# The immunostimulant OM-85 BV prevents wheezing attacks in preschool children

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**Background: No reagents have been shown to be effective in preventing wheezing attacks provoked by acute respiratory tract illnesses (ARTIs) in preschool children. New therapeutic agents and preventive strategies are needed.**
**Objectives: We assessed the effect of OM-85 BV (Broncho-Vaxom; OM Pharma, Geneva, Switzerland) in preventing ARTI-provoked wheezing attacks in preschool children with recurrent wheezing.**
**Methods: A randomized, double-blind, placebo-controlled, parallel-group study was carried out between August 2007 and September 2008. The study included 75 children with recurrent wheezing who were 1 to 6 years old. Participants were randomly assigned to groups given either OM-85 BV or a placebo (1 capsule per day for 10 days each month for 3 consecutive months) at the start of the trial. Participants were followed for 12 months, which included the administration period of the test article.**
**Results: Subjects given OM-85 BV had a lower rate of wheezing attacks. The cumulative difference in wheezing attacks between the 2 groups was 2.18 wheezing attacks per patient in 12 months; there was a 37.9% reduction in the group given OM-85 BV compared with the group given placebo ($P < .001$). Stepwise multiple (linear) regression analysis showed that the main difference between the OM-85 BV and placebo groups was a reduction the number of ARTIs ($R = -0.805$, $P < .001$). The duration of each wheezing attack was 2 days shorter in the group given OM-85 BV than in the group given placebo ($P = .001$).**
**Conclusion: Administration of OM-85 BV significantly reduced the rate and duration of wheezing attacks in preschool children with ARTIs. (J Allergy Clin Immunol 2010;126:763-9.)**

***Key words:*** *Wheezing, OM-85 BV, children*

*Abbreviations used*
ARTI: Acute respiratory tract illness
ICS: Inhaled corticosteroid

The prevalence of asthma has increased over the last 20 to 30 years.[1] Most preschool children have episodic asthma exacerbated by viral colds, with few or no interval symptoms, such as activity-induced coughing or wheezing.[2,3]

Inhaled steroids are the mainstay of treatment for persistent asthma; their use is associated with reduced risk of exacerbation.[4] The Physical Exercise and Activity in Kids study reported that daily use of inhaled corticosteroids (ICSs) reduced exacerbations in preschool children.[5] However, in a subgroup of young children with intermittent wheezing induced by only respiratory tract viral infections, symptoms improved modestly after episodic use of relatively high-dose ICSs[6,7]; these attacks could not be prevented with a maintenance dose of ICSs.[8-10] A Cochrane meta-analysis showed no benefit from continuous use of preventative anti-inflammatory medications among children of any age in this subgroup.[11] Montelukast, an antagonist of the cysteinyl leukotriene receptor, significantly reduced the rate of asthma exacerbations in young children (by 32%).[12] The data on montelukast are promising but require replication in a large independent trial.

Current therapies have limited efficacy in preventing virus-provoked wheezing attacks; new therapeutic agents and primary or secondary preventative strategies need to be developed.[13] Because infants and preschool children catch an average of 6 to 8 colds per year and respiratory tract viral infections are detected in most children with asthma exacerbations (80% to 85%),[14] secondary approaches to prevent wheezing attacks in preschool-ages children should focus on preventing acute respiratory tract illnesses (ARTIs).[15]

OM-85 BV (Broncho-Vaxom; OM Pharma, Meyrin/Geneva, Switzerland) is an immunostimulant extracted from 8 bacterial pathogens of the upper respiratory tract. Several randomized clinical trials[16-22] have shown that OM-85 BV can reduce the number of ARTIs by 25% to 50% compared with placebo in adults and children with a history of recurrence. However, these studies were designed to demonstrate the preventive effect of OM-85 BV on ARTIs in children with recurrent infections; recurrent wheezing and asthma were among the exclusion criteria.

We propose that ARTIs are the main cause of recurrent wheezing attacks in preschool-aged children and that ARTI-induced wheezing attacks could be reduced by OM-85 BV.

