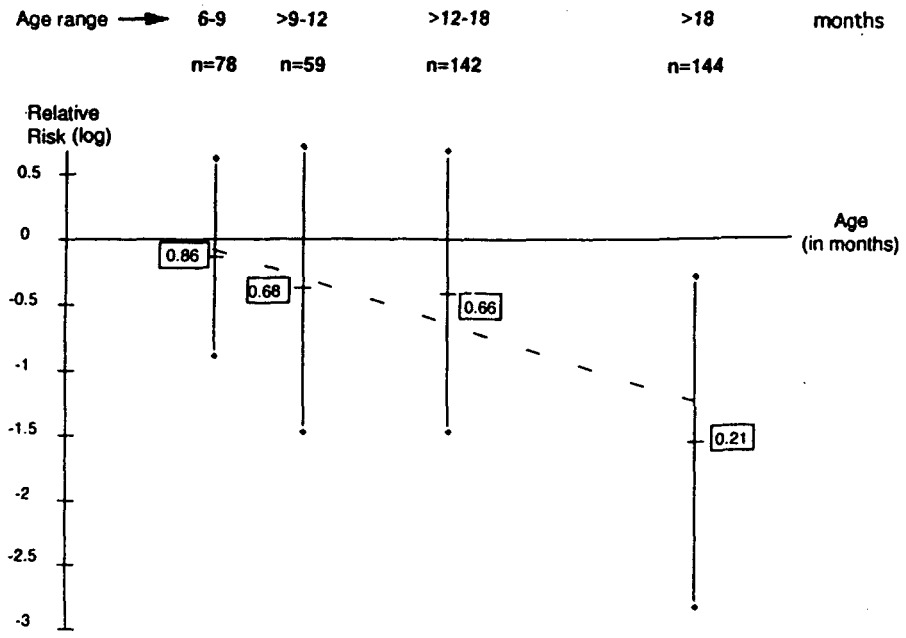

FIG. 1. Relative risk (Imocur® *vs.* placebo) of recurrent upper respiratory infections. Variation of efficacy with age. *Boxed value*, Point estimate of the relative risk, thus, 0.25 denotes a relative risk of 0.25.

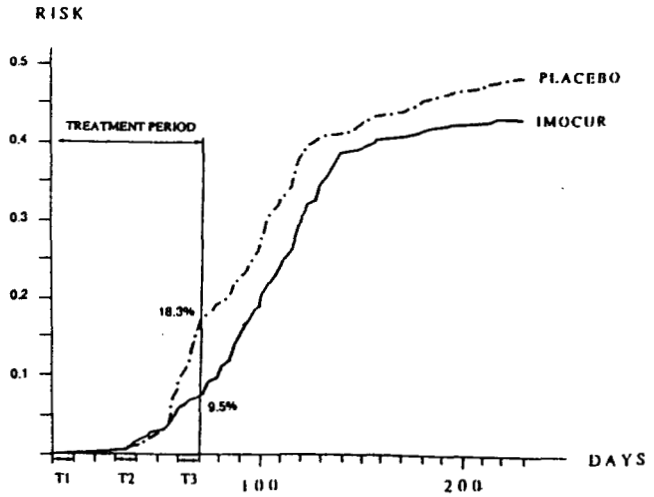

FIG. 2. Cumulative risk of recurrent upper respiratory infections in children treated respectively by Imocur® and placebo, during the total study period (7.5 months). The treatment was administered orally 10 days/month for 3 consecutive months (*T1, T2, T3*).

statistically nonsignificant by the end of the follow-up (owing to a constant risk difference at a higher absolute risk). The phenomenon displayed on Figure 2 is consistent with a nonspecific, nonanamnestic response of the immune system.

Similar results were observed for the risk of ≥1 episode of gastroenteritis, which was 38% lower in the treated group than in the placebo group during the treatment period. The effect of an immunostimulating agent on gastroenteritis has never been examined in previous studies of Imocur®, which have focused only on upper respiratory infections. This observation of a prophylactic benefit for gastroenteritis is consistent with an induced nonspecific immunity, which could be effective against a large variety of microorganisms that enter the body through the oral pathway.

The increase in treatment efficacy with age was also not hypothesized *a priori* but is likely to be related to the maturation of the immune system with age, the immunostimulant being more effective as the immune system matures. Such effect modification by age deserves further study, both to confirm our findings and to explore possible mechanisms.

The health-related events identified during the course of the study were very infrequent and appear unlikely to be related to the drug. After 20 years of extensive use in many countries, no severe adverse events have been reported to the national adverse reaction surveillance programs. Moreover, the likely mechanism of action (i.e. nonspecific macrophage stimulation) is likely to be safe.

Although the results of our exploratory analysis suggest an interesting hypothesis about the action of immunostimulating agents and their potential future applications, the results require verification in other randomized trials. We have recently begun a new trial to test this hypothesis. Confirmation of an important reduction in recurrent upper respiratory infections and gastroenteritis during the treatment period may have far-reaching clinical, public health and economic implications. These infections lead to frequent morbidity, antibiotic and antipyretic treatment, loss of time from work by parents, physician visits and surgical procedures. In the absence of effective vaccines for these infections, stimulation of nonspecific immunity represents a potentially important preventive strategy that merits further study.

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