## METHODS

### Patients

The study included children who were 1 to 6 years old with 3 or more acute wheezing attacks induced by respiratory tract illness in the previous 6 months (according to medical records from outpatient clinics). Exclusion criteria were as follows: anatomic alterations of the respiratory tract; chronic respiratory diseases (tuberculosis and cystic fibrosis); autoimmune disease; liver or kidney failure; malnutrition; cancer; treatment with inhaled or systemic corticosteroids within the previous month; and treatment with

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immunosuppressants, immunostimulants, gamma globulins, or anticonvulsive drugs within the previous 6 months.

## Study design

This study was a randomized, double-blind, placebo-controlled, parallel-group study with OM-85 BV in patients with recurrent wheezing. It was carried out from August 2007 to September 2008 at the outpatient Department of Pediatric Allergy of Kecioren Education and Research Hospital in Ankara, Turkey.

The primary aim of the study was to investigate the effect of OM-85 BV on the total number of wheezing attacks induced by ARTIs over a 12-month period (excluding the first 15 days' randomized assignment to study groups). The secondary aims were to investigate the effect of OM-85 BV on (1) duration of wheezing episodes, (2) the number and duration of $\beta_2$-agonist and steroid uses during the attacks, (3) the rate of hospitalization, (4) the number of ARTIs, and (5) the number of cases of acute nasopharyngitis over the 12-month period.

The characteristics of wheezing attacks were recorded in case report forms as they were observed. As patients were enrolled in the study, consecutive numbers were assigned (double-blind code). The numbers were randomly assigned to the treatment groups in balanced blocks of 10 by using a random allocation software computer program. The treatment for each patient number was prepared in advance. K. H. prepared the randomization list and the rest of the materials but was blind to the patient list. The double-blind code for the treatment numbers were enclosed in opaque sealed envelopes and kept available for the researcher in the study center to be opened in case of a serious adverse event. Sealed envelopes were recovered by the primary investigator (C. H. R) at the end of the trial. All investigators were blind to the allocation of treatment until data analysis was completed.

The study was approved by the Ethics Committee of the Turkish Ministry of Health, and written informed consent was obtained from parents of patients on entry into the study.

## Study protocol

OM-85 BV contains 3.5 mg of standardized lyophilized fractions per capsule from the following bacteria: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Neisseria catarrhalis*.

The children received 1 capsule of OM-85 BV (3.5 mg) or placebo per day for 10 consecutive days in each of 3 months. The test articles were given to parents by the training nurse, who was not involved in the study design or analysis. The boxes, blisters, and capsules had the same appearance, and the tastes of the powders were similar. Children less than 5 years old received powder from open capsules, and children older than 5 years received capsules. The capsules or powder were administered by the parents, and the empty blisters were kept from control compliance (to count any missing capsules).

Patients were assessed monthly and every time they had respiratory tract symptoms. If the patients had a wheezing attack, the number of days to clinical cure, the number of days that $\beta_2$-agonists and oral steroids were used, and the number and duration of hospitalizations were recorded. All the physical examinations and data collection were performed by the primary investigator (C. H. R.), who also wrote all prescriptions.

An acute wheezing attack was defined as an episode of progressively increasing shortness of breath, cough, wheezing, chest retraction or tightness, or any combination of these symptoms that lasted at least 6 hours with normal results on chest radiographic examinations. When repeated symptoms were observed, attacks were counted separately only if the patient had been without symptoms for at least 1 week between the end of one episode and the beginning of another. All the wheezing attacks were followed until a complete disappearance of all the symptoms was observed; clinical cure was defined as the complete resolution of all symptoms.

ARTIs (acute nasopharyngitis, sinusitis, acute otitis, tonsillitis, viral croup, or pneumonia) were defined by the presence of diagnostic symptoms for at least 48 hours. Multiple illnesses were counted only if the patient was without symptoms for at least 72 hours between the end of one episode and the beginning of another.[20]

Adverse events were recorded on the case report forms as soon as they were detected. Afterward, they were noted in the monthly adverse event report form and case report form.

## Treatment of asthma symptoms during the study period

Based on the child's asthma symptoms, the need for hospitalization, and the number of wheezing attacks or the number of prednisolone courses required (for acute exacerbations), children were treated with ICSs or montelukast as the baseline therapy. Additions or reductions of asthma medications and treatment of wheezing attacks were performed according to the National Asthma Education and Prevention Program's Expert Panel Report 3.[4]

## Statistical analysis

The primary efficacy parameter was based on the total number of wheezing attacks per patient induced by ARTIs over the 12-month period. Virus-provoked wheezing attacks in the first 15 days of the trial were disregarded because they were probably associated with wheezing present during the initial visit. All analyses were performed with a commercially available software program (SPSS Statistical Software, version 11.5; SPSS, Inc, Chicago, Ill). The Shapiro-Wilks test was used to evaluate normality of the distributions collected. When variables were normally distributed, they were expressed as means (SDs); otherwise, they were expressed as medians and interquartile ranges (25th-75th percentiles). The $\chi^2$ test was used for categorical variables and expressed as observation counts (in percentages). Because the variables of wheezing episodes and ARTIs were not distributed normally, they were expressed as medians and interquartile ranges (25th-75th percentiles). This study was powered to demonstrate a 30% reduction of wheezing episodes compared with placebo, and therefore data were expressed as means $\pm$ SDs to demonstrate percentage differences between the groups. A Bonferroni multiple comparison test was used to compared paired intervals (0-3, 0-6, 0-9, and 0-12 months). All $P$ values were 2-tailed; a $P$ value of less than .05 was considered statistically significant.

## Power and sample size

Based on a pilot study and clinical experience, we expected to observe a 30% decrease in the rate of virus-provoked wheezing attacks in the OM-85 BV group compared with the placebo group. During the 6-month pilot study, the number of virus-provoked wheezing attacks was 2.4 $\pm$ 1.3 in the placebo group. Using a difference of 0.8 $\pm$ 1.1 virus-provoked wheezing attacks between the groups with an $\alpha$ value of .05 and a $\beta$ value of .10 (ie, with a power of 90%), the required sample size was calculated to be 29 patients per group. Sample size estimation was performed by using the NCSS and PASS 2000 software.

# RESULTS

Eighty of 100 children were selected to participate in the trial. All participants in the placebo group completed the trial, but 5 patients in the OM-85 BV group did not. In the OM-85 BV group 1 patient refused to take the drug at the beginning of the study and was excluded from the study, 2 patients moved to another city (within the first 3 months of the study), and 2 patients did not attend any follow-up visits. The remaining 75 subjects (35 in the OM-85 BV group and 40 in the placebo group) completed all the follow-up visits (Fig 1). All the envelopes that contained the double-blind code for the treatment numbers were collected on completion of the study. Based on the empty blisters, compliance was greater than 90% for all patients. In the OM-85 BV group 32 children received powder, and 3 children received capsules; in the placebo group 36 children received powder, and 4 children received capsules. Analysis of the main demographic

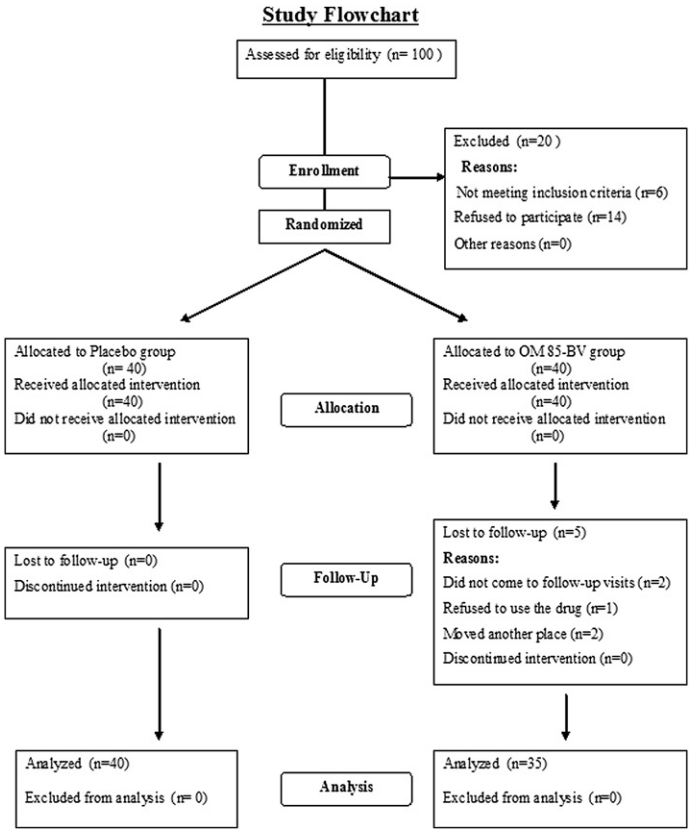


**FIG 1.** Study flowchart.

characteristics showed that although family histories of asthma and smoking were of borderline significance, the groups were fairly homogeneous and therefore comparable (Table I).

The cumulative mean rate of wheezing attacks per 3 months per patient was consistently lower in the group given OM-85 BV (Table II), and the difference between groups increased progressively throughout the course of the study. Over the 12-month study period, OM-85 BV significantly reduced the mean incidence of wheezing attacks by 37.9% (ratio of the final mean difference between the 2 groups, 2.18, to the final mean incidence of wheezing attacks in the placebo group, 5.75). OM-85 BV also reduced the mean incidence of ARTIs by 31.4% (ratio of 2.44-7.75, Table III) and the mean incidence of acute nasopharyngitis by 37.5% (ratio of 2.11-5.62, Table IV).

We performed an explorative analysis using stepwise multiple (linear) regression analysis with accumulated rate of wheezing attacks by the 12th month as a dependent variable; age, treatment, number of wheezing attacks in the previous year, sex, atopy, history of allergy, and history of smoking at home were used as independent variables. The differences observed between groups given OM-85 BV and placebo were independent of these variables; the major discrepancy was OM-85 BV administration ($R = 0.431$, $P < .001$). After adding the numbers of ARTIs and acute episodes of nasopharyngitis during the study period into the model with or without OM-85 BV administration, the main difference between the OM-85 BV and placebo groups was a reduction in ARTIs ($R = -0.805$, $P < .001$).

Hospitalization rates, duration of hospitalization, duration of systemic steroid therapy during attacks, and number of wheezing attacks that required systemic steroid therapy did not differ between groups (Table V). The total duration of wheezing attacks and duration of each wheezing attack were shorter in the OM-85 BV group (Table V).

## Seasonal effect

The incidence of acute wheezing attacks was higher in the first 3 months of the study (from September to November) in both groups and decreased slightly thereafter. The majority of acute wheezing attacks occurred in the first 6 months of the study (from September to February); the benefits of OM-85 BV were the greatest during this period.

## Safety

Five patients (3 patients who received OM-85 BV and 2 patients who received placebo) reported 5 adverse reactions that were considered to be related to the test materials. These were diarrhea (1 patient), abdominal pain (1 patient), and erythema nodosum (1 patient) in the OM-85 BV group and diarrhea (1 patient) and abdominal pain (1 patient) in the placebo group. All adverse events were minor and transient and did not lead to discontinuation of the test materials.

# DISCUSSION

We investigated the effects of OM-85 BV treatment on virus-provoked wheezing in preschool children with recurrent

**TABLE I.** Demographic characteristics of the study population

| | OM-85 BV (n = 35) | Placebo (n = 40) | *P* value |
|---|---|---|---|
| Age (mo)* | 26 (16-37) | 24.5 (14-45) | .992 |
| Sex, no. (%) | | | |
| Male | 28 (80) | 27 (67.5) | .297 |
| Female | 7 (20) | 13 (32.5) | |
| Family history of asthma, no. (%) | | | |
| Yes | 1 (2.9) | 6 (15) | .113 |
| No | 34 (97.1) | 34 (85) | |
| Family history of smoking, no. (%) | | | |
| Yes | 19 (54.3) | 14 (35) | .108 |
| No | 16 (45.7) | 26 (65) | |
| Delivery, no. (%) | | | |
| Mature | 31 (88.6) | 36 (90) | 1.00 |
| Premature | 4 (11.4) | 4 (10) | |
| Atopy, no. (%) | | | |
| Yes | 7 (20) | 11 (27.5) | .589 |
| No | 28 (80) | 29 (72.5) | |
| Diagnosis, no. (%) | | | |
| Transient wheezing | 2 (5.7) | 2 (5) | .858 |
| Nonatopic wheezing | 22 (62.9) | 23 (57.5) | |
| Persistent asthma | 11 (31.4) | 15 (37.5) | |
| No. of wheezing episodes in the previous 12 mo* | 8 (6-10) | 8 (6-10) | .759 |
| No. of ARTIs in the previous 12 mo* | 9 (8-10) | 9 (7-10) | .601 |
| No. of antibiotic courses in the previous 2 mo* | 4 (3-5) | 4.5 (3-6) | .478 |
| No. of hospitalizations in the previous 12 mo* | 1 (0-2) | 1 (0-2) | .862 |

*Data represent medians (25th-75th percentiles).

**TABLE II.** Cumulative number of wheezing attacks per patient in the 2 groups

| Period (mo) | OM-85 BV | Placebo | Mean difference (95% CI) | Cumulative % difference | *P* value* |
|---|---|---|---|---|---|
| 0-3 | 1.60 ± 0.88 | 2.30 ± 1.34 | −0.70 (−1.23 to −0.17) | 30.4 | .013 |
| | 1 (1-2) | 2 (1-3) | | | |
| 0-6 | 2.54 ± 1.12 | 3.87 ± 2.10 | −1.33 (−2.12 to −0.54) | 34.3 | .003 |
| | 3 (2-3) | 4 (2-5) | | | |
| 0-9 | 3.20 ± 1.41 | 5.00 ± 2.50 | −1.80 (−2.75 to −0.85) | 36.0 | .001 |
| | 3 (2-4) | 5 (3-7) | | | |
| 0-12 | 3.57 ± 1.61 | 5.75 ± 2.71 | −2.18 (−3.22 to −1.13) | 37.9 | <.001 |
| | 3 (3-4) | 5.5 (4-8) | | | |

Values are shown as means ± SDs and medians (25th-75th percentiles).
*The *P* value is for the comparison of OM-85 BV versus placebo. A *P* value of less than .0125 was considered statistically significant according to the Bonferroni correction.

wheezing. We demonstrated in our study that treatment with OM-85 BV significantly reduced the incidence of acute wheezing attacks. The effects seem to be secondary to a reduction in respiratory tract illnesses. Much of the difference in the placebo group in terms of the rates of illness is certainly due to the seasonal fluctuations in respiratory tract illnesses. The rate of illness simply went down because of the seasonal change, but the relative benefit of OM-85 BV was quite stable throughout the entire study.

OM-85 BV has been widely used in several European countries for more than 2 decades in children and adults. Several randomized clinical trials[16-22] have shown that OM-85 BV can reduce the number of ARTIs by 25% to 50% compared with placebo in children with a history of recurrence. In all of these studies, recurrent wheezing, asthma, or both were always among the exclusion criteria. We chose a population of preschool children with recurrent wheezing usually triggered by viral colds, with few or no interval symptoms, atopic or not.[23,24] Although daily use of ICSs significantly reduces wheezing exacerbations, it does not reduce the number of respiratory tract illnesses.[6] Moreover, there seems to be no effective agent to prevent virus-induced wheezing attacks.[8-11] Efforts for the secondary prevention of wheezing attacks in these patients should focus on reducing ARTIs.[15]

In a review of 5 pediatric studies, Schaad[25] reported that OM-85 BV reduced the risk of respiratory tract illnesses in children with a history of these infections. In young children with at least 3 reported upper respiratory tract illnesses that occurred mainly during the winter, preventative treatment with OM-85 BV reduced the incidence of these infections by 20% to 40%.[25] In accordance with these findings, we found that OM-85 BV significantly reduced the mean incidence of ARTIs and acute nasopharyngitis by 31.5% and 37.9%, respectively; stepwise multiple regression analysis showed that the main factor associated with the reduction in wheezing attacks was a reduction in ARTIs.

OM-85 BV acts as an immunomodulator by stimulating the humoral immune system, cellular immune system, or both in several different ways.[26-33] OM-85 BV also enhances antimicrobial defenses by eliciting IL-12–dependent synthesis of IFN-γ by $CD4^+$ T cells.[34] Huber et al[35] analyzed the immunomodulatory effects of OM-85 BV *in vitro* and *in vivo* and found that in

**TABLE III.** Cumulative number of ARTIs per patient in the 2 groups

| Period (mo) | OM-85 BV | Placebo | Mean difference (95% CI) | Cumulative % difference | *P* value* |
|---|---|---|---|---|---|
| 0-3 | 2.25 ± 0.98 | 2.87 ± 0.93 | −0.62 (−1.05 to −0.17) | 21.6 | .009 |
| | 2 (2-3) | 3 (2-3) | | | |
| 0-6 | 3.82 ± 1.15 | 5.30 ± 1.84 | −1.48 (−2.19 to −0.75) | 27.9 | <.001 |
| | 4 (3-5) | 5 (4-7) | | | |
| 0-9 | 4.80 ± 1.53 | 6.80 ± 2.34 | −2.00 (−2.92 to −1.07) | 29.4 | <.001 |
| | 5 (3-6) | 7 (5-8) | | | |
| 0-12* | 5.31 ± 1.79 | 7.75 ± 2.68 | −2.44 (−3.50 to −1.36) | 31.4 | <.001 |
| | 6 (4-6) | 7 (5-10) | | | |

Values are shown as means ± SDs and medians (25th-75th percentiles).
*The *P* value is for the comparison of OM-85 BV with placebo. A *P* value of less than .0125 was considered statistically significant according to the Bonferroni correction.

**TABLE IV.** Cumulative number of cases of acute nasopharyngitis per patients in the 2 groups

| Period (mo) | OM-85 BV | Placebo | Mean difference (95% CI) | Cumulative % difference | *P* value* |
|---|---|---|---|---|---|
| 0-3 | 1.45 ± 0.95 | 1.97 ± 0.97 | −0.52 (−0.96 to −0.07) | 26.4 | .032 |
| | 1 (1-2) | 2 (1-3) | | | |
| 0-6 | 2.37 ± 1.13 | 3.55 ± 1.29 | −1.17 (−1.74 to −0.61) | 32.9 | <.001 |
| | 3 (1-3) | 3 (3-4) | | | |
| 0-9 | 3.14 ± 1.37 | 4.87 ± 1.63 | −1.73 (−2.43 to −1.03) | 35.5 | <.001 |
| | 3 (2-4) | 4.5 (4-6) | | | |
| 0-12* | 3.51 ± 1.56 | 5.62 ± 1.99 | −2.11 (−2.94 to −1.27) | 37.5 | <.001 |
| | 3 (3-5) | 5 (4-7) | | | |

Values are shown as means ± SDs and medians (25th-75th percentiles).
*The *P* value is for comparison of OM-85 BV with placebo. A *P* value of less than .0125 was considered statistically significant according to the Bonferroni correction.

**TABLE V.** Secondary efficacy parameters according to treatment group

| | OM-85 BV | Placebo | Mean difference (95% CI) | *P* value |
|---|---|---|---|---|
| No. of hospitalizations (mean no. per patient) | 0.14 ± 0.35 | 0.40 ± 0.81 | −0.26 (−0.55 to −0.39) | .195 |
| Duration of hospitalizations (mean days per patient) | 0.80 ± 2.09 | 2.02 ± 4.49 | −1.22 (−2.88 to −0.42) | .310 |
| Duration of wheezing attacks (cumulative days per patient) | 20.80 ± 13.15 | 43.22 ± 22.57 | −22.42 (−31.09 to −13.75) | <.001 |
| | 19 (11-27) | 43 (26-57.5) | | |
| Duration of each wheezing attack (days per patient) | 5.57 ± 2.10 | 7.66 ± 2.14 | −2.09 (−3.06 to −1.10) | <.001 |
| | 6 (4.5-7) | 7.5 (6-8.5) | | |
| Duration of systemic steroid therapy (cumulative days per patient) | 2.68 ± 4.26 | 4.72 ± 5.76 | −2.04 (−4.39 to −0.32) | .102 |
| | 0 (0-5) | 5 (0-5) | | |
| No. of wheezing attacks requiring systemic steroid therapy (no. per patient) | 0.57 ± 0.88 | 0.90 ± 1.03 | −0.33 (−0.77 to −0.11) | .116 |
| | 0 (0-1) | 1 (0-1) | | |

Values are shown as means ± SDs and medians (25th-75th percentiles).

spleen cell supernatants levels of the $T_H1$-associated cytokine IFN-γ were increased and levels of the $T_H2$-associated cytokine IL-4 were decreased. The immunoprotective effects of OM-85 BV might result from its ability to upregulate the $T_H1$ response.[35]

We observed that the reduction in ARTI-induced wheezing attacks was paralleled by a reduction in acute nasopharyngitis, which is mainly caused by rhinoviruses. We were not able to thoroughly examine the children's immune responses, but we speculate that an increase in IFN-γ production after OM-85 BV administration could mediate its benefits. This hypothesis is supported by data from several studies. Stimulation of PBMCs from adult patients with atopic asthma using active or inactive rhinoviruses stimulated insufficient production of IFN-γ and IL-12 to fight the viral infection.[36] In a study of primary bronchial epithelial cells from patients with asthma, rhinovirus-induced production of IFN-λ and IFN-β was deficient in alveolar macrophages, leading to increased viral replication and cell lysis compared with that seen in cells obtained from subjects without asthma.[37,38] Furthermore, infants whose cells were found to have low *ex vivo* interferon responses were more likely to have severe and frequent viral respiratory tract illnesses, including those associated with wheezing; these might produce long-term airway damage.[39-41] In a prospective study by Bisgaard et al,[42] children at risk for asthma were followed from birth to age 5 years; neonates who had hypopharyngeal infections with *S pneumoniae*, *H influenzae*, or *Moraxella catarrhalis* (the same pathogens included in OM-85 BV) had increased risks of recurrent wheezing and asthma early in life. *S pneumoniae* colonizes the nasopharynx in healthy subjects, but infection rates decrease from more than 50% in infants to 5% to 10% in adults. According to von Mutius,[43] early colonization of the hypopharyngeal region with these pathogens indicates defective clearance; clearance requires the $T_H1$-mediated immune response.[44] Bacterial colonization of the hypopharynx in the first 4 weeks of life might result in a defective innate immune response early in life that promotes the development of asthma; this model might account for the findings of Bisgaard et al.[42]

We speculate that the decrease in the number and duration of wheezing attacks after administration of OM-85 BV could have

positive secondary effects, such as reduced use of short-acting $\beta_2$-agonists or systemic/topical corticosteroids. It could also result in fewer visits to emergency services and lost work days by parents. Use of drugs as systematic decongestant, topical decongestants, or both might also decrease during ARTIs.

Although the power of this study was sufficient to demonstrate a difference in the number of wheezing attacks between the OM-85 BV and placebo groups, the study had a small sample size. The small sample size might have affected the statistical significance of differences observed in wheezing attacks that were severe enough to require steroid treatment, hospitalization rates, and durations of hospitalization (which were lower in the OM-85 BV group, although differences were not found to be statistically significant). Larger trials are needed to investigate whether OM-85 BV affects these outcomes. The exclusion of children who received ICSs within previous month limits generalization about the efficacy of OM-85 BV because it is commonly used to treat children with persistent asthma. However, all the subjects began taking ICSs as the initial therapy, and most subjects used ICSs at some other point in the study period, and therefore OM-85 BV appears to be effective in preschool children with asthma.

Analysis of the baseline characteristics of the study population showed that a family history of asthma and smoking were of borderline significance. We do not believe that these affected the final results of the study because the rates of wheezing attacks, ARTIs, or nasopharyngitis did not differ within the placebo group. Furthermore, an exploratory, stepwise regression analysis showed no effect of these variables on the rate of wheezing attacks. We did not evaluate the children for infection, although no children were observed to have symptoms of infections at their physical examinations.

In conclusion, effective therapies for the prevention and treatment of virus-induced wheezing in children are needed. We show that recurrent virus-induced wheezing in preschool children can be safely and significantly reduced by administration of OM-85 BV, which might be further developed as a new therapeutic approach for this common problem.

**Clinical implications: OM-85 BV might be used as a complementary therapy to reduce the number and duration of ARTI-provoked wheezing attacks in preschool children with recurrent wheezing.**

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